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The Design and Characterisation of Multiparticulate Lipidic Systems for Oral Drug Delivery

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Declaration

Dedicated to my parents, Ian and Lynne.

Throughout my life their constant support and encouragement has enabled me to develop the confidence within, to believe the only boundaries are the ones you put on yourself.

In loving memory of Baz and Gramps,

My inspiration.

Acknowledgements

My deepest affection and gratitude I extend to my family and partner, Tristan, for their constant love, guidance and support. I would not be who I am today without their continued encouragement to follow my dreams. Their love is the source of my inspiration and motivation.

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Collaborations:

Prof. Alastair Florence for X-ray powder diffraction.

Laurence Tetley at Glasgow University for scanning electron microscopy.

Dr. Alistair Ross for assistance with design of experiments.

Abstract

The aim of the current research was to develop a sustained release hydrophobic matrix drug delivery system utilising extrusion spheronisation. The initial formulation supplied was Sebomin® MR 100mg capsules, an oral modified release commercial product. A technological transfer was undertaken to reproduce the Sebomin® multiparticulate product utilising lab-scale extrusion/spheronisation equipment. On successful completion, modulation of various processing parameters and the effect on the resultant granule and pellet characteristics evaluated.

The potential to develop a sustained release wax matrix formulation via the current technology was unsuccessful and led to the development of a hot-melt spray system. To characterise and validate the hot-melt spray system, OFAT and experimental design approaches were utilised. The process proved to be robust and reproducible in the production of sprayed wax granules. A stability study of the sprayed glyceryl monostearate (GMS) granules indicated the production of the unstable α-form of GMS, during storage the GMS reverted into the stable β-form.

Incorporation of active pharmaceutical ingredients and additional excipients into the sprayed wax matrix system enabled in-vitro properties to be evaluated from both sprayed solid solutions and solid dispersions. Screening techniques including differential scanning calorimetry, FT-IR, hot-stage microscopy, X-ray powder diffraction, scanning electron microscopy and dissolution testing were successfully employed to identify changes to the physicochemical properties of materials that may impact product performance.

Nomenclature

A	Absorbance
A(1%, 1cm)	Absorbance of a 1%w/v solution of a 1cm cell
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ATR	Attenuated total reflectance
b	Pathlength in centimeters
BP	British Pharmacopeia
c	Concentration (g/100ml)
CMC	Critical Micelle Concentration
DCP	Dibasic calcium phosphate dehydrate (Encompress®)
DDEP	Drug delivery enhanced products
DOE	Design of experiments
DSC	Differential Scanning Calorimetry
θ	Diffraction angle
EMEA	European Agency for the Evaluation of Medicinal Products
F_1	Difference factor
F_2	Similarity factor
FDA	Federal drug agency
FT-IR	Fourier transform infrared spectrophotometer
g	Grams (weight)
GIT	Gastrointestinal tract
GMS	Glyceryl monostearate

HCl	Hydrochloric acid
HEC	Hydroxyethyl cellulose
HGC	Hard gelatin capsule
HLB	Hydrophilic-lipophilic balance
HME	Hot-melt extrusion
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropylmethyl cellulose
HSM	Hot stage microscopy
IBFN	Ibuprofen
ICH	International conference of harmonisation
IPA	Isopropyl alcohol
IR	Immediate release
IVIVC	*In-vitro* and *in-vivo* correlation (IVIVC)
KBr	Potassium bromide
Log P	Lipid/water partition coefficient
MCC	Microcrystalline cellulose
MR	Modified release
MW	Molecular weight
OFAT	One factor at a time
PAT	Process analytical technology
PC	Powder cellulose
PCM	Paracetamol
PIT	Processing- induced transformation

PEG	Polyethylene glycol
PLGA	Copolymer (L-lactic/glycolic acid)
PSD	Particle size distribution
PSR	Particle size reduction
PVP	Polyvinylpyrrolidine
QbD	Quality by design
Q8	ICH guidelines – pharmaceutical development
Q9	ICH guidelines – Quality risk management
Q10	ICH guidelines – Pharmaceutical quality system
SD	Standard deviation
SEM	Scanning electron microscopy
SR	Sustained release
t	Time
T	Transmittance
ΔT	Thermal differences
$t_{70\%}$	Time to 70% drug release
UV	Ultraviolet
λ	wavelength
XRPD	X ray pattern diffraction

Contents

1. Introduction

2. Materials and Methods

3. Preparation and Characterisation of Pellets Utilising Extrusion/Spheronisation

7. Characterisation and Compatibility of Minocycline HCl Incorporated into Sprayed Material

8. Conclusions and Future Work

9. References

1. Introduction

1.1 General Introduction

Despite the current economic downturn ongoing in many parts of the world, the patient demand for pharmaceutical products remains globally unaffected. Global pharmaceutical growth is anticipated to grow by $300 billion over the next five years reaching $1.1trillion by 2014 (Gatyas, 2011). Pharmaceutical industry business has shifted in the last decade with the number and market share of generic products significantly increasing. This places pressure on the cost-effectiveness of the new drug discovery and development programs due to the ever increasing financial and time implications associated with development of new chemical entities.

Successful drug compounds cost approximately $800 million and undergo 10 to 15 years development including collaborations with a number of research fields such as pharmacology, chemistry, toxicology, clinical research and formulation development (Woodcock & Woosley, 2008). For every successful drug compound on the pharmaceutical market it is estimated 5,000 to 10,000 new chemical entities with therapeutic potential fail to reach the market (Qiu et al., 2009). This can be due to variety of reasons such as unacceptable toxicity or their low therapeutic potential in clinical trials.

Many aspects of drug development are aimed at satisfying the regulatory requirements of the drug licensing authorities. However, in order to obtain regulatory control of the drug discovery process innovation has been suppressed. As a result the regulatory authorities

have revised their approach to new and generic drug development by introducing an initiative. The risk based approach proposed by the FDA includes concepts of ‘quality by design’ and product ‘design space’ intended to enhance and modernise regulation of pharmaceutical manufacturing and product quality when adopting modern and innovative technology (Dickinson et al., 2008; ICH Harmonised Tripartite Guideline., 2009; Woodcock & Woosley, 2008).

Oral formulations account for 60% of the entire global pharmaceutical market, with sustained release products representing 95% of the total oral drug delivery enhanced products (DDEP’s), which was estimated as $31 billion in 2009 (Espicom Limited, 2011). Oral drug delivery is recognised as the most convenient route for regular drug administrations as it is non-invasive, requires simple administration and has a higher patient compliance in comparison with other administrative techniques.

Sustained release oral dosage forms for new drug entities not only improve patient compliance but are advantageous over other multiple-dosing products produced and marketed for the same therapeutic category. SR dosage forms produced for established drugs also improve patient compliance in repeat daily dosing, compared to their conventional (IR) equivalents, and can lead to extended patent protection as the generic equivalents could be based on multiple-dosing formulations.

From a physiological perspective, the use of a sustained release oral drug delivery system is to obtain controlled, predictable and extendable drug release into the GI tract post-

administration and enables maintenance of drug-plasma concentrations within a desirable therapeutic range with minimum side effects. Fluctuation of drug concentration in the blood plasma is undesirable if it exceeds the therapeutic range. The drug plasma concentration should be maintained above the minimal therapeutic effective range and below the minimal toxic concentration, this will prevent the drug becoming physiologically insignificant or causing unwanted side effects and toxicity (Figure 1.1).

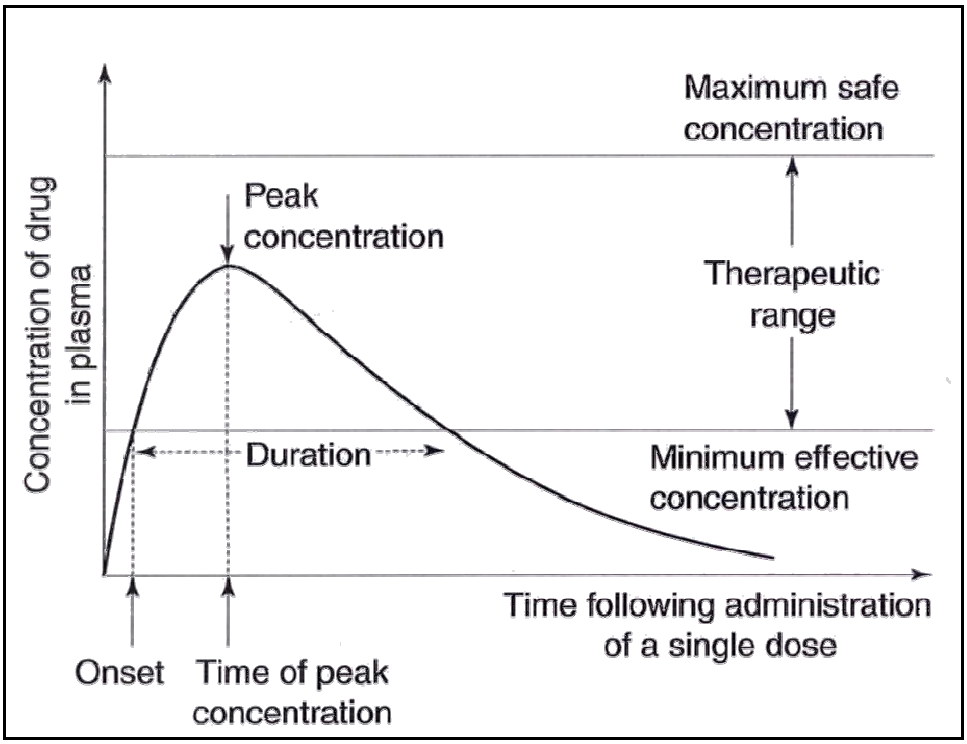

Figure 1.1 Relationship between the plasma concentration and time following administration of a single dose (Adapted from Aulton, 2002).

For an oral dosage form to achieve the desirable drug-plasma concentration, the drug must successfully dissolve in the GI fluid post administration, to enable drug absorption from the GI tract into the blood plasma. However, the GI tract is a challenging

environment for drug compounds and various physiological factors may impact on the rate of dissolution and drug absorption. The rate of gastric emptying, first-pass metabolism, chemical and enzymatic degradation and diffusion across the gastrointestinal site may impact on the bioavailability of the drug (Section 1.8.4.7).

Commercial products are able to prolong the economic cycle of the drug by updating formulation design of the generic equivalents, extending their patent protection. Marketed immediate release products could achieve this by producing a sustained release formulation for the same therapeutic indication. Sustained release reduces dosage frequency and regulates drug release within a safe therapeutic range for extended periods of time, providing continuous drug therapy. The controlled drug release rate also protects the drug from the gastrointestinal environment and minimises the risk of adverse side effects often associated with conventional immediate-release (IR) dosage forms (Bacon et al., 2002).

The aim of this research was to investigate drug release from a hydrophobic multiparticulate dosage form as a drug delivery platform. This introduction reviews the relevant topics associated with this project including, sustained release dosage forms, hydrophobic matrix pellet delivery systems, solid dispersions, formulation excipients and drug monographs.

1.2 History of sustained release oral dosage forms

The earliest written evidence of slow releasing oral dosage forms for therapeutic administration was in traditional Chinese medicines in the mid-thirteenth century but the discovery may have been as early as the second century where it is suggested animal fat was utilised as a binder in ancient dosage forms (Wen & Park, 2010). However, it is in recent decades the development of sustained release dosage forms advanced into the extensively researched science it has become.

Between the 1940's and 1990's, increased availability of semi-synthetic cellulose derivatives and fully synthetic polymethacrylates aided the advancements in enteric coatings (Gazzaniga et al, 1994; Phillip & Phillip, 2010), simultaneously followed by availability of hydrophilic gel-forming polymers impacting on the development of enhanced oral dosage form design (Barakat et al, 2009; Lee & Peppas, 1987). Other significant milestones in the evolution of oral dosage form design were the introduction of Spansule® technology by Smith Kline & French (Tiwari & Rajabi-Siahboomi, 2008; Wen & Park, 2010) and the development of commercial products utilising oral osmotic drug delivery systems which revolutionised concepts for controlled release systems (Theeuwes & Higuchi, 1974).

This increased interest was further encouraged by the high market demand for the controlled release products and was followed by the establishment of pharmaceutical related disciplines such as biopharmaceutics, pharmacokinetics and physical pharmacy fields. These advancements in our knowledge of materials, physicochemistry, drug

delivery mechanisms and GI physiology further propelled the development of controlled release drug delivery systems.

The growth of oral controlled drug delivery systems initiated the requirement for robust technologies, improved process monitoring and analytical support. To achieve these major advances in equipment and processes a number of technical challenges were met and overcome, these were primarily dictated by the physicochemical properties of drug compounds. These include solubility, drug loading, particle size, surface properties, stability and polymorphism which have to be considered prior to a successful dosage form being achieved. Formulations lacking these considerations may exhibit batch to batch variability, impacting on the quality of processing and product performance (Section 1.8.4).

To overcome these technical and physiological challenges there are two main stages involved in the development of an oral modified drug delivery system. The first is to characterise drug characteristics and define an appropriate clinical rationale. The second is to determine a suitable technology that will produce the desired dosage form and is also practical when advancing from feasibility to scale up batches and experimental analysis to identify any risks that may lead to potential challenges. Additionally, determining suitable test methods the *in-vitro* and *in-vivo* correlation (IVIVC) can assist in formulation, process and scale-up development and optimisation.

1.3 Characterisation of sustained release dosage forms

Sustained release dosage forms can be characterised into two groups; single unit dosage forms and multiple unit, or multiparticulate, dosage forms. Single unit dosage forms consist of a unit containing one dose of drug. Multiparticulate dosage forms, also referred to as pellets or beads, are spherical (or near spherical) subunits that comprise of the oral active formulation. They are regular in shape and homogenous in size but typically range between 0.5 and 2mm depending on their desired application (Aulton, 2002; Gandhi et al., 1999) and exhibit surface texture, inter-granular and intra-granular porosity characteristics. The pellet surface texture and porosity can influence the rate of drug release from both matrix pellets and coated pellets and also impact on the degree of deformation of pellet compression into tablets (Abdul et al., 2010; Galland et al., 2007; Tunón et al., 2003).

Multiparticulate dosage forms have been produced in the pharmaceutical industry for decades (Galland et al., 2005) and have processing advantages. Processing advantages of multiparticulates include low friability, better flowability properties, narrower particle distributions, high drug loading without increasing the size of the dosage form and the ability to combine different API's within the dosage form. (Chukwumezie et al., 2002; Vervaet et al., 1995). Disadvantages associated with multiparticulates are the complexity of process development, for example pellet coating and extrusion/spheronisation, making manufacture often more difficult, time-consuming and expensive compared to manufacturing processes utilised for single unit systems. Pelletisation techniques are discussed in Section 1.8.3.

1.4 Definition of sustained release dosage forms

A sustained release (SR) dosage form is a device that accommodates and releases a drug at a predetermined rate over an extended period of time. The British Pharmacopoeia (2012) recommends dissolution testing as a 'golden standard' to characterise the rate of drug release in oral dosage forms and describes sustained released as:

- Normally expected to consist of 3 or more time points expressed in hours.
- The first specification point is set after a testing period corresponding to a dissolved amount of typically 20 per cent to 30 per cent.
- The second specification point defines the dissolution pattern and so is set at around 50 per cent release.
- The final specification point is intended to ensure almost complete release which is generally understood as more than 80 per cent release.

Whereas, the rate of drug release for a conventional immediate release dosage form is expressed as one time point to ensure at least 75 per cent of the active substance is released within 45 min.

1.5 Mechanisms of drug release

Common release mechanisms associated with sustained drug release include diffusion, dissolution, swelling, solvent-activated systems and polymeric degradation (Aulton, 2002; Grassi & Grassi, 2005; Wesselingh, 1993). In hydrophobic matrix systems, the most common mechanisms are pore diffusion, surface erosion or a complex combination of both.

Diffusion is usually associated with non-disintegrating dosage forms such as matrix formulations and reservoir systems. The mechanism of drug release is based on diffusion of the drug through the matrix and into the dissolution media in accordance with Ficks laws and the Noyes-Whitney equation for spherical particles (Aulton, 2002). The rate of diffusion is controlled by the concentration gradient between the drug in the dosage form, the rate of dissolution media penetration into the matrix and the drug solubility in the media.

Erosion is exhibited in homogenous formulations with a disintegrating matrix, for example, polyanhydride polymers (Gandhi et al., 1999). The mechanism of drug release is based on surface erosion or bulk hydrolytic degradation of the dosage form when dissolution media interacts with the matrix surface, thus liberating the drug when disintegrating. The rate of erosion is controlled by the polymer composition of the matrix, formulation geometry and mass transfer phenomenon (Gopferich & Tessmar, 2002).

1.6 Kinetics

A variety of drug release kinetics can be exhibited by orally sustained release delivery systems. These include zero-order, first-order, second-order, Higuchi and anomalous models (Table 1.1). A general drug release equation that can be applied to oral polymeric dosage forms is (Ritger & Peppas, 1987a):

$$M = Kt^n \qquad \text{(Equation 1.1)}$$

[Where M = amount of drug dissolved, K = dissolution constant, t = time, n = release exponent]

The release exponent of a dosage form (n) is indicative of the mechanism of drug release from oral formulations (Siepmann & Peppas, 2001). This enables release profiles to be fitted to mathematical models allowing mechanistic understanding and theoretical predictions of products undergoing pharmaceutical development.

Table 1.1 Drug release kinetics exhibited by orally sustained release dosage forms (Adapted from Costa & Sousa Lobo, 2001; Korsmeyer et al., 1983).

Release exponent (n)	**Drug transport mechanism**	**Equation**	**Characteristics**
0.5	Higuchi (Fickian Diffusion)	$M_t = K_H t^{1/2}$	The drug diffusion pathway through an inert matrix is a linear function to the square root of time. Includes water soluble/low water soluble drugs incorporated into semi solid/solid matrices of waxes and plastic polymers (Agrawal et al., 2003; Quadir et al., 2003; Rinaki et al., 2003; Said & Al-Shora, 1980; Sung et al., 1996; Zhou et al., 1997).
$0.5<n<1$	Anomalous (non-Fickian)	$M_t/M_\infty = K_K t^n$	Release mechanism deviates from the Fickian equation following an anomalous behaviour but can be applied to Korsmeyer-Peppas model, also known as the Power law, where a combination of diffusion and erosion pathways are involved. This release mechanism is exhibited in coated granule/tablet, microencapsulated and HPMC based formulations (Colombo et al., 1999; Ochoa et al., 2005;.Rekhi et al., 1999; Ritger & Peppas, 1987a; Ritger & Peppas, 1987b, Serra et al., 2006; Zhou et al., 1997)

1.0	Zero-order release (linear)	$M_t = M_0 + K_0 t$	Dosage forms do not disaggregate and release the drug slowly. Release mechanism is independent of area changes, equilibrium conditions and time. Exhibited in matrix tablets with low solubility drugs, coated dosage forms, osmotic and transdermal systems (Conte et al., 1993; Costa & Sousa Lobo, 2001; Hossain et al., 2004; Varelas et al., 1995; Yonezawa et al., 2002).
n>1.0	First-order release (non-linear)	$M_t = M_0 e^{K1t}$	Mechanism of drug release involves the swelling of polymers within the matrix, enabling drug to dissolve and diffuse through a boundary layer. Diffusion rate is dependent on the concentration gradient. Exhibited in hydrogel polymer and hydrophilic HPMC matrix formulations (Ehtezazi et al., 2000; Hayashi et al., 2005; Siepmann & Peppas, 2001; Sood & Panchagnula, 1998).

[Where t = time, M_t = amount of drug dissolved in time t, M_∞ = amount of maximum drug dissolved, M_0 = initial amount of drug dissolved, K_H = Higuchi dissolution constant, K_K = Korsmeyer-Peppas dissolution constant, K_0 = Zero order release constant, K_1 = First order release constant, K_2 = Second order release constant].

Ideally drug release would follow zero-order kinetics (n=1) and the drug plasma concentration would remain constant throughout drug delivery. However, for most tablets, capsules, coated or sustained release forms the theoretical fundament of zero-order does not exist. Most multiparticulate dosage forms have an initial zero-order release when the drug remains undissolved but once the entire drug load of the formulation is dissolved, first-order kinetics and Higuchi release are exhibited due to formulation factors including particle size, porosity and compression characteristics, the dose and

physicochemical properties of the drug and the matrix binder used. First-order kinetics can be problematic because initial high-blood levels of the drugs are obtained leading to an exponential decrease. This rapid increase and decrease in the drug plasma concentration makes achieving a balance between toxic and effective drug therapy extremely challenging (Figure 1.1).

1.7 Matrix pellet delivery systems

A matrix system is defined as a heterogeneous dispersion of drug particles in a solid matrix that can be biodegradable or non-biodegradable (Gandhi et al., 1999) and is commonly used in the manufacture of sustained release dosage forms. The drug release within the formulation involves diffusion, erosion, swelling or a combination of both as previously discussed in Section 1.5. The rate of drug release from the matrix is controlled by formulation factors including the amount of drug, porosity, length of pores, drug solubility and matrix characteristics.

Matrix characteristics such as matrix structure, release kinetics, controlled release properties and chemical nature and properties on component materials can be used to classify matrix systems into five groups (Table 1.2).

Table 1.2 Matrix classification system.

Matrix Type	Characteristics
Hydrophilic	Diffusion is the rate determining factor in unlimited swelling. Drug release is controlled by limited swelling of gellable polymers such as HPMC, HPC, HEC (Aulton, 2002; Bravo et al., 2002; Gandhi et al., 1999).
Inert	Drug is embedded in an inert polymer e.g ethylcellulose. Drug release is controlled by diffusion (Agrawal et al., 2003; Aulton, 2002; Barra et al., 2000).
Hydrophobic	Drug release is controlled by diffusion, surface erosion or both. Lipophilic waxes including GMS, carnuba wax, bees wax, stearic acid, cetyl alcohol, cetostearyl alcohol can be used (Dredan et al., 1996; Tiwari et al., 2003; Quadir et al., 2003; Vergote et al., 2001).
Biodegradable	Non lipophilic in nature. Drug release is controlled by surface erosion. Examples are poly(anhydride) and PLGA matrices (Gandhi et al., 1999).
Resin	Drug release is from the resin-drug complex which is dependent on the surrounding ionic environment. Example Ion exchange resin (Gandhi et al., 1999).

Matrix systems have several advantages over other oral dosage forms including, availability of a wide range of excipients, possibility of using difference mechanisms of drug release control and high drug loading capability, eliminates the use of solvents and

the need for film coatings reducing process expense and time. Removing the requirement of polymeric film coatings also reduces erratic drug release profiles associated with film thickness, film coating and polymer ageing, that often causes batch-to-batch variability during production (Gandhi et al., 1999). However, wax matrix pellets and granules have demonstrated aggregation issues during production as a result of their small size (Miyagawa et al., 1996). Irreproducible drug release profiles may also result from the variable nature of the waxes, particle size distribution and excipient concentrations which must be considered prior to matrix pellet design (Section 1.8.4).

1.8 Hydrophobic materials

For several decades hydrophobic materials have been thoroughly investigated and incorporated into drug delivery systems, they are commonly used as matrix forming components and extensively used in dosage forms when incorporated with drug to achieve sustained release, tastemasking, stability improvements or amorphous form. These materials are lipophilic in nature, water insoluble but have some solubility in organic solvents such as ethanol, chloroform and ether.

The use of a hydrophobic material provides a particular advantage when it is unchanged by erosion or swelling during drug release (Gren & Nystrom, 1999). This ability of the material to be chemically inert and stable in composition when in the presence of other materials at different pH values and moisture levels, makes it non-toxic and safe for human use. Production of a hydrophobic matrix can be produced by simple melt techniques as these hydrophobic materials have low melting points.

1.8.1 Classification

Hydrophobic materials can also be referred to as lipids, which are organic substances present in all living organisms and include fats, oils, waxes and other related materials. Simple lipids can be classified into two main groups; waxes and glycerides (Table 1.3).

Table 1.3. Classification of simple lipids.

Lipid type	**Characteristics**
Waxes	Waxes are simple esters of fatty acids with alcohols (other than glycerol). They may contain free hydroxyl groups (hydroxyoctanosyl hydroxystearate) or free fatty acid functions within the molecule. They are hydrophobic, plastic solids with low melting temperatures (above 45˚C) and have relatively low viscosity when molten. Polymorphism of waxes is less common compared to glycerides due to the differences in subcell arrangements. Examples include beeswax, carnauba wax and microcrystalline wax (Jenning & Gohla, 2000).
Glycerides	Glycerides are esters of triglycerides or partial glycerides and fatty acids. They can be monoacidic or polyacidic depending on their fatty acid composition. Fats are glycerides of saturated fatty acids including capric, lauric, myristic, palmitic and stearic acids (Lide, 1981) and polar in nature. Oils are glycerides comprising of unsaturated fatty acids such as oleic acid and linolenic acid and are non-polar in nature. Glycerides appear obdurate and dull. They can form three or more polymorphic forms due to their ability to crystallise into different subcell arrangements. Examples include Gelucires® such as glyceryl behenate (Compritol®), glyceryl monostearate (Imwitor®), glyceryl palmito-stearate (Precirol®) gelucires (Hamdani et al., 2003; Jenning & Gohla, 2000; Sutananta et al., 1994b).

1.8.2 Hydrophile-lipophile balance (HLB) system

The HLB system was first introduced in 1949 by William C. Griffin of the Atlas Powder Company, who devised an arbitrary scale of values to measure the degree of hydrophilic and lipophilic component of non-ionic surfactants, including oils and waxes. All non-ionic surfactants have a HLB value between 0 and 18 which is an indication of the surfactant solubility, the higher this value the more hydrophilic the agent, the lower the value the more lipophilic the agent (Figure 1.2).

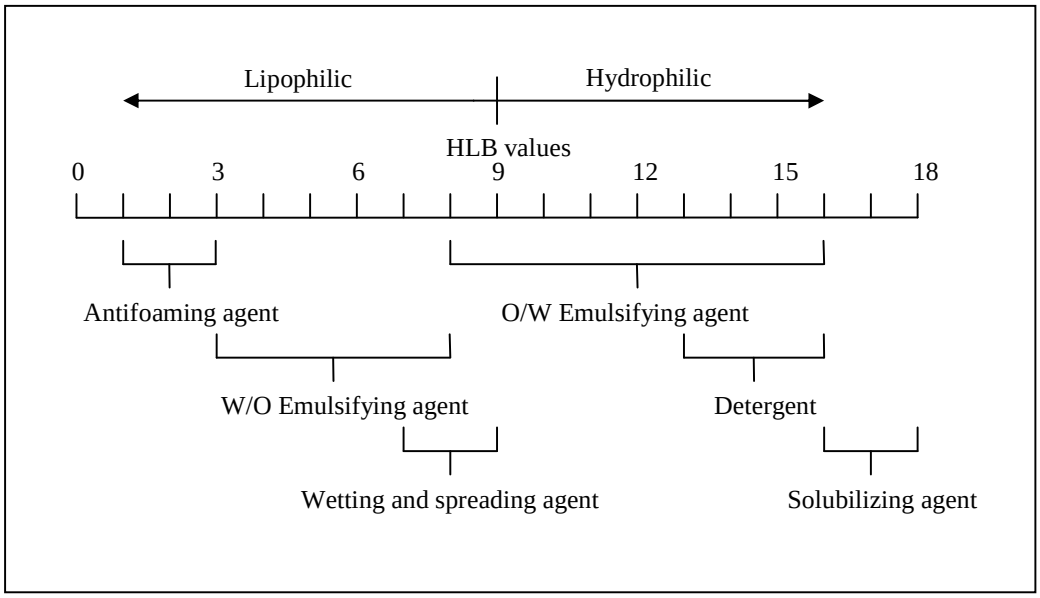

Figure 1.2 A HLB scale of the surfactant properties (Adapted from Martin, 1993).

In addition, the HLB values of oil and waxes can be determined from products and mixtures based on molecular weight percentages of each component (Equation 1.2). This enables an individual to select the surfactants of a blend based on the required application of the final product.

$$HLB_{AB} = x_A(HLB_A) + x_B(HLB_B) \qquad \text{Equation [1.2]}$$

Where: AB = mixture, A = component A of mixture, B = component B of mixture, x = % of component (Adapted from Aulton, 2002).

1.8.3 Hydrophobic matrix pelletisation

Lipids are the most favourable carriers for many techniques including melt granulation, melt extrusion, melt solidification and extrusion spheronisation. Manufacturing methods must have robust processes to facilitate scale-up of the equipment that does not impact the quality of pelletisation or the properties of the active dosage form during mass-produced pellets, whilst maintaining relatively low manufacturing costs. Pelletisation techniques applied primarily depend on the desired application and manufacturer. Common manufacturing processes are summarised in Table 1.4.

Table 1.4. Common wax matrix pelletisation techniques

Pelletisation Technique	**Characteristics**
Extrusion/Spheronisation	Section 1.8.3.1
Spray Congealing	Section 1.8.3.6
Melt granulation	Melt granulation is a rapid, solvent free, inexpensive technique. Homogenisation of drug, carrier and excipients are achieved in a heated high shear mixer, with a controlled temperature. It involves the use of a carrier with a low melt temperature, which acts as a liquid binder. It is either added in a molten state or melts due to friction generated heat due to the impellor blades during mixing. (Campisi et al., 1999; Passerini et al., 2002; Passerini et al., 2006; Walker et al., 2006).

Hot-melt extrusion (HME)	HME is a rapid, simple, water/solvent free, continuous procedure that can produce pellets from a molten binder. A hopper feeds the drug, binder and excipients directly into a heated screw-feed extruder at a pre-determined temperature, above the binder melting point. The extrudate is formed and then shaped in a jacketed spheroniser. This process is utilised when instability issues arise with wet granulation. Pellets produced do not require film coating as drug release is controlled by diffusion (Breitenbach, 2002; Rahman et al., 2009; Six et al., 2004).
Direct warm spheronisation	This one step technique is rapid, simple and eliminates complications associated with wet granulation and extrusion. Homogenisation of active, carrier and excipients is achieved by producing a hot-melt mixture. On cooling, the matrix mixture is milled into granules and directly spheronised to form spherical pellets (Phajongwiriyathorn, 2008).
Freeze pelletisation/ melt solidification	This is a simple and rapid technique, where the active ingredient is dispersed in the hydrophobic molten carrier and the mixture is introduced in droplet form to an inert, immiscible liquid. In reaction to the liquid, the droplets solidify into spherical, non porous pellets with a narrow size distribution. Hydrophilic coolants can include liquid PEGs (MW 200-600), propylene glycol, glycerin, ethyl alcohol and water. The droplets are introduced from the bottom of the column as the matrix density is less than that of the liquid (Cheboyina et al., 2004; Cheboyina & Wyandt, 2008; Kamble et al., 2004; Rahman et al., 2009).

1.8.3.1 Extrusion/spheronisation

One of the most common and preferred methods of pellet production is by utilising extrusion/spheronisation technology (Chukwumezie et al., 2002; Galland et al., 2005; Gandhi et al., 1999; Vervaet et al., 1995). Extrusion/spheronisation involves four main stages, including granulation, extrusion, spheronisation and drying, with the granular material morphologically evolving with each stage (Figure 1.3).

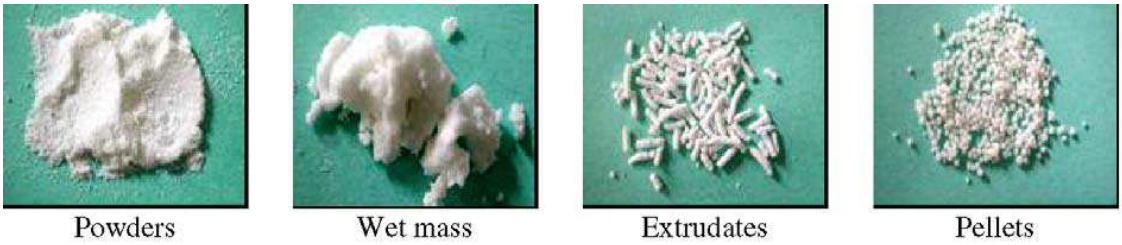

Figure 1.3 Morphological evolution of granular material during extrusion/spheronisation (Galland et al., 2005).

Advantages of this process include ease of operation, high through-put with low wastage, more sustained and reproducible drug release profiles, narrower particle size distribution and the ability to incorporate high levels of active ingredients without increasing the size of the dosage form (Aulton, 2002; Gandhi et al., 1999). Extrusion/spheronisation is a more labour intensive technique than melt techniques (Kamble et al., 2004) and is usually considered when the other methods are inappropriate or when spherical products are required.

1.8.3.2 Wet Granulation

Granulation can be described as an agglomeration process that results in the production of moist agglomerates/granules of a wide size distribution (0.1-2mm). Particle movement enables granule growth to the required size and is achieved by placing material into rotating drums or onto vibrating surfaces. Granulation can be subdivided into low, medium and high-shear granulation and relate to how the movement of particles is achieved (Table 1.5).

Table 1.5 Wet Granulation Classification

Type of Granulation	**Method of particle movement**
Low-shear	Movement of particles is induced by an air stream in a closed system. Example: Fluid bed (Aulton, 2002; Gao et al., 2002; Vervaet et al., 1995).
Medium-shear	Particle movement achieved by forceful mechanical movement of the impellor or rotating plate. Example: Rotating drum or planetary mixer (Aulton, 2002; Chevalier et al., 2009).
High-shear	Particle movement by forceful mechanical mixing. Can granulate all types of formulations and requires less granulation fluid, than low and medium shear versions, to produce pellets of same quality. Example: High-shear mixer or rotary processor (Aulton, 2002; Chevalier et al., 2009; Gao et al., 2002; Knight, 2004).

Granulation commences by dry mixing the ingredients until homogeneous powder dispersion is achieved. Granule formation occurs during liquid addition to form a wet powder mass. Granulation fluids include water or water/alcohol mixtures and are often

mixed with a polymeric binder, such as PVP (Knight, 2004; Schmidt, 1999; Wells & Walker, 1983). Use of alcohol or alcohol/water mixtures in granulation of extrusion/spheronisation results in the formation of granules/pellets with different structural and mechanical properties from those produced from water (See Sections 1.8.4.4-1.8.4.5). Granulation fluid has two major roles; to increase the plasticity of the mixture and to lubricate the extrusion die wall.

Wet granulation is particularly suitable for high-dose, readily water-soluble actives. For example, some formulations with high drug content can exhibit improved flow and cohesion properties from tablet compaction (Agrawal et al., 2003). In addition, this granule enlargement process reduces dustiness and controls the dissolution rate of material (Tardos., 2005). Disadvantages of wet granulation are the wetting and drying steps, these can be problematic for water sensitive materials and water absorbing components (disintegrants), with a risk of processing-induced transformations (PITs). This can include changes in drug polymorphic/solvate state, resulting in varying drug release rates and bioavailabilities (Jorgensen et al., 2004). Additional granulation factors affecting granule quality are summarised in Table 1.6.

Table 1.6 Granulation processing factors affecting granule production.

Processing Variables	Characteristics
Amount of granulating fluid	Formulation variable (Section 1.8.4.4)
Composition of granulating fluid	Formulation variable (Section 1.8.4.5)
Type of mixer/granulator	High shear mixers can introduce a large amount of energy which can be transformed into heat, leading to granulation liquid evaporation which influences extrusion behaviour of the wet mass (Baert & Remon, 1993a; Hellén et al., 1993b; Schmidt & Kleinebudde, 1999; Zhou et al., 1997).
Impellor speed and mixing time	The impeller and chopper speeds along with mixing time have been illustrated to increase product temperature due to high frictional forces, promoting granule growth. Mixing time is the principle factor influencing drug release rate, with prolonged mixing causing slower drug release due to increase in particle size and insufficient mixing leads to non-homogeneous distribution of formulation ingredients, including granulation fluid (Knight, 2004; Vervaet et al., 1995; Zhou et al., 1997).

1.8.3.3 Extrusion

Following granulation the resultant wet mass undergoes an extrusion step, allowing the formation of uniform rod-shaped particles. This is achieved by compressing the wet mass through a perforated screen under high load. The formulation mixture must have suitable plastic properties to enable extrusion of the wet mass. Formulations lacking this property require a greater force for successful extrusion (Vervaet et al., 1995).

Extruders are classified into three groups; screw-feed, gravity feed and piston feed (ram). There are two main types of screw-feed extruder; radial and axial. In radial extruders, the direction of extrusion is perpendicular to the direction of the rollers. In axial extruders, the direction of extrusion is parallel to the direction of the piston (Figure 1.4). Extrudates of 0.5 to 3mm diameter are usually produced from a radial extruder, whereas extrudates of 2 to 15mm diameter are produced from an axial extruder (Gebbett, 1973).

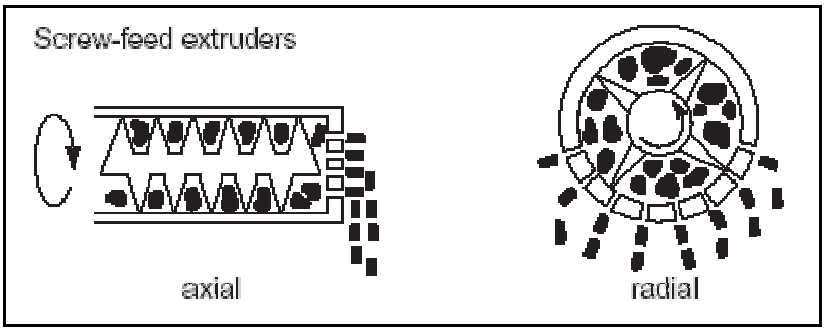

Figure 1.4 Schematic representation of extruders (Adapted from Aulton, 2002).

High quality extrudate must be smooth cylindrical segments that are uniform in length, diameter and density. The quality of the extrudate directly affects spheronisation and the quality of the pellets produced. However, the principle factor in successful extrusion is the plasticity of the wet mass. Factors affecting extrusion of wax matrix material are summarized in Table 1.7.

Table 1.7 Processing factors affecting extrudate production.

Processing Variable	Characteristics
Moisture content	Formulation variable (Section 1.8.4)
Type of extruder	The type of extruder used in pellet production can cause variations in pellet sphericity and particle size distribution affecting drug release rates. Comparative studies of different extruders revealed the type of extrusion equipment utilized in pelletisation to be critical on the resultant product properties due to the varied rates of shear and shear stresses inflicted during the process. These influences can also affect the spheronisation time required for pellet production (Baert et al., 1993b; Fielden et al., 1992; Schmidt et al., 1997; Schmidt & Kleinebudde, 1999).
Extrusion screen	Extruder screen die diameter and thickness is the main contributing factor to the resultant particle size of the product by directly modifying the cylindrical rod size produced during extrusion. The force required to pass the wet mass through the die wall is dependent on die diameter and thickness (Harrison et al., 1987; Juppo et al., 1997).
Extrusion speed	An increase in screw extruder speed increases the extrusion pressure. This results in a build up of heat energy and subsequently an evaporation of the water content within the wet mass and can lead to reduced plasticity during extrusion. High quality extrudate can still be produced if the extrusion time is reduced to a short compression stage or by optimising the wet mass composition (Harrison et al., 1985; Harrison et al., 1987).

1.8.3.4 Spheronisation

Spheronisation, also known as marumerisation, involves shaping the extrudate into regular-shaped spheres with low friability. During spheronisation, the exudate is placed on a rotating friction plate in the spheroniser. The rotational and frictional forces within

the spheroniser throws the cylindrical material to the periphery of the revolving plate, where reaction with the stationary cylinder wall causes the 'dumbbell' shaped extrudate to break up into equal size pieces. The continued application of these toroidal forces enables the rounding of particles (Figure 1.5 and 1.6).

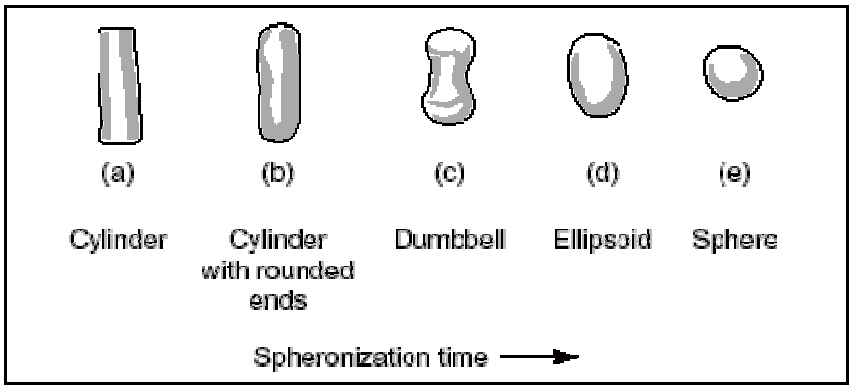

Figure 1.5 Transition from cylindrical particles (a) into cylindrical particles with rounded edges (b), then dumbbells (c), to ellipsoids (d) and finally spheres (e) (Adapted from Aulton, 2002).

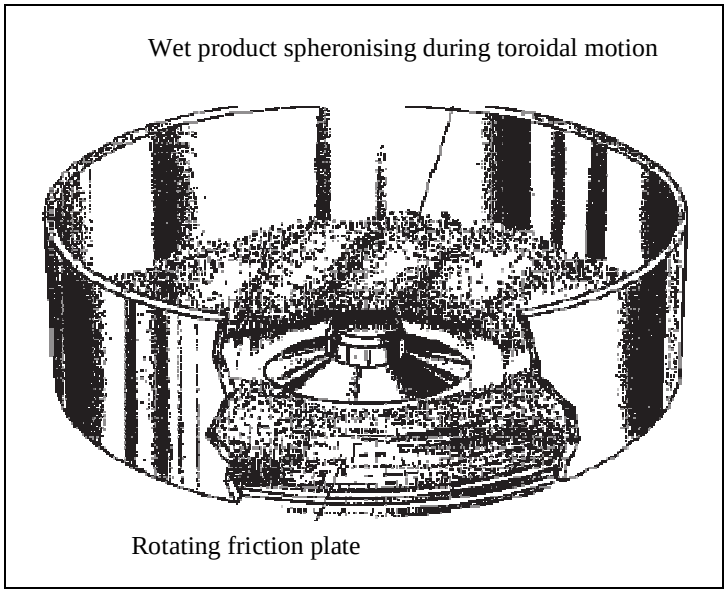

Figure 1.6 Toroidal movement of the forming pellets in the spheronizer chamber during operation (Adapted from Aulton, 2002).

Success of spheronisation is dependent on exudate properties, the material must be brittle enough to break up in the spheroniser but be plastic enough to shape into a sphere. Spheronisation processing factors that can impact on the quality of the pellet produced are summarized in Table 1.8.

Table 1.8 Spheronisation processing factors affecting pellet production.

Processing Variable	**Characteristics**
Moisture content	Formulation variable (Section 1.8.4)
Spheronising speed	Improved pellet sphericity and size distribution can be achieved by modifying spheronisation speed. At low spheronisation speeds, water content and spheronisation speed can significantly influence pellet sphericity but insufficient densification leads to imperfect spheres. High spheronisation speeds increases sphericity but can also increase agglomeration of individual pellets (Hellén et al., 1993a; Hellén et al., 1993b; Woodruff & Nuessle, 1972; Vervaet et al., 1995).
Spheronisation time	Increasing spheronisation time decreases pellet porosity, increases sphericity and narrows particle size distribution. Changes in pellet porosity are thought to be due to increased collision and frictional forces subjected to the pellets. Increasing the spheronisation time above optimum can cause pellet agglomeration and pellet adherement to the spheronising chamber. Detachment of these pellets produce rough pellet surfaces decreasing release profile reproducibility (Fielden et al., 1993; Galland et al., 2005; Hellén et al., 1993a; Hellén et al., 1993b; Juppo et al., 1997; Lee, 2003; Mehta et al., 2000; Wan et al., 1993; Vervaet et al., 1995).
Spheronisation load	Spheronisation load can influence pellet porosity and particle size distribution. Lighter spheronisation loads (50g) decreases the average pellet size than for heavier loads (100-200g). For heavier spheronisation loads, pellet size is predominantly

	determined by water content (Galland et al., 2005; Hellén et al., 1993a; Hellén et al., 1993b).
Friction plate design	The type of friction plate can impact on the pellets sphericity and density. There are two types of geometry; cross-hatch and radial (Vervaet et al., 1995).

1.8.3.5 Drying

After spheronisation, surplus moisture is removed from the pellets, by drying. This process is required to enhance the stability of the final product, reducing the opportunity for chemical changes of the constituents. Drying has been shown to have a strong influence on the final matrix structure of pellets (Table 1.9).

In the initial stages of drying, the rate of heat transfer and mass transfer are balanced, the rate of drying is determined by variables including air temperature, air flow and humidity. The drying rate of the pellets declines when the rate of heat transfer and mass transfer are no longer balanced, this is due to incomplete pellet surface wetness as the liquid front descends into the pellet pores. Drying rate then becomes dependent on the water migration within the pellets until the moisture content is reached where no more liquid can be extracted under the given drying conditions.

There are several drying techniques utilising various heat or mass transfer techniques including, open atmosphere, conventional hot air oven, fluidised bed, freeze drying, dessication and microwave. The effects of drying techniques on pellets are summarized in Table 1.9.

Table 1.9 Drying factors affecting pellet characteristics.

Processing Variable	Characteristics
Drying techniques	The influence of drying techniques has an important effect on the pellet quality. Different drying techniques cause varied drying behaviours within pellets that impact on the drying rates. This has a quantifiable effect on pellet porosity, strength and compactibility, contributing to the in vitro drug release rates of pellets. Fluidised bed, microwave and freeze drying methods exhibit fast drying rates, exhibiting the least shrinkage of the pellets, with a higher porosity but lower hardness. The slowest rate of drying, exhibited by open atmosphere, oven and dessication techniques have the greatest pellet shrinkage but lower pellet porosity. (Bashaiwoldu et al., 2004; Berggren & Alderborn, 2001a; Berggren & Alderborn, 2001b; Berggren, 2003; Johansson et al., 1995; Vervaet et al., 1995; Wlosnewski et al., 2010).
Moisture content	Formulation variable (Section 1.8.4)

1.8.3.6 Spray Congealing

The production of lipid microparticles by spray congealing was first described by Eldem et al. (1991). Spray congealing is a rapid and uniform procedure where a molten carrier, of low melting point and narrow congealing range, is used to disperse an active ingredient to form a homogenous hot-melt mixture. The molten liquid/sheet mixture is then sprayed through a nozzle, where the energy of the liquid and air, in addition to nozzle geometry causes the liquid to emerge as ligaments that further break apart to form droplets (Figure 1.7). The droplets are directed into a cooled air chamber which allows the sprayed material to solidify. Moisture sensitive drugs and materials can be utilised in this technique, as no solvent evaporating or drying processes are involved, however the substances must be heat stable.

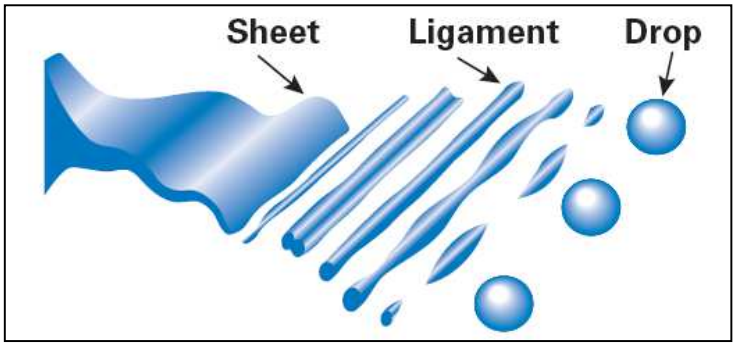

Figure 1.7 Morphological evolution of molten material during atomisation (adapted from http://service.spray.com/web/register/view_lit.asp?code=B459C, date accessed 03/06/11)

Equipment for spray congealing comprises of two components, the cooling chamber and the atomiser. The atomiser is placed inside the cooling chamber and is used to break up the molten bulk material into droplets by atomisation. There are many different ways to achieve atomisation, the most common methods associated with spray congealing are pressure (single-fluid nozzle), pneumatic (two-fluid/air-assisted nozzle), rotary and ultrasonic.

For my research an air-assisted, external mixing nozzle was utilised. This type of nozzle provides good atomisation and possesses large passages to prevent clogging. It can also atomise high-viscosity liquids and the construction prevents backing up of liquid into the air line. The drawback of this nozzle is that an external source of high pressure air is required and their power requirements are higher than for other atomisation methods (Lefebvre, 1989).

The primary factor to successful spray congealing is adequate atomisation, this leads to the production of pellets which are usually non-porous and strong. Processing parameters that can influence the resultant sprayed material are discussed in Table 1.10.

Table 1.10 Spray congealing processing factors affecting pelletisation.

Processing Variable	**Characteristics**
Type/size of nozzle	There are a number of types of nozzle for spray systems, they have different sized and shaped orifices that can be used to produce different spray patterns and droplet sizes. Larger nozzles produce larger particle sizes and air assisted nozzles produce a smaller particle size than hydraulic nozzles (Passerini et al., 2010; Nuyttens et al., 2007).
Atomisation pressure	Changes in atomization pressure can alter the flow rate of the molten liquid being fed through the nozzle. Nozzle flow rate can effect the particle size distribution (PSD) of the sprayed material. Increasing the atomization pressure reduces particle size, increases product yield. However, increasing the pressure increases the surface area required and decreases the spray angle, therefore droplet agglomeration can occur if insufficient chamber space is provided (Maschke et al., 2007; Nuyttens et al., 2007).
Spray temperature	Altering the spray temperature can influence the viscosity, surface tension and specific gravity of the molten lipid carrier which will impact on the overall PSD of the sprayed material. Increasing the spray temperature will decrease particle size and increase in product yield. (Maschke et al., 2007).
Cooling rate	When lipids are cooled they crystallise, if the cooling rate is not regulated then there is a risk of the lipid crystallising into different polymorphic forms. Rapid cooling rates, which are associated with spray congealing, could potentially lead to many triglycerides crystallising into their unstable α-forms or accelerating the transformation of lipids, including GMS, to more stable polymorphs (Eldem et al., 1991; Phajongwiriyathorn, 2008; Sutananta et al., 1994a).

1.8.4 Factors affecting quality of pelletisation

High quality pellets must be uniform in sphericity, size and density, exhibit low friability and are robust enough to withstand further processing, such as encapsulation. It is important to evaluate a variety of factors including physicochemical properties of raw materials for drugs and excipients, the composition and ratio of components within the formulation and processing parameters, influencing the rate of drug release. As a result, complex, time-consuming pre-formulation studies are required to develop a formulation with the desired drug release characteristics. Some formulation, processing and *in-vivo* aspects to consider prior to pellet production are discussed in Sections 1.8.4.1-1.8.4.7.

1.8.4.1 Drug Physicochemical Properties

The amount, particle size and solubility of the drug being incorporated into the formulation are the principle factors influencing in vitro dissolution and are applicable to both wax matrix systems and other oral drug delivery systems (Sudha et al., 2010; Wells & Walker., 1983). The drug physicochemical properties also determine the amount of excipients and granulation fluid required for successful extrusion/spheronisation process. No optimum formulation can be pre-determined based on the drugs physicochemical properties. Formulations must be developed on a systematic basis (Blanque et al., 1995; Chatchawalsaisin et al., 2005; Mehta et al., 2000; Zhou et al., 1996).

1.8.4.2 Excipient Grade, Type, Source and Amount

The type, grade and supplier of an excipient can affect pellet characteristics, including pellet roundness and size. Different types and grades of excipient may exhibit varied physicochemical properties such as elastic and shear flow behaviour. These changes can cause process-induced transformations effecting granule formation during wet granulation and the structure of the granules if evaporation rate is altered. However, high quality pellets can still be produced if other formulation factors including amount of granulation fluid and/or binders are optimized within the formulation. Excipients investigated include powder cellulose (PC), microcrystalline cellulose (MCC), lactose, α-lactose monohydrate, chitosan, microcrystalline wax, glyceryl monostearate and stearyl alcohol (Blanque et al., 1995; Chatchawalsaisin et al., 2005; Chohan and Newton, 1996; Dukic-Ott et al., 2009; Fechner et al., 2003; Jorgensen et al., 2004; Passerini et al., 2003; Santos et al., 2002; Zhou et al., 1996).

1.8.4.3 Viscosity and Surface Tension of Drug-Excipient Mixture

During spray congealing, the viscosity of the formulation at a given processing temperature can effect not only the particle size of the resultant product but the nozzle flow rate and spray pattern. At high viscosities, feed temperature had a larger impact on reducing the molten feed mixture viscosity than a higher atomisation pressure. The lower viscosity exhibited smaller micropellets and a reduced risk of nozzle clogging (Maschke et al., 2007). Viscosity can be controlled by the amount of drug dispersed in the mixture, water content and processing temperature (Eldem et al., 1991; Ghebre-Sellassie; 1994; Lefebvre, 1989).

Surface tension becomes more apparent when the operating pressure of the atomiser is low and effects spray angle and droplet size. High surface tension can reduce the spray angle of the material and increase the particle size produced, lower surface tensions enable the atomiser to be utilised at a lower operating pressure. Surface tension can be decreased by increasing the processing temperature (Ghebre-Sellassie, 1994; Lefebvre, 1989).

1.8.4.4 Amount of granulating fluid

The principle factor controlling the amount of liquid required during extrusion spheronisation is drug solubility. Granulation liquid is responsible for the wet mass's plasticity, granule growth, how it processes and eventually the rate of drug release from a formulation. In classical granulation, there is a direct relationship between extrudability and moisture content. As the water content in the extruder decreases, an increase in friction and particle resistance occurs, increasing die plate pressure and higher shear forces. During spheronisation, moisture content exceeding optimum leads to pellet agglomeration, while less than optimum generates fines and a large size distribution. The effect of moisture content has been well documented (Baert et al., 1993a; Blanque et al., 1995; Johansson et al., 1995; Fechner et al., 2003; Fielden et al., 1993; Hellén et al., 1993a; Knight, 2004; Lustig-Gustafsson et al., 1999; Mehta et al., 2000; Schmidt & Kleinebudde, 1999; Tomer & Newton, 1999, Vervaet et al., 1995, Wan et al., 1993; Wells & Walker, 1983).

1.8.4.5 Composition of granulating fluid

The composition and quantity of granulating fluid can impact the behaviour of the wetted material throughout the entire extrusion/spheronisation process. Generally, non-aqueous solvents are often used if a drug is readily hydrolysed or thermolabile. During granulation, mass friction can be modulated by substituting water for dilute acetic acid, the increased friction may produce a large amount of energy that could be transformed into heat, altering the extrusion behaviour of the wet mass (Steckel & Mindermann-Nogly, 2004). Pellets that are composed from water only and water/alcohol granulation fluids can exhibit different drying behaviours. During the drying, the varying rates of contraction and interaction between the solid and liquid can lead to differences in pellet densification and porosity. For high quality pellets to be produced a minimum amount of granulating fluid must be incorporated into liquid mixtures as identified with pellets containing Avicel and Theophylline. (Berggren, 2003; Dreu et al., 2005; Knight, 2004; Millini & Schwartz, 1990; Santos et al., 2002; Wells & Walker, 1983).

1.8.4.6 Processing factors

Processing factors for extrusion/spheronisation and spray congealing have already been discussed, their locations are documented in Table 1.11.

Table 1.11 Processing variables influencing pelletisation

Processing Variable	Section
Mixing/granulating	1.8.3.2
Extrusion	1.8.3.3
Spheronisation	1.8.3.4
Drying	1.8.3.5
Spray congealing	1.8.3.6

1.8.4.7 *In-vivo* variables

From a patient's perspective, orally administered drugs are considered the most convenient route, as it is non-invasive and self-administration is simple. In addition, there are a wide variety of dosage forms available that offer both systemic and local gastrointestinal effects (Aulton, 2002). The challenge for oral drug delivery is the gastrointestinal tract (GIT). Each of the three regions comprise of a different physiological environment and drug absorption characteristics must be considered to ensure a successful delivery system design.

The residence time of the dosage form plays an important role in successful drug delivery. If a dosage form passes through the GIT prior to releasing the full dose there will sub-therapeutic administration and the patient will not fully benefit from the treatment. To regulate GI transit times and drug bioavailability the gastric emptying rate can be optimised depending on the drug delivery requirements. The rate of gastric emptying is highly variable depending on food intake and prolonged gastric emptying rates can be achieved when oral drug administration takes place during or after food.

(Davis et al., 1986; Davis et al., 1987; Kenyon et al., 1995; O'Reilly et al., 1987; Yuen et al., 1993).

For orally administered drugs, the small intestine is the principle site of drug absorption (Aulton., 2002). If the drug is unstable in the stomach it may be desirable for drug release to be prolonged until the dosage form has reached the small intestine, typically taking 3-4 hours. In some cases, complete drug absorption must occur in the small intestine as the drug will become unstable entering the lower GIT due to metabolism by microflora, resulting in poor drug bioavailability (Qiu et al., 2009). Drug bioavailability can be modulated not only by food intake but also by variables summarised in Table 1.12.

Table 1.12 Effect of *In-vivo* variables on drug bioavailability.

Processing Variable	**Characteristics**
Type of dosage form	Abrahamsson et al., (1996) demonstrated multiple unit systems are transported at a more predictable rate through the GI tract than single-unit systems, making the bioavailability of drugs from multiparticulate formulations more reliable than those from single-unit formulations.
Chemical and Enzymatic Degradation	Drugs may bind to food or mucus and prevent free transit through the GI tract. Additionally, the drug must be resistant to chemical and enzymatic degradation potentially decreasing the bioavailability via first pass metabolism. Current approaches for acid-labile drugs are to coat the oral dosage form with enteric polymers or co-administrating with anti-acids. To protect protein and peptide formulations, prodrugs may be utilised (Aulton, 2002; Qiu et al., 2009).
pH of GI tract region	The pH of the GI tract varies considerably from the stomach to the colon. Poor drug solubility throughout the GI tract can lead to precipitation of the drug and

pH of GI tract region	poor bioavailability. Salt formation can be utilised in BCS class II compounds to enhance the solubility and dissolution of a drug than its free base/acid. Ionisable drug compounds can form salts but neutral drug compounds will not work and weak acid/base compounds may be difficult. Stable salts depend on a minimum difference of 3 units between the pKa of the salt-forming moiety of the drug and that of the salt counterion. These ionisable drugs will have enhanced dissolution until the pH exceeds the solubility limit of the salt. However, precipitation inhibitors can be used to prevent the salt forming its free base or acid (Qiu et al., 2009).
Composition of food	Foods are capable of influencing drug bioavailability and inhibiting biochemical barriers. For example, oleic acid and grapefruit juice can inhibit P450 (CYP3A), a cytochrome that is present not only in the liver but also in the intestinal brush border, resulting in increased bioavailability in CYP3A metabolised drugs (Qiu et al., 2009).

1.9 Classification of Solids

There are two main classes of solids these include crystalline and amorphous. A crystalline solid is a solid with repeated long-range order of its atoms. An amorphous solid is a solid with no long-range order of the positions of atoms. They are distinguished by their atomic arrangements and are discussed in Table 1.13.

Table 1.13 Differences between crystalline and amorphous solids

Amorphous	Crystalline
Solids have no defined geometric shape	Solids have a defined geometric shape
Wide melting point range	Have a sharp melting point
Amorphous solids are isotropic	Crystalline solids are anisotropic
Molecular packing in an amorphous solid is not completely random as it features short-range molecular order but does not have long-range order of molecular packing and subsequently has a lower packing energy than a crystal.	Molecular packing is symmetrical due to the presence of both short-range and long-range order. A crystal has a high packing energy.
Do not break at fixed cleavage planes	Break at fixed cleavage planes
Have better solubility, dissolution and sometimes better compressibility than the corresponding crystal due to its lower packing energy (Yu et al., 2001). Amorphous tablets have a higher tensile strength than crystalline forms due to the decreased particle size which enables a larger surface area for binding during compression (Gohel, 2005).	Crystals are more stable physically and chemically than amorphous forms due to its higher packing energy.

1.9.1 Crystallisation

In wax, glycerides and solid state systems, crystallisation involves the conversion of amorphous structures involving the formation of nuclei and crystal growth from the nuclei to produce a more stable crystalline state of the fat bases. Crystalline solids can exist in the form of polymorphs, solvates or hydrates.

Crystallisation can be responsible for physical changes in hydrophobic materials during melting, cooling and storage, affecting physicochemical and morphological characteristics (Laine et al., 1988; Vicente et al., 2000). The rate of crystallization in triglycerides is dependent on formulation factors including, the size of the molecule and the amount of triglyceride material present in the formulation and processing factors including, mechanical treatment of the sample and variations in process cooling rate.

1.9.2 Polymorphism

Hydrophobic materials can exhibit two or more phases with the same composition but different crystalline structures. As a result, these polymorphic forms have different unit cell structures and also different physical properties including packing, thermodynamic, spectroscopic, kinetic, surface and mechanical properties (Grant, 1999). Metastable changes occur due to external conditions at the time of formation but revert back to their more stable phase due to the favoured minimal thermodynamic energy. The chemical structure of a wax is not altered, a spontaneous physical rearrangement of intermolecular forces, based on the favoured thermodynamic stability of the more stable form, occurs via solid-state, melt-mediated or solvent-mediated phase transitions.

Triglycerides can exhibit polymorphism due to variations in thermal exposure during solidification from a melt. This leads to different assortments of structural arrangements involving the packing of hydrocarbons and orientation of the polar head groups along the glycerol backbone. Gelucires® (mono-, di- and triglycerides), fatty suppositories, GMS and Compritol have exhibited polymorphic changes during storage leading to variations

in melting point, softening time and drug release rate (Freitas & Muller, 1999; Jenning & Gohla, 2000; Phajongwiriyathorn, 2008; Yoshino et al., 1984). The transition rate can be dependent on the storage temperature, storage time and processing factors. Polymorphic forms are classified as α, β´ and β in order of their increasing melting points (Table 1.14).

Table 1.14 Wax polymorphic classifications

Polymorphic Classification	**Characteristics**
α	Corresponds to hexagonally packed unit cell structure which is the most disorderly packing and has the highest Gibbs free energy values. It is the least stable form and is quickly transformed into a more stable form with denser packing (β´ or β form). In many types of glycerides, the α form is produced post-melt during cooling, the crystal morphology is amorphous-like, crystallising as spherulites and sheath-like crystallites, growing radially from a primary crystal core, this results in a smooth surface of the crystallised sample (Sato, 2001; Yajima et al., 2002; Yoshino et al., 1984).
β´	β´ polymorphic form has orthrombic packed unit cell structure and exhibits intermediate Gibbs free energy values. This form appears as tiny bulky shapes and can further transform into the more stable β form. Both β´ and β polymorphic forms irregular structures on micropellet surfaces, the loss of a smooth surface indicates transformation into either of these forms.
β	β form is the most stable polymorphic form and has the most dense packing triclinic unit cell structure with the lowest Gibbs free energy values. For waxes, the crystal morphology for this polymorphic form is needle-like (Yajima et al., 2002).

Fatty suppositories, for example, are made up of various glycerides, each with a different unit cell structure. Both unstable and stable polymorphic forms can co-exist within the

same wax (Yajima et al., 2002). The ratios of these polymorphic forms can alter with time and transformations can be monotropic, enantiotropic or a combination of the two (Yoshino et al., 1984).

1.9.3 Methods of polymorphic detection

Molecular structures of the different polymorphs can be elucidated by the following techniques (Table 1.15).

Table 1.15 Analytical techniques used to differentiate between polymorphs

Analytical Technique	**Characteristics**
X ray powder diffraction (XRPD)	X ray diffraction patterns of GMS enabled identification of the amount of α and β forms present in the sample (E represents the β form of the content). When E=0.44 peaks of both α and β forms were exhibited but when E>0.85 only the β form was present (Yajima et al., 2002).
Differential Scanning Calorimetry (DSC)	GMS α- and β polymorphic forms could be distinguished by the two melting endotherms obtained at 67.9^{o}C and 71.9^{o}C respectively (Yajima et al., 2002). Ageing of Gelucires and triglycerides could also be detected using DSC (Laine et al., 1988; Sutanata et al., 1994a).
Fourier transform infrared spectroscopy (FT-IR)	In saturated monoacid triglycerides α-, β´- and β forms exhibit an IR sprectrum comprising of a single band at 720cm^{-1} , doublet at 719 and 727 cm^{-1} and a single band at 717 cm^{-1}respectively (Garti & Sato, 1988).
Hot-Stage Microscopy (HSM)	A phase transition of Gelucire 43/01 was detected in aged samples. HSM was utilised with polarised microscopy which

Hot-Stage Microscopy (HSM)	indicated the presence of unmelted portion of aged sample even at 45 ^{o}C. The energy required for ageing increased due to crystallisation of the glycerides (Shimpi et al., 2004).
Dissolution	Increases and decreases in drug release rate can often be correlated with transitions due to wax changes. A phase transition of aged Gelucire 43/01 caused a significant increase in the drug release rate of diltiazem HCl (Shimpi et al., 2004). Sutanata et al. (1995) showed that ageing of Gelucires® also increased drug release and was attributed to changes in physical structure and chemical composition.
Scanning electron microscopy (SEM)	Granules comprising of waxes, such as Gelucires, can exhibit different surface morphologies between fresh and aged samples. Fresh samples have smooth granule surfaces with no crystalline structures, whereas aged samples have rough surfaces with cracks and spaces (Shimpi et al., 2004). These changes can be attributed to phase transformations and may lead to changes in drug release profiles.

1.10 Solid dispersions

A solid dispersion involves two or more components, where an active ingredient is dispersed, as a solid, in an inert matrix utilising melting, solvent or melting-solvent methods (Chiou & Riegelman, 1971).

1.10.1 Applications of solid dispersions

Oral dosage forms are the most commonly developed drug delivery system due to their simple administration. However, as a large proportion of the new chemical entities

intended for oral administration are poorly water soluble drugs the improvement of drug oral bioavailability is of great importance (Vasconcelos et al., 2007). Solid dispersion technology is the most effective strategy used to address oral bioavailability, these types of formulation can be utilised to achieve sustained release formulations, increased dissolution rate, altered solid state properties, improved solubility and stability (Habib, 2001).

1.10.2 Solid dispersion classification

There are three modes of incorporating a drug into a solid dispersion including amorphous particles, crystalline particles and molecular dispersion. A matrix can be crystalline or amorphous. The dispersion properties are controlled by the molecular arrangements, influencing stability and dissolution of the solid dispersion (Figure 1.8).

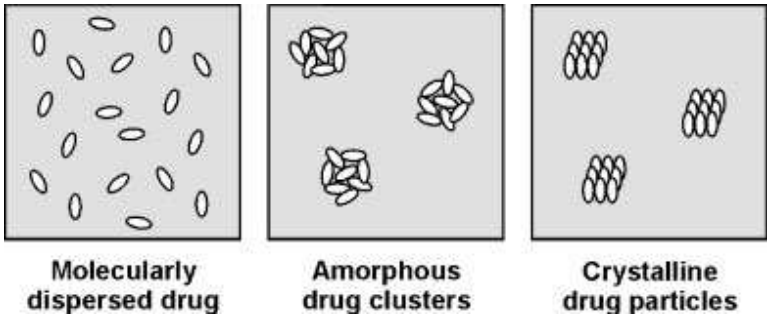

Figure 1.8 Schematic representation of different modes of incorporating a drug into a solid dispersion (Jan van Drooge et al., 2006).

By manipulating the solid state of a solid dispersion improved drug solubility and bioavailability can be achieved. The mechanisms by which these can be achieved include forming solid or glass solutions which molecularly disperse the drug. Decreasing the crystallinity of the drug into an amorphous state, enhancing drug wettability or

dispersibility due to the carriers solubilisation effect, or the formation of a metastable dispersion (Janssens & Mooter, 2009; Serajuddin, 1999).

Using these different mechanisms, six different types of solid dispersion can be obtained using crystalline, amorphous and molecularly dispersed drug incorporation. These include eutectic mixtures, solid solutions, glass solutions and suspensions, compound/complex formation, amorphous precipitates and combinations (Table 1.16).

Table 1.16 Classification of solid dispersions

Type of Solid Dispersion	**Characteristics**
Simple Eutectic Mixture • Matrix: crystalline • Drug: crystalline	A mixture of components either entirely solid or entirely liquid. It solidifies at a lower temperature than the components or any other composition involving them, crystallisation of the components is simultaneous at this low temperature. Usually prepared by rapid cooling of a co-melt. (Gordon et al., 1984; Lira et al., 2007; Passerini et al., 2002; Schmidt et al., 2000; Yong et al., 2004)
Solid Solutions • Matrix: crystalline • Drug: molecularly dispersed	A homogenous crystalline structure in which two or more components share a crystal lattice without changing the overall structure. This system increases rates of dissolution more than a simple eutectic mixture as the drugs particle size has been reduced to its minimum due to molecular dispersion. Solid solutions are classified by either their miscibility or by solvate molecular distribution (Janssens & Mooter, 2009; Kapsi & Ayres, 2001; Leuner & Dressman, 2000).
Glass Solutions • Matrix: amorphous • Drug: crystalline/amorphous	A glass solution is a homogeneous system in which a glassy carrier solubilises drug molecules in its matrix. A glass suspension refers to drug molecules that are suspended in the glassy matrix. Amorphous

Glass Suspensions • Matrix: amorphous • Drug: molecularly dispersed	carriers include PVP and HPMC. Glasses do not have sharp melting points and these systems have higher dissolution rates than for solid solutions. (Janssens & Mooter, 2009; Patterson et al., 2007; van Drooge et al., 2006).
Compound/complex formation • Matrix:crystalline/amorphous • Drug: molecularly dispersed	During solid dispersion preparation complexation occurs of two components in a binary system. This can decrease the availability of the drug because of formation of this insoluble complex and is dependent on complex solubility as seen in physical mixtures involving PVP 25,000. (Geneidi et al., 1976).
Amorphous precipitations • Matrix: crystalline • Drug: amorphous	This solid dispersion is rarely encountered and is similar to a simple eutectic mixture. However the drug precipitates out in the amorphous form not the crystalline form in the inert carrier. An example is sulfathiazole in crystalline urea. (Ozkan et al., 2000).

1.10.3 Methods of preparing solid dispersions

Solid dispersions can be prepared utilising various techniques (Table 1.17).

Table 1.17 Methods of preparing solid dispersions

Method	**Characteristics**
Fusion (Hot-melt)	The carrier is heated to a temperature slightly above its melting point and the drug is homogenously incorporated into the matrix by agitating. Cooling results in solidification of the dispersed drug within the matrix. Molecular dispersion is dependent on the amount of supersaturation and rate of cooling. Matrix polymers can include PVP, PEG and GMS. Scalable and industrial practical applications of the fusion method include hot-melt extrusion and spray congealing (Sections 1.8.3 and 1.8.3.6). Direct hot-melt filling into hard gelatin capsules is also a favoured solid dispersion preparation technique, exhibiting better content uniformity, weight and handling than powder fill methods. (Jan van Drooge et al., 2006; Leuner & Dressman, 2000, Lira et al., 2007; Ozkhan et al., 2000; Smith et al., 1990).

Solvent	The carrier and active ingredient are dissolved in a suitable organic solvent. During solvent evaporation (at higher temperature or vacuum), supersaturation occurs followed by precipitation of the solid dispersion mixture. A drying process ensures evaporation of all solvent present in the coprecipitate. This method is suitable for thermolabile compounds but the temperature, evaporation rate and solvent type influence the physical properties of the resultant solids. Solvents can include water, ethanol, chloroform, dichloromethane and methanol. Industrial applications include spray drying, freeze drying and fluidised bed systems, the latter for coating pellets with a solid dispersion. (Betageri & Makarla, 1995; Flippis et al., 1995; Janssens & Mooter, 2009; Ho et al., 1996; Ozkan et al., 2000; Tang & Pikal, 2004; Vehring, 2008).
Supercritical fluid method	The drug and carrier are mixed with a solvent then exposed to CO_2, resulting in the precipitation of drug and matrix due to the low drug solubility. There are three main process concepts involving the precipitation from supercritical solutions (RESS), saturated solutions using SCF (GAS, SEDS) and gas-saturated solutions (PGSS). (Jan van Drooge et al., 2006; Karanth et al., 2006; Pasquali et al., 2008; Sethia & Squillante, 2002).
Electrostatic spinning	Drug-matrix homogenous solution is pumped through an orifice and subjected to high voltages, inducing surface charges that overcome surface tension in a droplet to form and then solidify fibres. After solvent evaporation the fibres can be further processed or milled. (Verreck et al., 2003).

1.10.4 Advantages and limitations of solid dispersions

Solid dispersion technology is a more attractive approach to improving the drug solubility than other techniques such as salt formation, solubilisation by co-solvents and particle size reduction techniques. Salt formation is limited to acidic or basic drugs, solubilisation involves liquid products being formed which are less preferred by patients than solid dosage forms and particle size reduction techniques do not sufficiently reduce the particle

size to improve bioavailability, with drug powders often having poor mechanical properties.

Despite the advantages outlined for solid dispersion technology there have been limitations associated with this type of formulation that have prevented commercialisation of this product. These drawbacks include physical instability of the drug and carrier during processing, storage or ageing leading to phase separation, crystal growth, polymorphism or conversion of amorphous components to crystalline influencing solubility and drug release rates (Section 1.9). Manufacturing issues include the method of preparation, decreased reproducibility of physicochemical properties and scale-up. The future of solid dispersion technology has improved with the development of direct capsule filling and the availability of surface active and self-emulsifying carriers (Serrajuddin et al., 1999).

1.11 Formulation excipients

1.11.1 Glyceryl monostearate (GMS)

Glyceryl monostearate, is a white to cream-coloured, wax-like solid that can take the form of beads, flakes or powder. It has a fatty odour and taste, a melting point between 54-64^{o}C, a HLB value of 3, is insoluble in water, soluble in ethanol and can be dispersed in hot water.

GMS is a mixture of glyceryl esters of fatty acids, comprising of 65% glyceryl monostearate, 30% glyceryl monopalmitate and 5% glyceryl monomyristate, making the content of GMS over 90% monoglyceride.

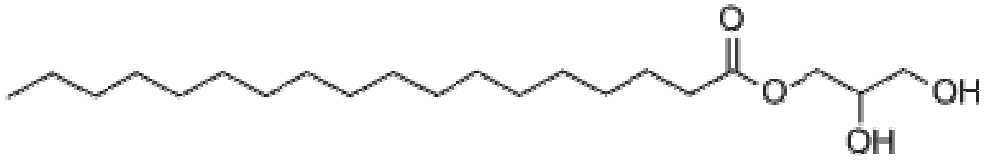

Figure 1.9 Chemical structure of glyceryl monostearate (GMS)

GMS has been used as non-ionic emulsifier, stabiliser, emollient and plasticizer in food, pharmaceutical and cosmetic applications. It acts as a lubricant for tablet manufacturing and has been used to form sustained release mechanisms in solid dosage forms (Rowe et al., 2003).

1.11.2 Aluminium monostearate

Aluminium monostearate is a fine, bulky, odourless white powder with a melting point of ~155-200˚C and a molecular weight of 344.5.

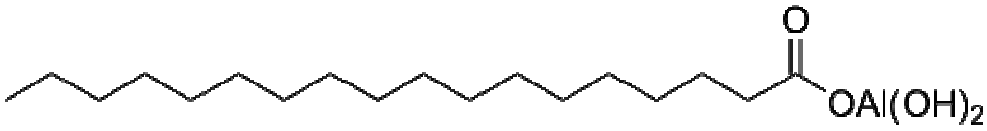

Figure 1.10 Chemical structure of aluminium monostearate

When heated it forms a plastic mass and has the properties of both organic and inorganic matter. It is soluble in all types of organic solvents and oils when heated (except castor oil), to form permanent, transparent, viscous solutions or gels.

Aluminium monostearate is considered an Aluminium Carboxylate which are used primarily in textiles, gelling and pharmaceutical industries due to its thickening and

gelling properties. It can be present in adhesives, ceramics, inks, lubricants, paints and coatings, polishes, polymers and plastics (Lower, 1982).

1.12 Drug monographs

1.12.1 Paracetamol

Paracetamol, also known as acetaminophen, is a white or off-white crystalline powder with no smell and a bitter taste. It comprises of a benzene ring core, substituted by one hydroxyl group and one nitrogen atom of an amide group in the *para* (1,4) pattern (Figure 1.11).

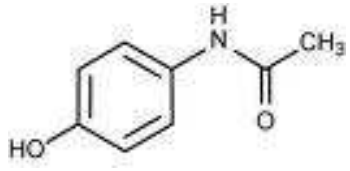

Figure 1.11 Chemical structure of paracetamol

Paracetamol has a melting point of 168-171^{o}C, log P (octanol/water) value of 0.5, molecular weight of 151.2 g/mol and is slightly soluble in water, freely soluble in alcohol and insoluble in benzene, chloroform and ether.

Paracetamol is an analgesic and antipyretic drug, commonly used to treat fever, headaches and is present in most cold or flu remedies. It is usually administered as a tablet, oral suspension or suppository and is available for both adults and children (British Pharmacopoeia, 2012).

1.12.2 Ibuprofen

Ibuprofen is a white powder belonging to the propionic derivatives. It has a melting point of 74-77^{o}C, log P value of 3.6, molecular weight of 206.28 g/mol and is very slightly soluble in water, but much more soluble in organic solvents such as alcohols.

Ibuprofen contains a stereocenter in the α- position of the propionate moiety, interconverting between two possible enantiomers. Ibuprofen is marketed as racemic mixtures but only one form is medicinally active. Its chemical structure is $C_{13}H_{18}O_2$ (Figure 1.12):

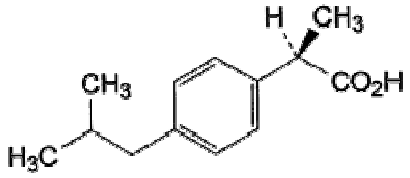

Figure 1.12 Chemical structure of ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory commonly used to relieve symptoms of arthritis, fever, skeletal and muscular pain. It is usually administered as tablets, oral suspensions and due to its stability can be available in a topical gel for sports injuries.

1.12.3 Minocycline HCl

Minocycline, also known as minocycline HCl, is a yellow crystalline powder that has a melting point of 217^{o}C where decomposition occurs, log P value of 1.48, molecular weight of 457.48 g/mol and is sparingly to slightly soluble in water, slightly soluble in ethanol.

Minocycline is known as a broad spectrum tetracycline antibiotic, named due to their four hydrocarbon rings derivation. Its chemical structure is $C_{23}H_{27}N_3O_7$ (Figure 1.13):

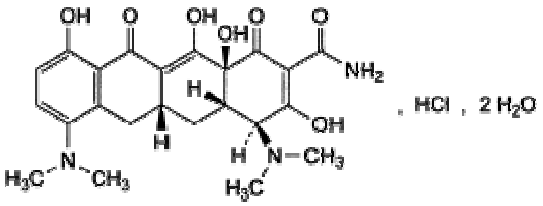

Figure 1.13 Chemical structure of minocycline HCl

Minocycline possesses bacteriostatic properties making its primary use to treat acne and other skin infections. It can be used similarly to other tetracycline antibiotics to treat infections of the respiratory tract, sinuses, urinary tract, intestines and gonorrhea and chlamydia.

Sebomin MR is a Minocycline HCl 100mg capsule, used to treat acne. Once orally administered the formulation exhibits a modified release over several hours. The formulation is a hydrophobic matrix pellet drug delivery system and manufactured utilising extrusion/spheronisation technology.

1.13 Aims and objectives

The aim of the research was to develop a modified release hydrophobic matrix pellet system utilising two manufacturing techniques: extrusion/spheronisation and an agitated hot-melt spray system. For this aim to be achieved the following objectives were defined:

- To investigate the effect of formulation composition and processing conditions on the *in-vitro* performance of a Sebomin formulation. To determine whether this hydrophobic matrix delivery system could be utilised with different patient critical molecules.
- To investigate the effect of formulation composition and processing conditions on the resultant sprayed wax material from an agitated hot-melt spray system.
- To incorporate model drugs in a sprayed GMS solid dispersion and determining their compatibility and *in-vitro* performance.
- To determine the effect of secondary excipients on the spray quality and in-vitro performance.
- Comparing a modified release Sebomin product produced by two manufacturing techniques.

Chapter 2

Materials and Methods

2.1 Materials

Details of formulation materials and equipment used in this study have been listed, along with the manufacturers or suppliers details (see Sections 2.1 – 2.2).

2.1.1 Formulation Excipients

Aluminium Chloride	Sigma-Aldrich Co. Ltd, UK
Aluminium hydroxide	Sigma-Aldrich Co. Ltd, UK
Aluminium monostearate	Sigma-Aldrich Co. Ltd, UK
Microcrystalline Cellulose (Avicel PH101)	FMC Corp., Brussels, Belgium, Europe
Glyceryl Behenate (Compritol ATO 888)	Gattefosse SAS, Saint-Priest Cedex, France
Glyceryl monostearate, Imwitor 900K	Alpharma., Barnstaple, Devon, UK.
Polyvinylpyrrolidone (Kollidon 29/32)	ISP Technologies, Inc., USA
Magnesium Stearate	Sigma-Aldrich Co. Ltd, UK
Polyvinylpyrrolidone, MW approx 35,000	BDH Chemicals Ltd, Poole, UK.

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2.1.2 Model Drugs

Ibuprofen	OBG Pharmaceuticals, Liverpool, UK.
Minocycline HCl	Alpharma, Barnstaple, Devon, UK.
Paracetamol	Sigma Chemical Co., St Louis, MO, USA.
Micronised Minocycline particle size: <100micron (100%)	Alpharma, Barnstaple, Devon, UK.

2.1.3 Solvents

Ethanol	BDH, Poole, UK.
Hexane	BDH, Poole, UK.
Iso-propyl alcohol (IPA)	BDH, Poole, UK.

2.1.4 Consumables

40µl Aluminium crucibles	Mettler Toledo Ltd, Leicester, UK.
70µl Aluminium crucibles	Mettler Toledo Ltd, Leicester, UK.
Aluminium foil	Happy Shopper Ltd., Northants, UK.
Coverglass, round 13mm	VWR International Ltd, Poole, UK.
Dissolution colour tubing, 3mm	Copley Scientific Ltd, Nottingham, UK.
Dissolution filters	Copley Scientific Ltd, Nottingham, UK.
Gilson pipette and tips, 5ml	Gilson Medical Electronics S.A., Villiers-le-Bel, France.
Greaseproof paper	Fruit market, Glasgow, UK.
Hard gelatin capsules	Capsugel, Bornem, Belgium.

Magnetic stirrer bar	Fischer Scientific, Loughborough, UK.
Spray Booth: Plastic Dust Sheets Plastic Conduit and connectors	B&Q, UK.

2.1.5 Gases

Carbon Dioxide	BOC Gases Ltd, Guildford, Surrey, UK
Helium	BOC Gases Ltd, Guildford, Surrey, UK
Nitrogen	BOC Gases Ltd, Guildford, Surrey, UK

2.2 Equipment

2.2.1 Manufacturing

Balances (x2), Sartorius AG 135	Sartorious AG, Goettingen, Germany Mettler Toledo Ltd, Leicester, UK.
Extruder, Roller Model 10/25	Caleva Process Solutions Ltd, Sturminister Newton, UK.
High Shear Mixer/Granulator, FP296	Kenwood Ltd., Watford, Hertfordshire, UK.
Hot Air Oven	No specification.
Magnetic Stirrer Bars	VWR International Ltd., Poole, UK.
Magnetic Stirrer/ Hotplate, 513612	Bibby Scientific Limited., Staffordshire, UK.
Miller/Hand Blender,	Cookworks., Argos, UK.

HM-918	
Motorised overhead stirrer, SS10, general purpose	Stuart Scientific, Surrey, UK.
Spheroniser, Model 120	Caleva Process Solutions Ltd, Sturminister Newton, UK.
Spray gun, NLE550HVLP	Performance Power Tools, UK.
Voltage Meter Model 38XR	Meterman Tools, UK.

2.2.2 Analytical

Absolute Digital Calipers	Mitutoyo (UK) Ltd, UK.
Automated Dissolution Apparatus (x2), Copley dissolution bath, ST7 Erweka heater, Watson Marlow peristaltic pump, 313S UV/ visible spectrophotometer, CE 3021 3000 Series	 Copley Scientific, Nottingham, UK. Erweka GmbH, Germany. Watson Marlow, Cornwall, UK. Cecil Instruments Ltd, Cambridge, UK.
Brookfield Viscometer,	Brookfield Engineering Laboraories, Inc., Massachusetts, USA.
Differential Scanning Calorimetry, DSC model 822^{e} Sample robot, TS0801RO	Mettler Toledo Ltd, Leicester, UK.

Fourier-transform infrared spectrophotometer (FT-IR) Model Bench 101: Genesis 1	Mattson Instruments, Madison, USA.
Mastersizer Hydro 2000SM	Malvern Instruments Ltd, Worchestershire, UK.
Peristaltic pump, IPC ISM 931 V4.00	Ismatec SA., Analytical Laboratories, Glattbrugg-Zurich.
pH 211 microprocessor pH meter	Hanna Instruments Ltd, Bedfordshire, UK.
Polarised light microscope, Polyvar Hot-stage platform Colour video camera, TK-1280E	Reichert Jung, Germany. Linkam Scientific Instruments Company JVC
JVC Scanning electron microscope, Jeol JSM 6400	Jeol, Herts, UK.
Sieves: brass, Range of sizes 53-2000μm	Endecotts Ltd., London, UK.
Sputter coater, Polaron SC515	Enutech Ltd, Ashford, Kent, UK.
Tap density volumeter Model TDV	Copley Scientific, Nottingham, UK.
UV1 UV-vis spectrophotometer	Thermo Fisher Scientific, Staffordshire, UK.
Vibrating ball mill Model 441 Model 441	Griffin and George Ltd, UK.

X-ray powder diffraction (XRPD) Model Bruker-AXS D8	Bruker AXS GmBH, Karlsruhe, Germany.

2.2.3 PC Software

Automated dissolution testing (x2), Datastream CE2000 series, Erweka,	Cecil Instruments Ltd, Cambridge, UK. Erweka®, Heusenstamm, Germany.
Jasco (FT-IR software)	Mattson Intruments, Madison, USA
Leutron Vision PicPort and PicProdigy Demonstration Programme, version 1.95.002	Leutron Vision, Switzerland.
Malvern software (Mastersizer software)	Malvern Instruments Ltd, Worchestershire, UK.
Minitab version 12	Minitab Ltd, Coventry, UK.
SEM software, Image Slave	Meeco-Dindema, Sydney, Australia
Stat-Ease Design Expert version 6.0.10	QD Consulting, Cornwall, UK
Thermal analysis software, STAR^{e}	Mettler Toledo Ltd, Leicester, UK.
X-ray powder diffraction software, EVA 9.0.0.2	Socabim, Germany.

2.3 Overview of the Generic Manufacturing Techniques

2.3.1 Wax fusion

Wax fusion is the incorporation of drug into an inert wax matrix. The production of granules from this method requires two steps; homogeneous powder dispersion and milling which are outlined below:

2.3.1.1 Homogeneous Powder Dispersion

	Powder Dispersion Method
1	Weigh amount of wax powder required, transfer into a container and melt on a hot plate at a maintained temperature above the wax melting point.
2	Weigh amount of drug required and gradually add to the molten wax. Mix well with a stirring rod until a homogeneous mixture is achieved.
3	Pour wax mixture onto a sheet of aluminium foil and allow to cool at room temperature for 1hr.

2.3.1.2 Mill and Sieving

	Milling and Sieving method
1	Break up the dried bulk wax/drug mixture and place into a plastic container.
2	Mill the fragments, using a hand-blender for 30secs.
3	Pass the resulting wax granules through a 2000 micron sieve.
4	Granules that are larger than 2000 microns are directly transferred back into the hand blender to be further milled.
5	The sieved granules are then collected, weighed and analysed.

2.3.2 Paracetamol Size Reduction

	Ball milling technique
1	100g paracetamol powder was transferred into a vibrating ball-mill (model 441 with stainless steel ball bearings) and milled for 20mins.
2	The powder was then sieved for size fractions less than 500 microns. Paracetamol greater than 500 microns were further milled for 20mins until an adequate fraction of the required sizes (53-250 microns) was obtained.
3	Paracetamol within the desired size range was collected for incorporation into formulation.

2.3.3 Extrusion/Spheronisation Techniques

Producing pellets utilising extrusion/spheronisation requires four stages, the details of the methodology for each are outlined below. This method was used for the production of minocycline HCl and paracetamol pellets.

2.3.3.1 Granulation

A homogeneous wet powder mass containing powder excipients and drug was prepared using a granulator.

	Granulation Method
1	Prepare a 50ml quantity of 56% w/v ethanol/distilled water solution for use as granulating fluid. o Using a measuring cylinder, add 28ml of ethanol to a 50ml volumetric flask and make up to the mark with distilled water.
2	Prepare a 38 % w/v solution of Povidone K-29/32. • Weigh 2.25g of Povidone K-29/32 into a glass beaker and dissolve with 6ml of 56% w/v ethanol distilled water solution. Stir until completely dissolved.
3	Weigh 23g of Avicel PH101 and transfer into the high speed mixer/granulator. Add the milled product from 2.2.3 into the high speed mixer/granulator and dry mix for 5 minutes with the impellor at slow speed (35rpm).
4	Granulate the blend, with the impellor blade on slow (35rpm) by adding the Povidone K-29/32 solution and continue mixing for a total of 5 minutes.
5	Add over approximately 2 minutes, with the impellor on slow speed (35rpm), 28ml of the granulating fluid and continue mixing for 20 minutes.
6	Add further granulation fluid, if required, until a homogeneous wet mass suitable for extruding is formed (Note additional fluid used).

2.3.3.2 Extrusion

	Extrusion method
1	Extrusion was performed on the homogeneous wet mass resulting from granulation, to produce uniform rod-shaped particles.
2	Extrusion occurred at room temperature through a stainless steel screen (15cm diameter) with perforations (1mm diameter).
3	Resultant extrudate was collected for spheronisation.

2.3.3.3 Spheronisation

	Spheronisation method
1	The rod-shaped particles produced from extrusion were placed immediately into the spheroniser in order to minimise moisture loss.
2	Spheronisation was carried out in a spheroniser fitted with a cross-hatched frictional plate (120mm in diameter) at room temperature for 2 mins. Processing parameters: Speed – Fixed Speed* Temperature – Uncontrolled ambient *Sawicki et al (2004) measured the fixed speed via tachometer 1200-1300rpm
3	Resultant pellets were collected for drying in an air oven.

2.3.3.4 Drying

	Drying method
1	The spheronised pellets were placed in the oven at 50ºC for approximately 4 hours until the weight of the pellets remains constant.
2	The pellets were then weighed and transferred into a suitable container ready for analytical testing.

2.3.4 Hot-melt Spray System

Granules were produced by addition of drug and excipient powders into an aluminium spray container, heated until the wax had become molten and atomised utilising an agitated hot-melt spray system (Figure 2.1) as outlined in the manufacturing steps below:

Figure 2.1 Agitated hot-melt spray system and spraying chamber

	Hot-melt spray method
	Technical information: Mains voltage: 230v Power: 550W Operating pressure 0.15 Bar Tank Capacity: 1 litre Nozzle: Butterfly nozzle, external mixing, 1mm size.
1	Glyceryl monostearate was weighed into the spray gun container. The container and spray gun were heated and maintained at 80^{o}C in an air oven until the wax has become molten.
2	Once molten, the wax solution was then agitated utilising a magnetic stirrer plate and the powder mixtures/drug were gradually added into the molten wax until a homogeneous formulation was obtained.
3	Prior to hot-melt spraying, carbon dioxide gas was used to cool the interior of the spray chamber and the spray gun and container were removed from the air oven and assembled onto a heated magnetic stirrer plate.
4	During hot-melt atomisation, the bulk molten wax mixture was transformed into small droplets dispersed into a carbon dioxide atmosphere. The granules were cooled in the gaseous chamber on descent and collected for analysis.
5	The resulting granules were then sieved and separated according to size range using sieves sizes between 75 and 1000 µm (Section 2. 4. 2. 1) and collected for analysis.

2.4 Overview of the Analytical Techniques

2.4.1 Statistical design of experiments

Conventional experimental development and optimisation has been performed utilising **o**ne **f**actor **a**t a **t**ime (OFAT) techniques. It involves varying one factor or variable at a time while keeping the remaining variables constant and assessing an effect of this single factor on the product or process. These types of investigations are not statistically efficient and are time consuming, requiring more runs and resources for the same precision in estimating main process effects. In addition, conclusions may not be accurate as interactions between factors cannot be determined and optimal process settings can be missed. In industry, multi-factor investigations are often required where several factors may influence the outcome of a process. Studies involving more than one factor have been efficiently investigated utilising design of experiments where multiple factors are varied simultaneously (Blanque et al, 1995; Hellen & Ylirussi, 1993b; Yajima et al, 1996).

Design of experiments is a systematic approach used to determine the relationships between different variables of a process and the outcome of the process. This type of statistical analysis can be used to identify the factors that are most influential on a process (main effects) and interactions between these variables. Each factor can be tested at a number of quantitative or qualitative levels that would represent typical operating specifications. The empirical knowledge gained when analysis of variance is applied to well-structured data matrices, even small data sets, enables optimisation of processes in many industries including pharmaceutics, engineering, food, rubbers and plastics,

reducing the time and money invested into experimental optimisation and development (Gardiner & Gettinby, 1998).

There are different types of experimental design that can be chosen to determine the effect of factors, these include full factorial, fractional factorial, full or fractional plus centre point and central composite design. Full factorial designs can be used to assess the effect of a response on two or more controlled factors. However, when the number of factors investigated exceeds four and above, the number of experimental combinations available in a full factorial becomes too high and a fractional factorial design may be chosen as a subset of the total tests (Agalloco & Carleton, 2008). This allows the performance of a process or product to be estimated within its design space (cube) without having to measure the response of every variable within that design space.

In order to develop a design of experiments, the overall objective of the investigation must be determined, followed by the experimental factors that control the outcome of the process or product and the quantitative or qualitative levels by which they will be tested. Finally, identification of the analytical techniques (response variables) used to measure the outcome of the experimental factors and their precision, both independently and in combination for interactions. Once these parameters have been determined a design matrix can be created, based on the type of experimental design selected, the runs to be performed are generated, undertaken and data analysis performed in a statistical package such as StatEase Design Expert or Minitab.

Experimental design was utilised in this thesis to assess a number of processing and formulation parameters including, voltage (air pressure), nozzle size, wax type and processing temperature in the development of an agitated hot-melt spray system (Chapter 4).

2.4.2 Particle size analysis

In pharmaceutical formulation and analysis, the particle size distribution of drug particles in solid dosage forms can influence the product characteristics. Particle size distribution has been shown to affect not only porosity and powder flowability properties of the dosage forms but also dissolution characteristics and drug bioavailabilities (Brittain, 1995). This leads to problems with efficacy, stability, safety and manufacturing of these products.

Particle size distributions can be obtained by a variety of methods including microscopy, sieving, electrical sensing zone methods and light scattering. During this study, sieving and light scattering were utilised and are discussed in Sections 2.4.2.1 and 2.4.2.2.

2.4.2.1 Sieve size distribution analysis

Particle size distribution of granules and pellets (Chapter 3) were performed using sieves of size 500, 850, 1000, 1800, 1400 and 1700µm (stacked in descending size order).

Particle size distribution of actives and sprayed materials (Chapter 4 to 7) were performed using sieves of size 53, 72, 90, 150, 250, 500, 1000 µm (stacked in descending size order).

Stacked sieves were placed on a sieve shaker (Model EFL 2; Endecott) for 10mins. The quantity of material was weighed, recorded and used to graphically represent the particle size distribution of the batch.

2.4.2.2 Light scattering size distribution analysis

The Malvern Mastersizer 2000SM operates by the laser diffraction principle, by using two lasers of different wavelength to measure particle or droplet size distributions in the range of 20nm to 2mm. The particles pass through a laser beam which causes the light to be scattered at an angle that corresponds to the particles size. Large particles scatter the light at narrow angles with high intensity, whereas smaller particles scatter the light at wider angles with a low intensity. A detector repeatedly reads the individual diffraction patterns and calculates a particle size distribution using one of two mathematical optical models, the Fraunhofer Approximation or the Mie Theory.

A methodology was developed for the particle size analysis of the sprayed GMS material using the Mastersizer software. Each sample was measured three times to calculate an average diameter. Sample and instrument preparation are outlined in Table 2.1.

Table 2.1 Mastersizer sample and instrument preparation

Sample Preparation	
1	Sprayed material was dispersed in a suitable suspension medium of isopropyl alcohol (IPA). *GMS is slightly soluble in IPA achieving solubilisation with the addition of heat (Shah &Pathak, 2010). Due to rapid sample preparation and analysis times, low solubility was not anticipated to impact the sample size.
2	Ultrasonic treatment was performed on the dispersed material for 1 minute.
Instrument Preparation	
3	Instrument was switched on one hour prior to sample analysis.
4	Dispersion unit was rinsed three times with the suspension medium with stirring increased to 3000rpm.
5	Prior to sample analysis, the dispersion unit was filled with the suspension medium, with increased speed to 1800rpm and the blank run performed.
6	When completed, the dispersed sample was pipetted into a dispersion unit until a suitable absorbance of 12-16% was reached (green range) and the measurement started.

2.4.3 Measurements of Powder Properties

Characterisation of powder flowability involves determining particle size (Section 2.4.2), shape, packing geometry and cohesive properties that may have an effect on particle-particle interactions within the powder particles. These measurements can be used to improve or maintain the quality of the manufacturing processes, such as blending,

tableting and encapsulation, and predict flow characteristics of bulk powder material and the resulting product uniformity.

2.4.3.1 Angle of Repose

The angle of repose is defined as the angle of the free surface of a pile of powder to the horizontal plane. Powders with excellent flow properties will have a value of near 25^{o} whereas poor flow properties have an angle of nearer 50^{o}. There are several methods of determining the angle of repose, in this research the fixed height cone method was utilised (Figure 2.2).

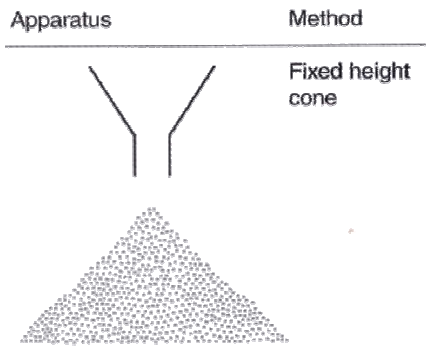


Figure 2.2. Illustration of the fixed height cone method (Adapted from Aulton, 2002)

2.4.3.2 Bulk tapped density

Bulk tapped density is an indirect measurement of the powders packing geometry and flowability. There are several ways in which bulk density measurements can be determined. In this research, a tap device was set to stop after the predetermined number of taps (10 taps) and the volume recorded (Figure 2.3).

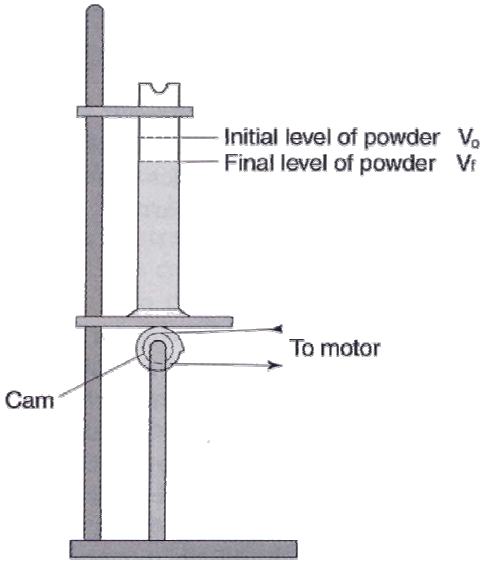


Figure 2.3 Illustration of a mechanical tapping device (Adapted from Aulton, 2002)

The tapping was repeated to 100 taps where the volume no longer changed and at that point the final tap density was determined and calculated (Equations 2.1).

$$\text{Bulk Density} = M/V \ (\text{kg m}^{-3}) \qquad \text{[Equation 2.1]}$$

[Where, M = Mass; V = Volume]

Initial bulk density measurements were calculated using the same equation prior to tapping.

The Hausner ratio can be used to determine the compressibility of a powder (Equation 2.2).

$$\text{Hausner ratio} = D_f / D_o \qquad \text{[Equation 2.2]}$$

[Where, D_f = Final tap density; D_o = Initial bulk density]

A Hausner ratio less than 1.25 indicates good flow properties whereas powders with values greater than 1.25 indicate greater compression but exhibit poor flow characteristics. The Hausner ratio can also be applied in characterising the flow properties of granules and pellets.

Similarly, the packing fraction can indicate the sphericity of the material (Equation 2.3).

$$\text{Packing fraction} = D_o / D_f \qquad \text{[Equation 2.3]}$$

[Where, D_f = Final tap density; D_o = Initial bulk density]

Particles that are more spherical have a packing fraction of approximately 0.63 whereas particles that have a 'disc-like' appearance have higher values of approximately 0.83 (Aulton, 2002).

2.4.4. Fourier-transform infrared (FT-IR) spectrophotometry

The main objective of FT-IR is to identify chemical functional groups in a sample. IR spectra are highly characteristic of the molecule enabling fingerprint identification and quantitative determination of drug substances for a wide range of solids, liquids and gases.

Infra-red (IR) is of longer wavelength than UV and visible wavelengths, spanning a region of the electromagnetic spectrum 10-1300cm^{-1} (0.8-1000µm). When IR is absorbed the energy is converted into vibrational and rotational excitation of electrons within atoms and molecules.

FT-IR involves passing electromagnetic radiation through a sample, the vibrational or rotational energy interacts with the bonds of the sample molecule causing bending or stretching. The wavelength/wavenumber that interacts with the bond is specific and functional groups have characteristic bandwidths of IR absorption (Table 2.2).

Table 2.2 Characteristic bandwidths of IR absorption

Functional Groups	**Bandwidths (cm^{-1})**
C=C (Benzene Ring)	< 1000
C=O	1600-1800
C≡N, C≡C	2000-2250
C-H	2800-3200
O-H or N-H	3200-3500

IR absorption spectra information is provided as a graph where the x-axis comprises of the wavenumber or wavelength and the y-axis comprises of the absorption intensity or % transmittance (*T*). Transmittance provides a better contrast between strong and weak bands and is calculated using Equation 2.4:

$$A = \log_{10}(1 / T) = -\log_{10}T = -\log_{10}I / I_0 \qquad \text{[Equation 2.4]}$$

[Where A = Absorbance, T = Transmittance, I = ratio of radiant power transmitted by the sample, I_0 = to the radiant power incident on the sample]

FT-IR instruments generally comprise of three main components; a radiation source, interferometer and a detector. The interferometer divides the radiation beam; half is directed to the fixed mirror and the other half to the moving mirror. An optical path difference of the beams is created momentarily but reflection from these mirrors results in the beams recombining. Changes in the position of the moving mirror to the fixed mirror produces interference signals which contain infrared spectral information from passing through the sample, this is focused on the detector and a spectrum can be extracted using the 'Fourier transform' (Figure 2.3).

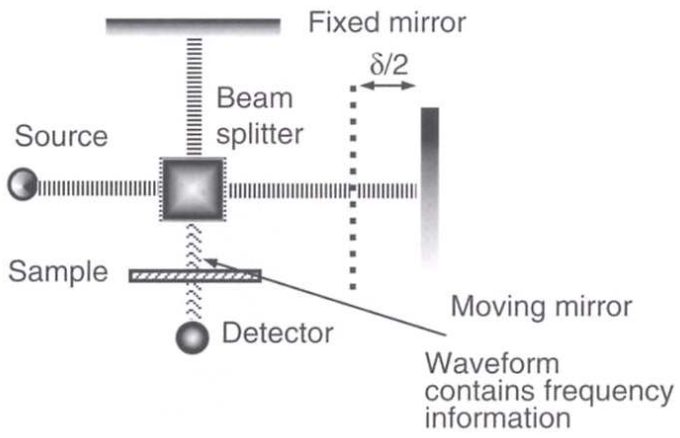


Figure 2.3 Michelson interferometer used in FT-IR (adapted from Watson, 2005)

Various sampling accessories, such as attenuated total reflectance (ATR), have been developed to use in conjunction with FT-IR to overcome conventional sample preparation issues. Poor sample reproducibility, complex preparation methods (KCl discs) and changes that impact the drug structure of the sample were hindering the quality of the measurements that could be obtained. ATR occurs when a radiation beam passes from a high refractive index to a lower refractive index. To generate an evanescent wave the

sample is situated closely to a high refractive crystal area and the radiation beam passed onto the crystal area and internally refracted through the crystal with single or multiple reflections (Figure 2.4). The intensity of the reflections is reduced by infrared absorption of the sample.

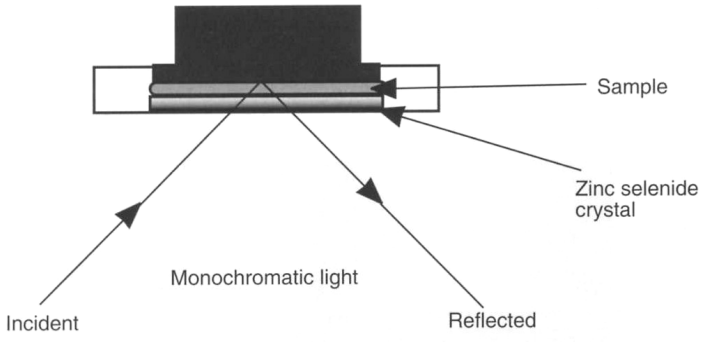


Figure 2.4 Multiple reflection ATR (adapted from Watson, 2005)

An ATR accessory was utilised with FT-IR in this study, sample preparation is outlined in Table 2.3.

Table 2.3 Sample preparation and instrumentation for ATR analysis.

Sample Preparation	
1	Powder sample was placed onto the small crystal area (just enough to cover the crystal area).
Instrument Preparation	
2	Instrument is switched on prior to sample analysis and the ATR accessory mounted in the spectrometer's sample compartment.
3	A background scan between 650cm^{-1} and 3750cm^{-1} was undertaken prior to running each sample.
4	Once sample has been loaded, the pressure arm is positioned over the crystal area and force is applied to the sample (20N).
5	The sample was analysed between 650cm^{-1} and 3750cm^{-1}, the spectrum was collected and the crystal area cleaned with methanol for the next sample.

2.4.5 Differential scanning calorimetry (DSC)

There are two main types of differential scanning calorimetry (DSC) systems: heat-flux and power-compensation. Studies were performed with a heat-flux DSC822e (Mettler Toledo, Leicester, UK).

DSC enables the measurement of heat flow in and out of sample and reference material versus time or temperature. Sample material is placed into an aluminium crucible and the lid sealed (may be pierced if required), usually an empty crucible of similar weight is used as a reference pan. The prepared crucibles are placed within the sample chamber,

where the symmetrical sample and reference compartments are simultaneously heated using the same temperature programme (Figure 2.5). At the thermocouple junction, multiple thermocouples are arranged between the heat source, sample and reference. The voltage developed by the pair is a direct measure of the thermal difference between the sample and reference. A flow of nitrogen gas is established to remove any volatiles within the furnace and to aid in heat transfer.

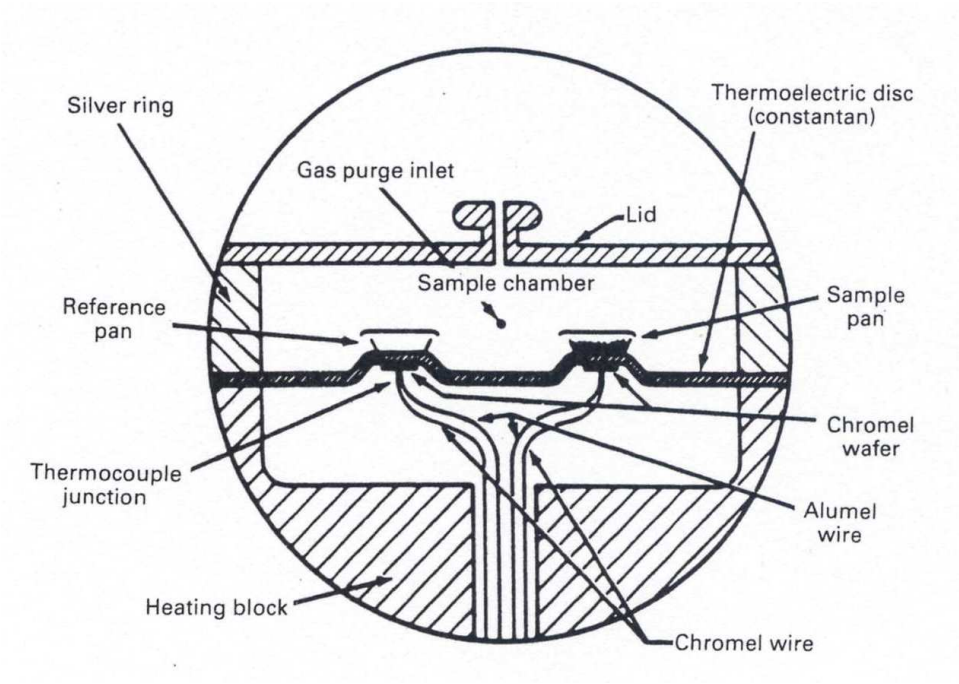


Figure 2.5 Heat Flux DSC (adapted from Ford & Timmins, 1989)

Thermal differences (ΔT) that occur between the sample and reference materials are converted and recorded, by the Star^{e} thermal analysis software, as heat flow (*dq/dt*) measurements versus time or temperature illustrated as a thermogram (Figure 2.6). The area under the DSC peaks on a thermogram can be quantitatively integrated into heat of reaction values (units include cal/s.g or J/s.g) and is directly proportional to the heat

absorbed or released by the sample. These differences in heat flow are the thermal effects exhibited when a sample absorbs or releases heat as a result of melting, crystallisation/nucleation, chemical reactions, polymorphic changes or glass transitions.

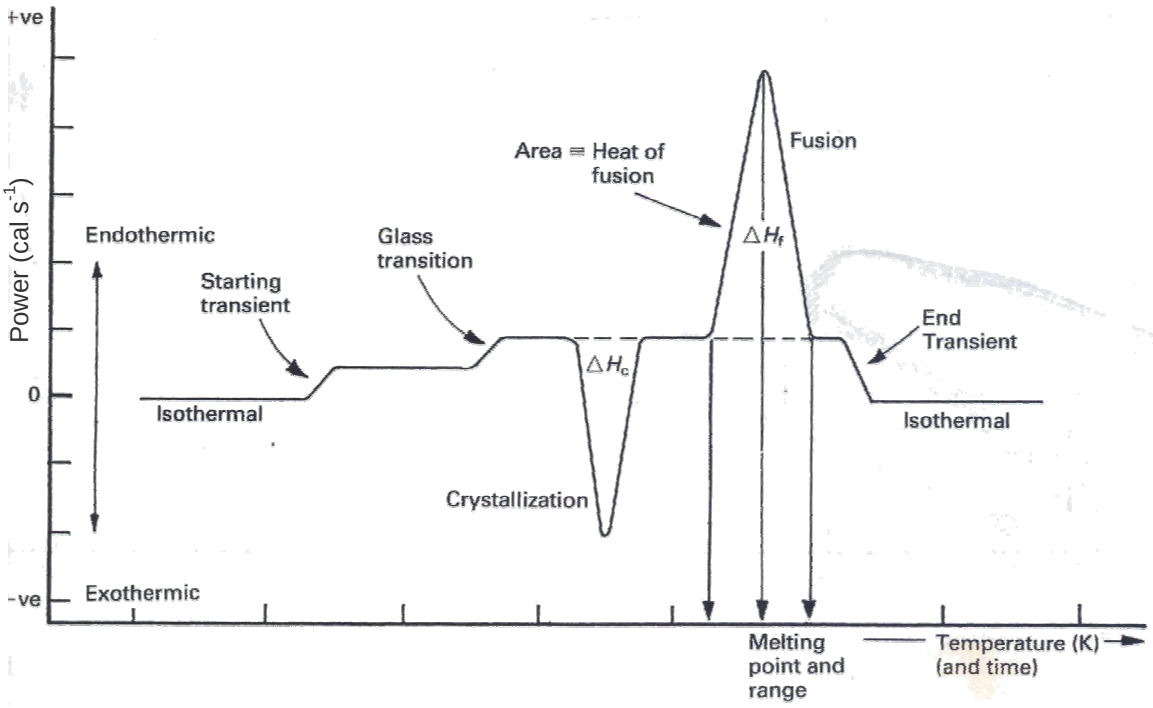


Figure 2.6 Schematic DSC Thermogram (Aulton, 2002)

DSC is an invaluable instrument that is commonly used within the pharmaceutical field. Its primary function is for the identification and purity of substances, although it has many additional functions including the determination of heat capacities and heats of fusion, the preparation of phase diagrams in identifying polymorphs and identification of decomposition kinetics of solids. In this research, DSC was used to determine compatibility between formulation components and the stability of GMS. The DSC methods and sample preparation are outlined in Table 2.4.

Table 2.4 DSC sample preparation and Instrument parameters.

Sample Preparation	
1	Place an empty aluminium crucible and lid on the balance and weigh by difference. Place the required amount of sample into the pan and record weight.
2	Transfer the pan into the sample press and once the lid is appropriately placed, turn the press hand wheel twice to seal.
3	The sample is then placed on the sample stage of the instrument ready for analysis.
4	A reference standard is prepared identically with the absence of any sample. The reference standard is used during all analysis.
Instrument Preparation	
1	The refrigeration unit is switched on next to the DSC, followed by the Nitrogen gas to the appropriate flow rate.
2	Once the software has started and run through the initial checks the instrument is ready for use.
3	A suitable method may be selected for analysis and the samples loaded.

The programme selected for a sample is dependent on the melting point of the components, those used in my analysis are outlined in Table 2.5.

Table 2.5 DSC methods used for drug sample analysis

Samples	DSC method (Temperature range)
GMS only	10 to 80^{o}C
Paracetamol only	20 to 200^{o}C
Ibuprofen only	15 to 95^{o}C

Samples comprising of GMS were analysed using methods ranging between 10-95^{o}C and a heating rate of 10^{o}C/min were used for all programs. Resulting thermographs were also normalised against the sample weight.

2.4.6 X-Ray Pattern Diffraction (XRPD)

X-rays are short-wave electromagnetic radiation ranging over 0.01-1nm and appear within the electromagnetic spectrum between gamma rays and ultraviolet. This makes X-rays in the order of 1nm readily available and of the same size magnitude as an atom. As a result, X-ray is particularly useful in solid state chemistry for the fingerprint characterisation of crystalline materials and identification of atomic arrangements of matter.

When X-rays fall on a samples surface, secondary beams are scattered due to the interaction with each atom of the sample. These scattered beams spread out from the atoms spherically (forming cones) and the intensity of the interference between these secondary x-ray beams can be related to the interplanar spacing in the crystalline sample. Each crystalline sample diffracts the x-rays differently according to the atomic

arrangement of the crystal lattice. This enables a unique diffraction fingerprint to be obtained for the sample by a mathematical relationship known as Bragg's law (Equation 2.5) which considers the intensity of the x-ray interference at a wavelength (λ) as a function of the diffraction angle (θ).

$$n\lambda = 2d \sin \theta \qquad \text{[Equation 2.5]}$$

[where n = order of reflection; d = interplanar spacing causing the diffraction]

Monochromatic x-ray beams in the order of 1 Angstrom (1Å = 10^{-10} m) are used to determine the atomic, molecular and ionic distances within a crystal lattice by the operating principles of Figure 2.7. The diffraction pattern obtained from the sample is described by the θ angle and can be further interpreted by comparing the diffraction 'fingerprint' to standard reference patterns. Crystalline compounds exhibit sharp peak diffraction patterns whereas amorphous compounds are characterised by more diffuse peaks or the absence of them.

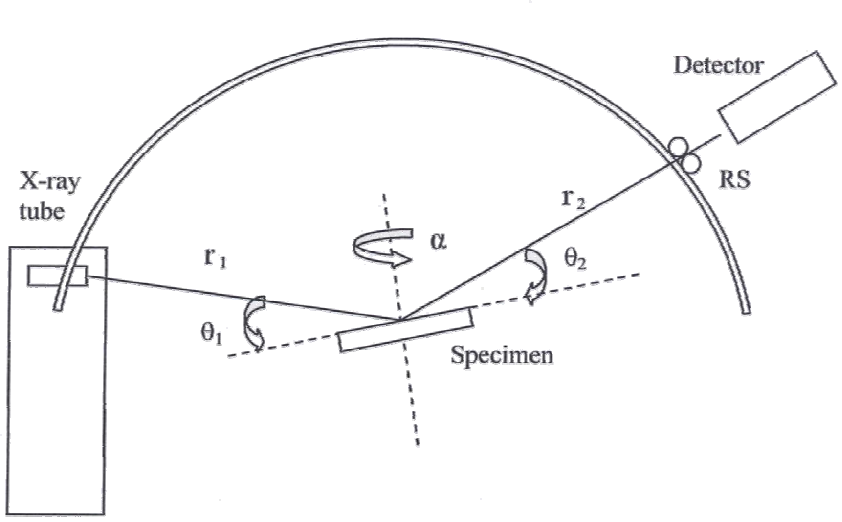


Figure 2.7 Principle of x-ray powder diffractometry (adapted from Jenkins & Snyder, 1996).

Table 2.6 Sample and Instrumentation preparation.

Sample Preparation
The samples were placed on a multi-well plate supported on a 7.5micron Kapton film and data collection ranged from 3 to 35º 2θ at a step size of 0.017º 2θ and 1s per step using Cu Kα_1 radiation (λ = 1.54056 Å).
Instrumentation
The XRPD used was a Bruker-AXS D8 Advance X-ray powder diffractometer with foil transmission geometry (Figure 2.7) and was equipped with a Bruker Vantec position sensitive detector where the data was plotted using the EVA programme.

2.4.7 Microscopy

A Polyvar microscope (Figure 2.8) coupled with a Reichert-Jung control unit, a hot-stage platform and a JVC camera were linked to a computer via the Pic Port Imaging software. This enabled live sample pictures to be captured using both bright-field and polarised light microscopy whilst undergoing a controlled temperature programme or simply monitoring the morphology with time.

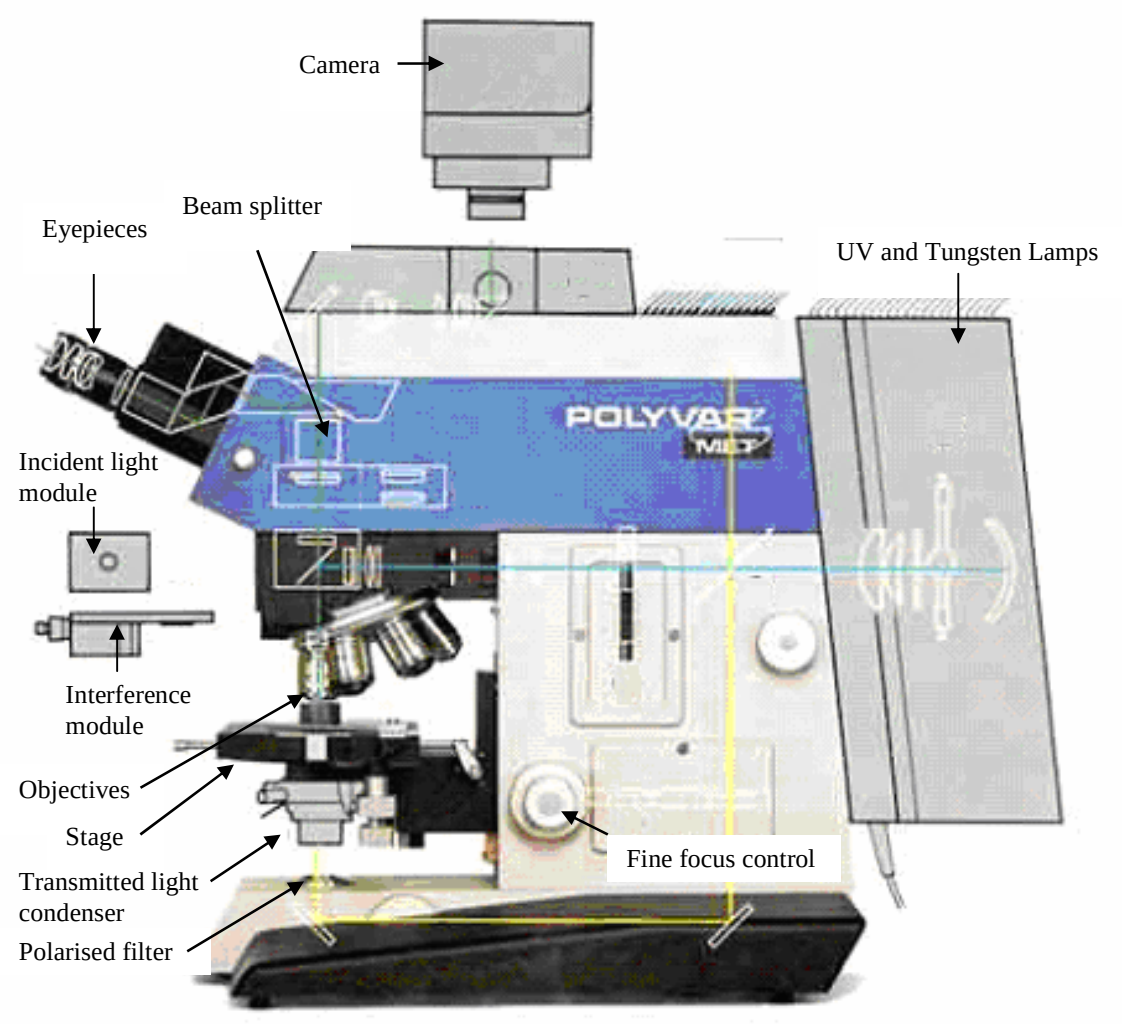


Figure 2.8 Components of a Polyvar Polarised Microscope (Modified from http://www.materials.co.uk/optical.htm, date accessed 04/06/11)

2.4.7.1 Light Microscopy

There are several types of light microscopy including bright-field, dark-field, polarised, fluorescence, phase contrast and differential interference contrast. Bright-field and polarised light microscopy were adequate microscopic techniques in these studies for the characterisation of samples and shall be discussed.

A compound microscope is utilised in light microscopy, it comprises of more than one refractive lens, one in the eyepiece and one in the objective. The degree of sample magnification is controlled by the selected objective and can typically range between ‘x10’ and ‘x100’ magnification. Visible light is transmitted through or reflected from a sample, when it is passed through each refractive lens it enables a magnified real image to be viewed by the eye or camera (Figure 2.9).

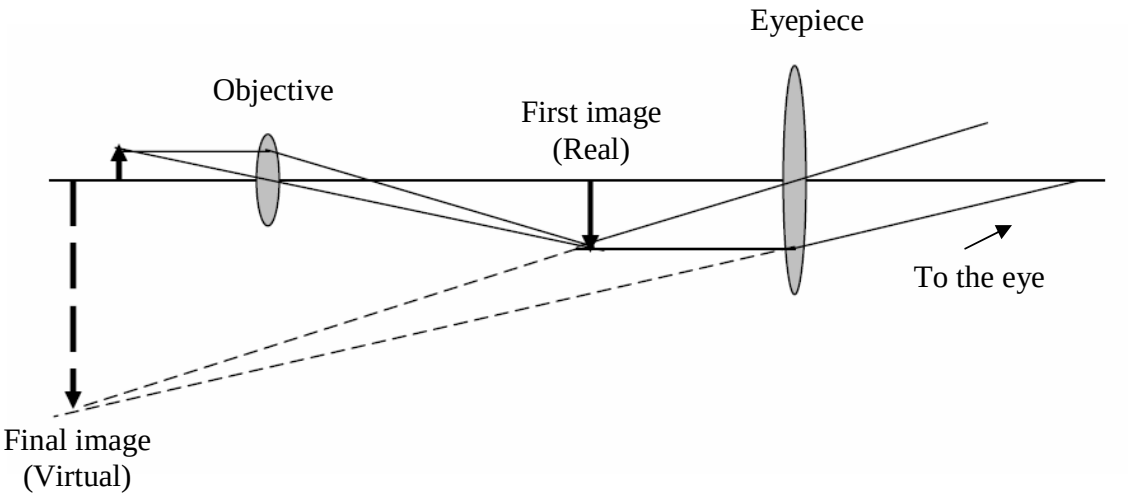


Figure 2.9 Formation of a magnified real image by a compound microscope (adapted from Rawlins, 1992)

Bright-field microscopy is the simplest form of light microscopy. Once the sample is mounted onto a microscopic slide, white light illuminates the sample from underneath the stage and the magnified image can be visualised from above. However, absence of colour or contrast of the sample material results in a poor image of insufficient resolution and is most suitable for coloured or stained samples.

2.4.7.2 Polarised Light Microscopy

Polarised light microscopy differs from bright-field microscopy as the microscope contains two disk accessories; the polariser is located below the condenser and the analyser is positioned near the eyepiece. Natural light is passed through the polarised filter, filtering the multi-directional light vibrations into a single direction of plane-polarised light (Figure 2.10).

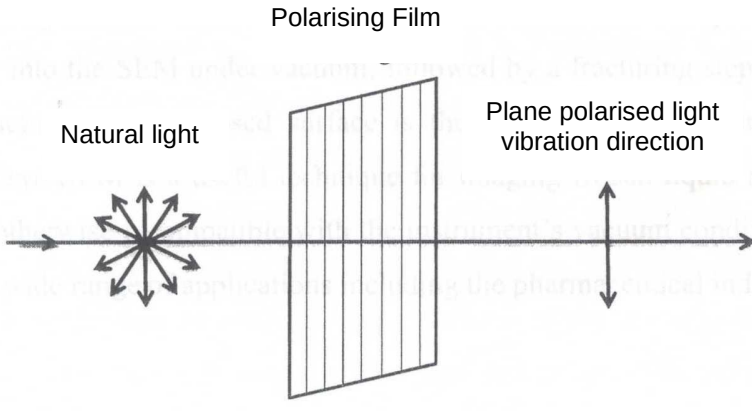


Figure 2.10 Polarisation of light (after Robinson and Bradbury, 1992)

Plane polarised light is used to analyse structures that exhibit birefringence, such as crystalline materials. An object that exhibits birefringence has multiple refractive indices and is also referred to as an anisotropic material. An anisotropic substance will therefore

appear illuminated against a dark background when placed in the light path of crossed polars. Although the birefringence of a particular crystalline material is constant, a thicker crystal will appear brighter than a thinner crystal as the optical path difference is being observed and this is affected by the thickness of the material.

2.4.7.3 Hot Stage Microscopy

Hot-stage microscopy, also referred to as thermal microscopy, involves the visual characterisation of a small amount of the sample whilst it undergoes a temperature controlled programme, involving heating and/or cooling. It is a rapid technique that provides a large amount of information including any thermal transitions, the degree of crystallinity and changes in the crystal structure and growth rates of the sample material. Visual analysis can also aid in the interpretation of results obtained from thermal analysis techniques including DSC and TG/sDTA. Hot-stage microscopy is widely utilised in the plastics, pharmaceutical, forensic, food and chemical industries.

Selected hot-melt or granule samples, produced throughout the PhD, were characterised by mounting on the hot-stage platform and subjected to a heating programme of 25-80^{o}C at 5^{o}C/min. The morphology and melting points of the components and sample mixtures were documented.

2.4.7.4 Scanning Electron Microscopy

Scanning electron microscopy (SEM) is a method used to obtain high resolution images of solid material surfaces. The degree of magnification is controlled by the ratio of sample area scanned to the area of the TV screen and can range from ‘x10’ to ‘x300 000’ magnification. Unlike a conventional light microscope, where refractive lenses and lightwaves are used to magnify the sample image, electrons are focused onto the sample via magnetic lenses which scan the sample surface in a series of gridlines.

An incident electron beam, produced by an electron gun, is scanned across the sample surface and the emitted electrons (secondary electrons) from the sample surface are attracted to a low charged positive grid. The electrons pass through the grid to a positively charged disc, as the electrons strike the disc it is translated and amplified into a signal then generated as an image on a TV screen. This image can then be used to identify the surface structure and be further analysed, qualitatively or quantitatively, in conjunction with the computer software (ImageSlave).

Samples were mounted onto 10mm aluminium stubs with a carbon dot. A splutter coater was then used to splutter a thin conducting gold layer onto the samples to prevent charging effects in the SEM by promoting electron reflection and to also protect the sample from the high-energy beam which may have damaged the sample surface.

2.4.8 UV/visible spectrophotometry

Radiation within the UV/visible spectral region, 200-700nm, is passed through a chemical solution. Electrons within the molecular structure become excited and occupy a higher electronic state and absorb energy passing through the chemical solution. This absorption of energy within the visible range directly influences the perceived colour of the chemical solution.

Development of quantitative methods for colour determination was necessary to eliminate the variability in which individuals can visually perceive and evaluate colour. UV/visible spectrometry is quantitatively undertaken to determine the concentrations of chemical solution in accordance with the Beer-Lambert Law. The Beer-Lambert Law states that the absorbance of a solution is directly proportional to the concentration of the absorbing species in the solution and the pathlength (Equation 2.6). This linear relationship applies to dilute solutions but at higher concentrations the relationship can become non-linear.

$$A = \log I_o/I_t = abc \qquad \text{[Equation 2.6]}$$

[Where A = absorbance; a = A(1%, 1cm); c = concentration (g/100ml); b = pathlength (cms)]

A UV/visible spectrophotometer comprises of three main elements outlined in Table 2.7 and illustrated in Figure 2.11.

Table 2.7 Summary of UV/Visible Instrumentation

UV/Visible Spectrophotometer
Two light sources; a deuterium lamp for the UV region (190 to 350nm) and a tungsten lamp for the visible region (350 to 900nm).
Monochromator; disperses the light into constituent wavelengths, the appropriate wavelength is passed into the sample through a slit. During scanning the monochromator is rotated to allow the selected wavelength range to pass through the sample slit.
Optics; split the light beam to pass through the samples in both the reference and sample compartments.

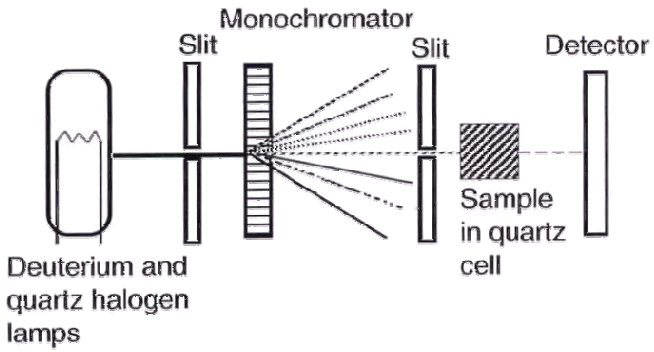


Figure 2.11 Schematic diagram of a UV/visible spectrometer (Adapted from Watson, 2005).

2.4.8.1 Generation of a calibration curve

The validity of the Beers law can be checked by a linear plot of Absorbance (A) against concentration (c). Table 2.8 outlines the procedure to obtain absorbance (A) values for generating a calibration curve.

Table 2.8 Generation of a calibration curve

Preparation of stock and standard solutions	
1	A stock solution of the drug in a soluble aqueous media is prepared.
2	The stock solution is diluted into five standard solutions and scanned within a predetermined wavelength range to determine the λmax.
3	The absorbance (A) of the standard solutions are measured at the fixed λmax of the drug solution.
4	Absorbance values are plotted against drug concentration to produce a calibration curve. The equation of the calibration curve is derived from the gradient of the fitted regression line.

2.4.8.2 *In-vitro* Dissolution Studies

Dissolution studies involve determining the rate of drug release into solution from a tablet or capsule dosage form. These studies are important in establishing the therapeutic efficacy of dosage forms by assessing batch variability or comparisons between formulation release characteristics during development. Correlations can also be assessed between *in-vitro* dissolution and *in-vivo* data, although caution is advised when interpreting this data due to the physiology of the GI tract and the complexity of lipid digestion for dosage forms of this nature.

There are various methods described for measuring the rate of drug release including, beaker method, flask-stirrer method, rotating basket method, paddle method and the rotating and static disc method (Aulton, 2002). During this research, the paddle method

was used, also known in the pharmacopoeias as USP Method XXIII Apparatus 2 method (Figure 2.12). In this system the cylindrical vessel has a spherical bottom which allows the sample to sink prior to agitation commencing via the rotating paddle.

Figure 2.12 Paddle dissolution apparatus

Utilising this dissolution system and the parameters outlined in Table 2.9, release profiles were successfully obtained to characterise various pellet and granule formulations during this research. The dissolution profiles were derived from the absorbance values of the sample media and converted into a graphical representation of the percentage drug release against time using equations from the corresponding calibration curves. Comparisons between each formulation series were conducted utilising statistical tests summarised in Section 2.5.1.

Table 2.9 Sample and instrument preparation

Dissolution Equipment and Settings	
1	Paddle speed of 50rpm.
2	Peristaltic pump at 30rpm.
3	6 x 1000ml of dissolution media maintained at 37ºC ± 0.5.
4	Drug release was typically assessed performed for between 4 to 8 hours.
5	Samples were measured in a 1cm³ quartz cell in a UV-spectrophotometer operated at an appropriate λ for the drug substance being analysed.
Dissolution Media	
6	Distilled water was used as a dissolution media for paracetamol and minocycline HCl formulations and the samples analysed at 249nm and 348nm, respectively. 900ml was incorporated into each dissolution vessel.
7	Phosphate buffer (pH 7.2)* was used as a dissolution media for ibuprofen formulations and analysed at 319nm. 900ml was incorporated into each dissolution vessel. *pH 7.2 was utilised to maintain sink conditions (British Pharmacopoeia, 2012).
Sample Preparation	
8	6 x samples weighed and dissolution blanked prior to run commencing.
9	Samples added to dissolution pots with aqueous media and dissolution system initiated.
10	A 5ml filtered sample of dissolution media was removed at predetermined intervals, measured and replaced into the same sample pot.

2.5 Statistical Analysis

Statistical analysis throughout this study was performed using Fit Factors and Two-Way ANOVA methods. Direct comparisons of dissolution release data could be undertaken using fit-factors (Section 2.5.1), whilst experimental design and comparisons of particle size distributions utilised ANOVA techniques (Section 2.5.2).

2.5.1 Fit Factors

Fit factors is a mathematical model designed specifically to analyse dissolution release profiles. This statistical test allows the comparison of each time point between two dissolution profiles, one profile is assigned a reference profile and the other the test profile (Moore & Flanner, 1996). This method is the preferred method of analysis for dissolution profiles by the Centre for Drug Evaluation and Research (FDA) and the European Agency for the Evaluation of Medicinal Products (EMEA).

There are two elements to fit factors analysis; the difference factor, F_1, and the similarity factor, F_2. The difference factor, F_1, (Equation 2.3) measures the percentage error between two curves over all time points (Costa & Lobo, 2001). When the reference and test samples are equal the F_1 value is 0.

$$F_1 = \frac{\sum^{n}_{t=1} (R_t - T_t) \times 100}{\sum^{n}_{t=1} R_t} \qquad \text{[Equation 2.3]}$$

[Where n = the number of time points, R = Percent reference sample dissolved,

T = Percent test sample dissolved, t = specific time point]

The similarity factor, F_2, (Equation 2.4) is a function of the mean differences and does not take into consideration differences in dissolution within the test and reference batches (Costa & Lobo, 2001). The test and reference samples are considered similar when the F_2 value is between 50 and 100.

$$F_2 = 50 \text{ x } \log [\ 1 + (1/n)\sum_{t=1}^{n} (R_t - T_t)^2\ ]^{-0.5} \text{ x } 100 \qquad \text{[Equation 2.4]}$$

[Where n = the number of time points, R = Percent reference sample dissolved,

T = Percent test sample dissolved, t = specific time point]

2.5.2 ANOVA

ANOVA, also known as analysis of variance, is a test of the statistical significance of the differences among the mean scores of two or more groups on one or more variables. For the two-way ANOVA analysis, the same number of replicates can be used in each group but data with only one replicate can be analysed using ANOVA but no interaction between the variables can be determined. The assumptions of ANOVA analysis include the data to be normally distributed, have the same sample size and have equal variances.

The performance of the two-way ANOVA produces results using a sum of squares decomposition. The total sum of squares is a measure of the variability for all the data in the set. The analysis of variance separates variability within groups and between groups, if the variability between the groups is larger then there is a significant difference. This result is expressed as a p-value, if it is less than the specified value $p<0.05$ (5% significance level) there is a statistically significant difference between the two variables.

4. Preparation and Characterisation of Pellets Utilising Extrusion/Spheronisation

3.1 Introduction

Sebomin MR capsules are a modified release product incorporating minocycline hydrochloride, they belong to the tetracycline antibiotics groups and are used to treat acne.

An objective of the PhD research was to assess the performance of an 'in-house' generic formulation of minocycline for equivalence to the commercial Sebomin® MR generic product. The ability to develop a sustained release hydrophobic matrix delivery platform was also to be evaluated by modulating the existing formulation components and manufacturing process. No product design space was previously defined during traditional formulation development.

The formulation development was empirical and led to the manufacturing process becoming fixed early in pharmaceutical development with product testing only being undertaken post manufacture of the clinical or commercial batches. As a result, there was limited knowledge of the commercial attributes required to achieve successful scale up and support continuous improvement of the generic product quality for Sebomin® MR utilising extrusion/spheronisation (Dickinson et al., 2008).

Quality by design (QbD) was introduced to the pharmaceutical industry as a systematic approach to pharmaceutical development of both new and generic drug products. ICH

regulatory guidelines Q8, Q9 and Q10 outline the implementation of QbD by utilising design of experiments, risk assessment and process analytical technology to define a design space of acceptable product quality (ICH Harmonised Tripartite Guideline, 2009; Lionberger et al., 2008). By understanding product design, critical formulation and manufacturing parameters could be identified and their impact on product performance quantified. This enables development of products with a pre-defined quality leading to continuous process improvements and product optimisation.

Under QbD, dissolution is an important tool in assessing the impact of parameters on product performance (Dickinson et al., 2008). As a result, the drug release characteristics of Sebomin MR 100mg capsules were evaluated and the ability to manufacture and reproduce the product quality utilising extrusion/spheronisation at bench scale was assessed. Once the process had been transferred in-house from Actavis, to reproduce the Sebomin MR formulation, paracetamol would be used as an inexpensive marker. Both APIs are hydrophilic in nature and remain undissolved in the molten GMS, melting beyond 80^{o}C.

To develop a sustained release hydrophobic matrix pellet drug delivery system for commercial use, process analytical technology (PAT) was utilised to facilitate QbD. Formulation and manufacturing parameters that could potentially impact product safety, efficacy and quality were identified. The high risk variables included formulation composition, pellet particle size analysis, spheronisation time, milling time, wax fusion

parameters and granulation liquid composition. These variables were modulated and their drug release performance evaluated to establish the product design space.

3.2 Methods

Hydrophobic pellet production was achieved utilising extrusion/spheronisation and the effects of five formulation variables; milling and granulation fluid composition, wax content, spheronisation time, pellet size distribution and their effects on in vitro dissolution were investigated.

- All granule formulations were prepared from glyceryl monostearate and Minocycline HCl (Sections 3.2.1 & 3.2.2) or Paracetamol (Sections 3.2.2, 3.2.3, 3.2.4 & 3.2.5), utilising wax fusion.
- The wax granules produced were incorporated into pellets utilising extrusion/spheronisation technologies.
- In vitro release profiles of the resulting granules and pellets were determined utilising an automated dissolution apparatus (Section 2.4.8.2).

Details of pellet manufacture and the analytical methods are summarised in Sections 3.2.1-3.2.5. Further information is available and referenced in Chapter 2.

3.2.1 Investigation of Milling and Wax Fusion

Drug release was observed for the granules and pellets produced by different milling and wax fusion processes. All granule formulations produced in this investigation consisted

of 15%w/w GMS and 85%w/w minocycline HCl. Pellets were produced from the same granules. The alterations in the wax fusion/milling processes are detailed in Table 3.1.

Table 3.1 A summary of parameters investigated in the wax fusion and milling processes.

Process	Variables altered within the process
Wax Fusion (Section 2.3.1.1)	• Cool GMS/Minocycline HCl mixture on foil with no stirring. • Continuous stirring of GMS/Minocycline HCl mixture with homogenizer whilst cooling until 40˚C.
Milling (Section 2.3.1.2)	• Mill GMS/Minocycline HCl mixture with a hand-blender and obtain a suitable particle size through a sieve. • Manually pushed through a 2000 micron sieve, utilising a palette knife.

The release profiles of the resultant 'in-house' generic minocycline granules and pellets were compared with Sebomin MR (Actavis UK Ltd) granule and pellet release profiles. These granules, supplied from Actavis, were produced from the bulk blend by passing through a 2000 micron oscillating mill.

3.2.2 Investigation of Granulation Liquid Composition

Drug release was observed for both paracetamol and minocycline pellet formulations with varying granulation fluid compositions. The granulation fluid comprised of an ethanol and distilled water mixture. Two types of granulation liquid were utilised in this study as detailed in Table 3.2.

Table 3.2 In-house Sebomin, paracetamol and comparator (Sebomin® MR) pellets produced utilising different compositions of granulation liquid, batch size 65g.

Granulation Fluid (ethanol:water)	**Formulation**
56% w/v ethanol	A. In-house generic minocycline B. Paracetamol-equivalent
56%v/v ethanol	C. Actavis Sebomin® MR D. In-house generic minocycline E. Paracetamol-equivalent

The release profiles of the resultant, 'In-house' generic formulation of minocycline and paracetamol-equivalent pellets were compared with Sebomin® MR pellet release profiles.

3.2.3 Investigation of Wax Content in Paracetamol Pellets

Production of granules and pellets (pellets produced from the granules) with varying wax content (5-90% w/w) were performed and the effects on in vitro drug release was observed (Table 3.3).

Table 3.3 Granule and pellet formulations with varying PCM:GMS compositions

Formulation	Concentration (%w/w)	
	Glyceryl monostearate	Paracetamol
A	0	100
B	5	95
C	10	90
D	25	75
E	30	70
F	40	60
G	50	50
H	60	40
I	70	30
J	80	20
K	90	10

3.2.4 Investigation of Spheronisation Time of Paracetamol Pellets

Production pellets with varying spheronisation times (2-14mins) were performed and the effects on in vitro drug release was observed (Table 3.4). All granule formulations utilised in this investigation consisted of PCM:GMS (10:90 w/w), at a fixed speed and ambient temperature.

Table 3.4 Paracetamol pellet formulations manufactured at different spheronisation times

Pellet Formulation	Spheronisation Time (mins)
A	2
B	4
C	6
D	8
E	10
F	12
G	14

3.2.5 Investigation of Particle Size Distribution of Paracetamol Pellets

Production of granules and pellets from the granules with varying particle size distributions (0.5mm-1.4mm) was achieved by using brass sieves to separate the resulting pellets into these fractions (Table 3.5). The effect of each pellet size fraction on in vitro drug release was observed. All granule formulations in this investigation consisted of 60% w/w of glyceryl monostearate and 40% w/w paracetamol.

Table 3.5 Particle sizes of paracetamol granules and pellets investigated

Formulation	Particle Size
A	<500µm
B	500-850µm
C	850-1000µm
D	1.00-1.18mm
E	1.18-1.40mm
F	1.40-1.70mm

3.3 Results and Discussion

3.3.1 Investigation of Milling and Wax Fusion

3.3.1.1 Minocycline Granules

The resultant granule release profiles obtained by manipulating the milling and wax fusion process parameters are illustrated in Figure 3.1.

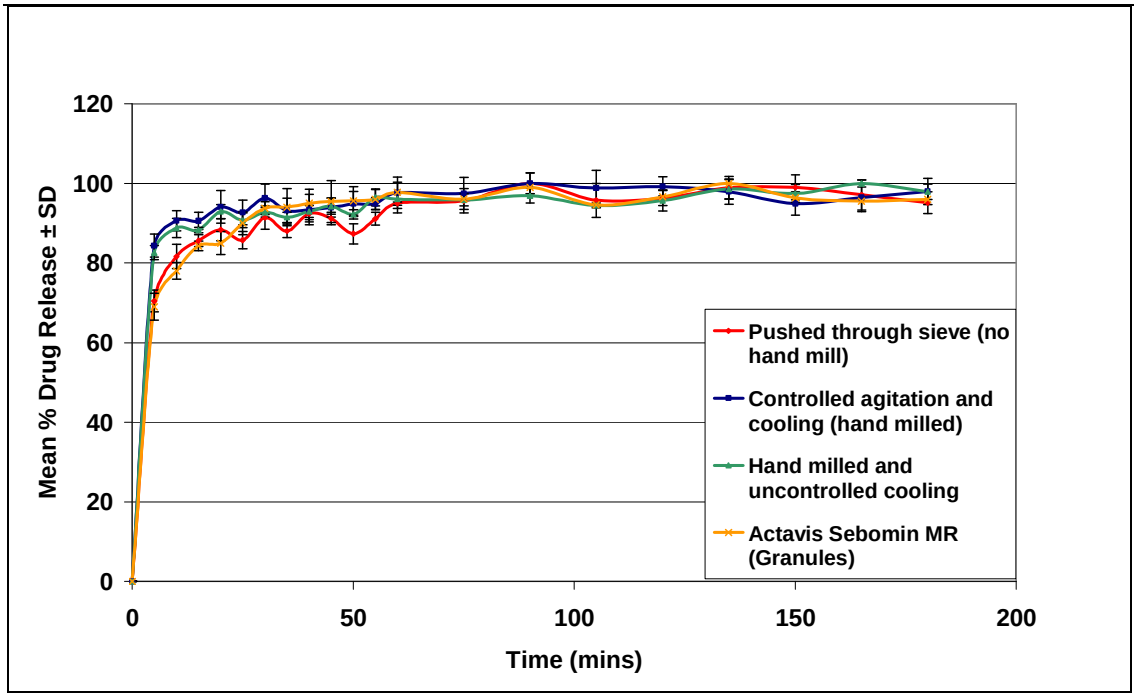


Figure 3.1 Mean release profiles of granules with varying wax fusion/milling processes ± SD (n=6)

From Figure 3.1, no significant difference was observed between any of the in vitro release profiles obtained for the granules with modulated milling/wax fusion processes (f_2 values > 50, f_1 value < 10). The granules exhibit immediate release properties for minocycline formulations manufactured both 'in-house' and from Actavis.

3.3.1.2 Minocycline Pellets

Minocycline pellets were produced utilising extrusion spheronisation whilst manipulating the milling and wax fusion process parameters during minocycline:GMS granule formation. The resultant pellet release profiles from this investigation are illustrated in Figure 3.2.

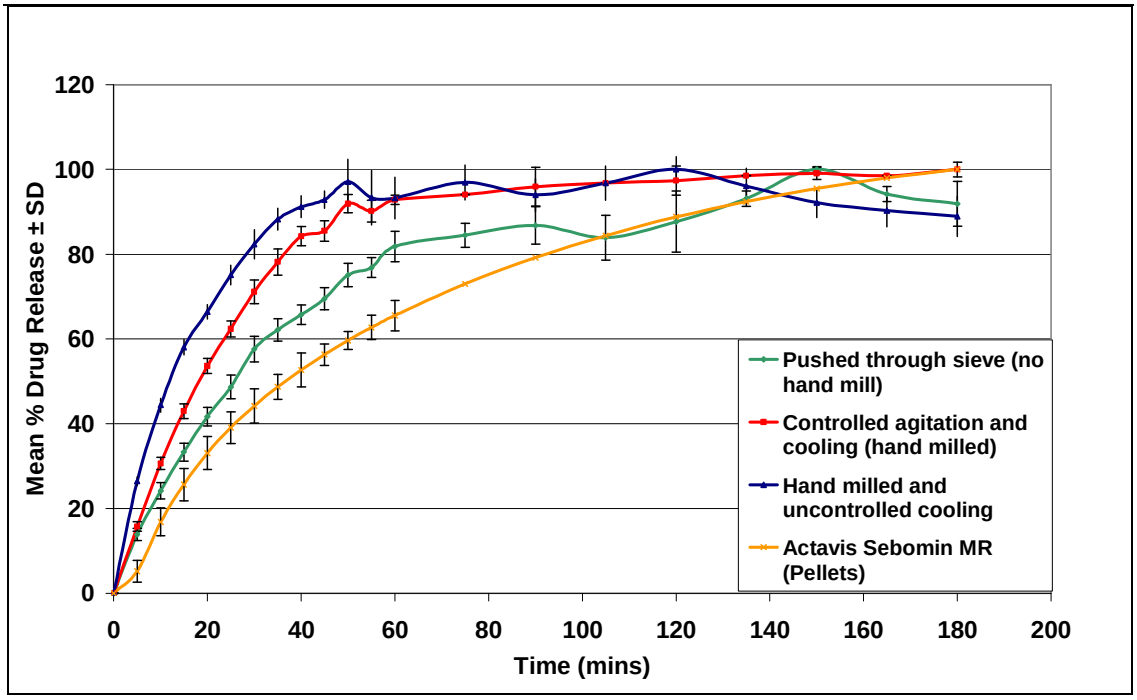


Figure 3.2 Mean release profiles of pellets with varying wax fusion/milling processes ± SD (n=6).

From Figure 3.2, the in vitro release profiles of pellets were significantly different between pellets that were hand milled and pellets that were not hand milled i.e manually pushed through a 2000 micron sieve (f_2 values < 50, f_1 value > 10). Pellets formulated from hand milled granules have a significantly increased drug release rate than pellets formulated from granules that had undergone no hand milling (Mullin, 1996). Hand-

milled formulations exhibited immediate release characteristics with greater than 75% drug release in 45 minutes (British Pharmacopoeia, 2012).

No significant difference was observed between the release profiles of the pellets that had been milled and cooled on foil and the pellets that were continuously stirred when cooling until approximately 40˚C when complete solidification had been achieved (f_2 values > 50, f_1 value < 10). This indicates that the cooling rate of the formulation from 65 to 40˚C did not affect the drug release rate in the immediate post-manufacture time period. However, to determine long term product stability thermal analysis would need to be undertaken utilising techniques such as FT-IR, XRPD or DSC (see Chapter 7).

Despite the decreasing trend between the pellets (Figure 3.2), there was no significant difference (f_2 values > 50, f_1 value < 10) between release profiles of the Actavis Sebomin MR pellets formulated from granules passed through a 2000 micron oscillating mill and the pellets formulated from granules manually pushed through a 2000 micron hand held sieve. This not only indicated the industrial process could be reproduced in house, in a small scale, but that both formulations achieve modified drug release properties. Actavis Sebomin MR exhibited 56.3% mean drug release and the in house generic minocycline pellets exhibited 69.5% mean drug release, within 45 minutes (British Pharmacopoeia, 2012).

The milling process appears to be a critical parameter in the production of minocycline pellets impacting product quality. The mechanism significantly impacting the dissolution

performance could be attributed to differences in the particle size distribution of the resultant product, investigated in figure 3.3.

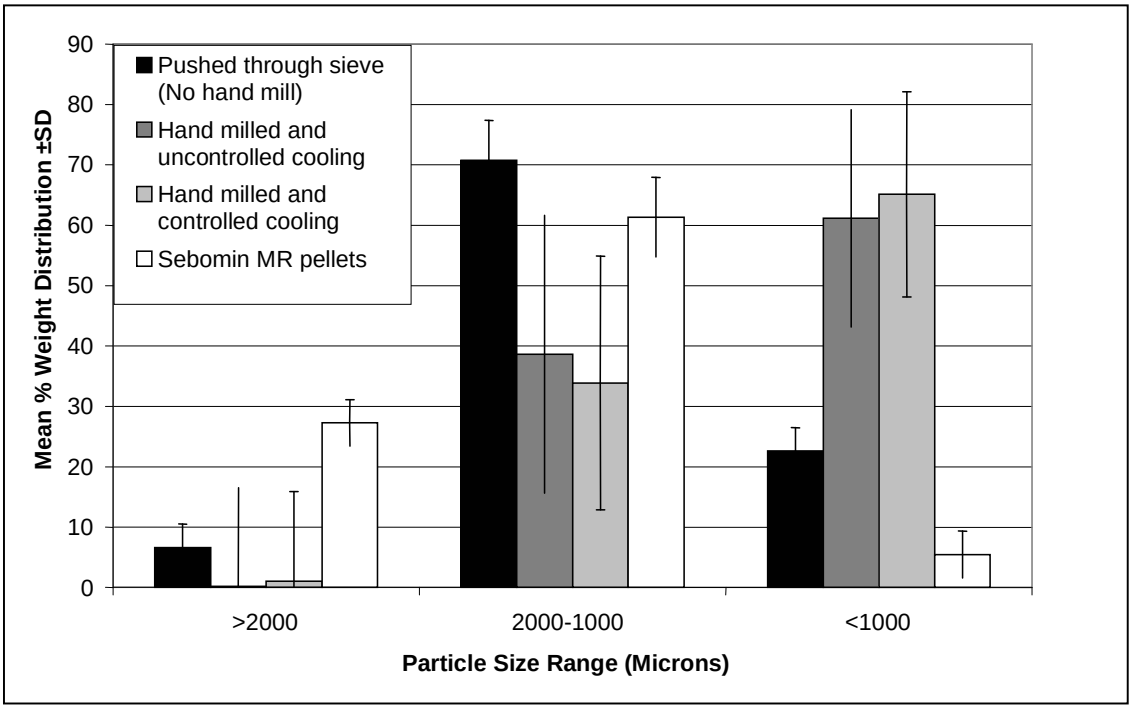


Figure 3.3 Particle size distribution of pellets produced by varying wax fusion/milling process.

The particle size distribution (Figure 3.3) for both pellet batches produced via hand milling indicates the majority of the particles are within the sub-1000 micron size range. Whereas the majority of the pellets produced by granules manually pushed through the 2000 micron sieve are within the 2000-1000 micron range. The prolonged drug release exhibited by the pellets manually pushed through a sieve appear to be controlled by the same mechanism as the Actavis pellets, the particle size distribution of the products are similar and are significantly larger than the hand-milled products. These findings correlated to the release performance exhibited in figure 3.2.

Pellets produced from hand milled granules exhibit less control on the particle size of the granules produced (figure 3.3), resulting in a greater proportion of pellets in the sub-1000 micron range. Milling techniques incorporating a 2000 micron sieve produce a greater proportion of granules with a larger size range, producing a larger proportion of pellets within a 1000-2000 micron size range. The resultant pellets composed of a smaller particle size granule will have a faster drug release rate than those composed of larger particle sizes (Aulton, 2002; Qiu et al., 2009). A correlation between milling and particle size distribution has also been identified with milling time and type of mill utilised (Mullin, 1996; Phajongwiriyathorn, 2008).

3.3.2 Effect of granulation liquid composition

The pellets produced from both minocycline and paracetamol granules were prepared utilising different ratios of ethanol and water mixtures, to determine whether the different granulation liquid compositions have a significant effect on the drug release rate of the resulting pellets (Section 1.2.2).

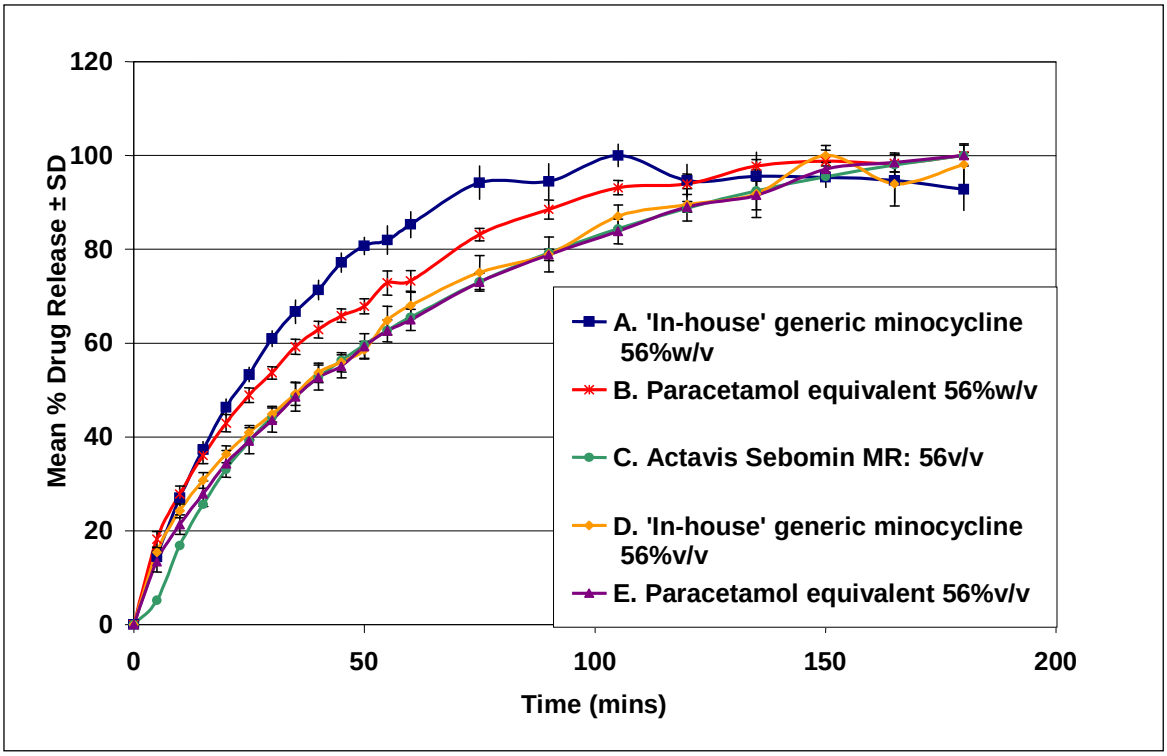


Figure 3.4 Mean release profiles of in-house and Actavis Sebomin® and paracetamol pellets with varying ethanol:water mixtures ± SD (n=6).

The paracetamol equivalent formulation was incorporated into figure 3.4 to assess its suitability as a marker during development work. The drug release profile for the paracetamol equivalent formulation is similar to the commercial Sebomin product and therefore acceptable for use during pre-formulation activities.

From Figure 3.4, there is a significant difference in the release profiles (f_2 values < 50, f_1 value > 10), for both types of drugs, when the ethanol:water composition of the granulation liquid is altered from 56%w/v to 56%v/v of ethanol. The release profiles of all the pellets produced using 56%v/v ethanol:water solution are extremely similar (f_2 values > 50, f_1 value < 10) and also replicate the drug release profile of the Actavis

Sebomin MR product. This indicates the composition of the granulation fluid is a critical parameter in the manufacturing process impacting on product quality. Optimisation of this parameter enables the Actavis Sebomin® formulation to be reproduced successfully when produced utilising the scaled down equipment.

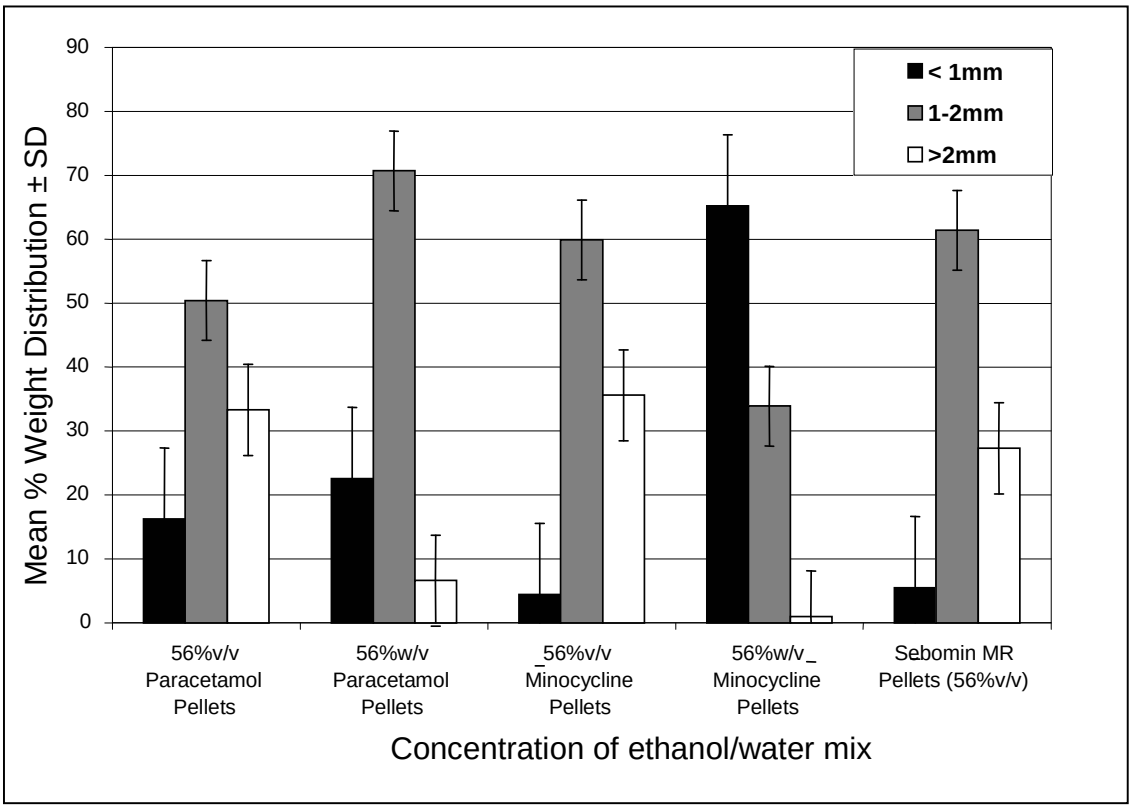


Figure 3.5 Particle size distribution of minocycline and paracetamol pellets with varying ethanol:water mixtures (n=3).

The particle size distributions obtained for minocyline and paracetamol pellets produced from varying alcohol mixes (Figure 3.5) both indicate the same correlation. Pellets produced from a granulation liquid containing more ethanol (56%v/v) have a higher proportion of pellets greater than 2mm. Whereas pellets produced from a granulation

liquid with less ethanol than water (56%w/v) have a greater size fraction of pellets less than 1mm.

The increase of particle size distribution is attributed to the increase in ethanol content. The GMS wax matrix is practically insoluble in ethanol, whereas minocycline HCl or paracetamol present on the surface of the wax granule readily dissolve in ethanol. As the content of ethanol increases in the PVP-ethanol:water solution, the drug on the surface of the wax matrix dissolves to form viscous liquid pores. This decreases the pore volume occupied by air eventually producing a funicular or capillary state where more liquid bridges can be formed increasing the contact surface area between the granule particles and enhances bonding capabilities. This promotes adherence of smaller granule particles to form larger particles (Qiu et al., 2009; Wells & Walker, 1983). On drying, the PVP binder present in the granulation fluid will harden, as the granulating fluid evaporates, to form solid bridges that bind the granule particles (Aulton, 2002).

The increased ethanol content may increase the proportion of pellets greater than 1mm in size but the binder viscosity would be the rate-limiting factor for continued particle growth, as a minimum binder viscosity is required to form granules for a given size (Keningley et al., 1997). To further increase the particle size of the resultant pellets the binder viscosity would need to further increase. Further consideration to increase the particle size would involve managing the rate of breakage during granulation. Larger particles exhibit steady movement during granulation making them more prone to breakage than smaller granules. Therefore, to prevent a wide particle size distribution

being achieved, equilibrium between granule growth and breakage would be required (Knight, 2004; Reynolds et al., 2005).

The minocycline and paracetamol hydrophobic matrix pellets shown in Figure 3.4 are not classified as sustained release formulations as the time point exhibited at 25% drug release was not expressed in hours but minutes. All formulations released less than 75% within 45 minutes eliminating immediate release therefore classifying the drug release characteristics of the minocycline and paracetamol pellets as modified release (British Pharmacopoeia, 2012).

3.3.3 Effect of glyceryl monostearate concentration

3.3.3.1 Granules

Modification of paracetamol release was achieved by varying the GMS content of the granules (Figure 3.5).

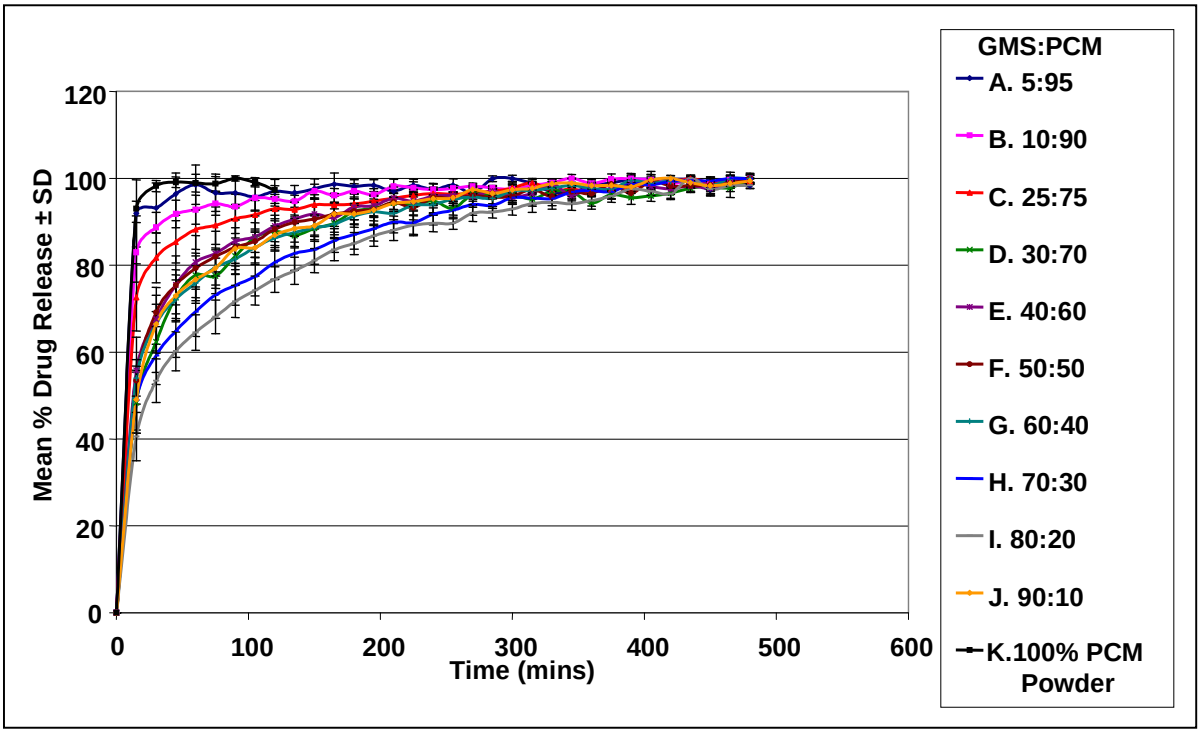


Figure 3.5 Mean Release Profiles of granules with varying GMS: PCM contents ± SD (n=6).

From Figure 3.5, all formulations exhibited at least 70% drug release within 1.5 hours (Table 3.6). As the GMS content increased from 5-80% w/w the drug release rate gradually decreased. A significant difference was observed (f_2 values < 50, f_1 value > 10) between the paracetamol powder release profile and the paracetamol:GMS release profiles obtained for formulations consisting of at least 30% w/w GMS or more. No significant difference was identified between the drug release profiles for granules comprising of 40-90%w/w GMS, using fit factors (f_2 values > 50, f_1 value < 10).

Granules comprising of 90%w/w GMS did not follow the decrease in drug release rate anticipated but actually showed similar drug release characteristics as for granules

comprising of 40%w/w GMS, confirmed by fit factors (f_2 values > 50, f_1 value < 10). A primary consideration for compromising the anticipated dissolution rate is the granule PSD, this would significantly impact on the drug release rate via Noyes-Whitney. Further characterisation of PSD of granules and pellets were undertaken in section 3.3.5.1. Alternatively, an interaction between the API and GMS may impact the anticipated dissolution rate (Giordano et al., 2002; Tomassetti et al., 2005), however no interaction between paracetamol and GMS has been reported in the literature. Further investigation of the thermal properties of paracetamol-GMS binary mixtures were characterised in Section 5.3.1.

The mechanism of drug release cannot be correlated to Higuchian release kinetics for the granules or pellets (figure 3.5 and 3.6) indicating the release is not primarily via diffusion and may involve two drug release mechanisms. Further investigation into the surface characteristics via SEM would be required to assist in defining the mechanisms of release and why the high drug loading of GMS (90%w/w) imparts difference behaviour than anticipated.

Due to the hydrophilic nature of paracetamol an initial burst release can be observed for all formulations due to liberation of the surface drug from the granule. Once the surface drug has been released the drug release rate becomes slow and steady. As GMS concentration within the formulation increases, the extent of initial release decreases suggesting less drug exposure on the granule surface and the extragranular porosity decreases (Quadir et al., 2003). From an intragranular perspective, an increase in the

GMS content increases the distance between the embedded drug particles and the dissolution media. This leads to a decreased rate for the dissolution media to penetrate the granule and decreases the rate of drug diffusion out of the matrix (Tiwari et al., 2003).

Formulations A-F and K (Figure 3.5) are characterised by the BP specifications as a conventional immediate release dosage forms as at least 75% of the active was released in 45 minutes. Formulations G-J are characterised as modified release formulations (British Pharmacopoeia, 2012).

3.3.3.2 Pellets

Modification of the drug release was achieved by varying the GMS content of the granules and further processing into pellets (Figure 3.6).

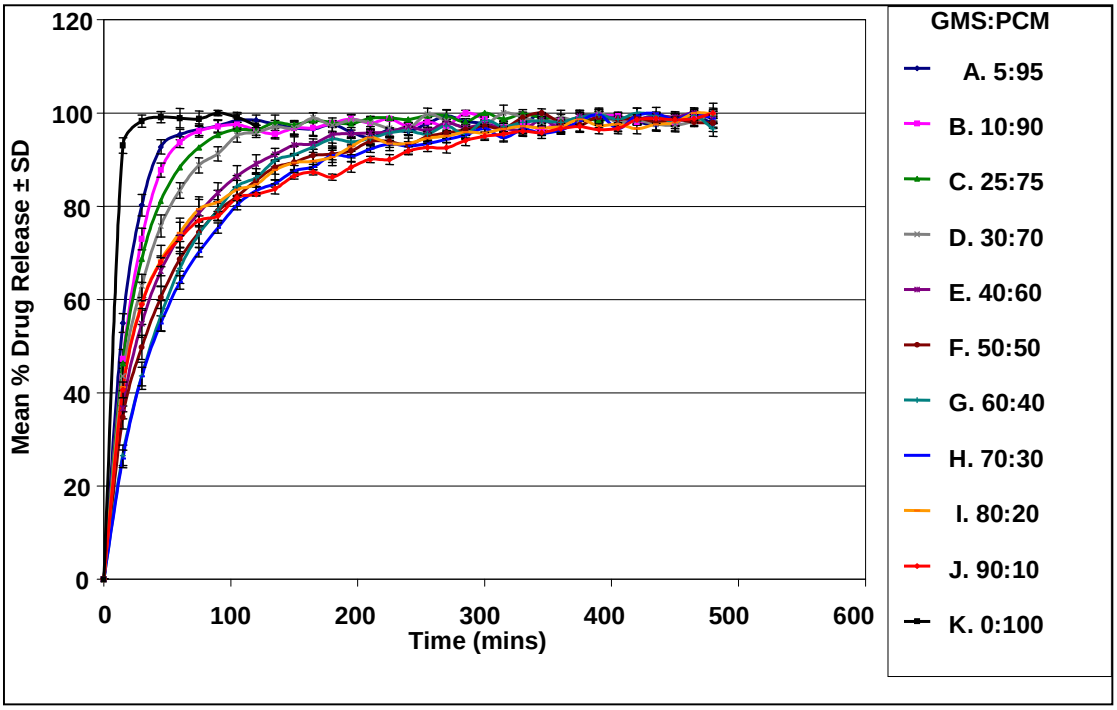


Figure 3.6 Mean Release Profiles of paracetamol from pellets with varying GMS: PCM contents ± SD (n=6).

From Figure 3.6, all formulations exhibited at least 70% drug release within 1.5 hours. As the pellet GMS content increased from 5-90% w/w the drug release rate gradually decreased. A significant difference was observed between the paracetamol powder release profile and formulations consisting of at least 10% w/w GMS or more (f_2 values < 50, f_1 value > 10). No significant difference in drug release rate was observed between pellets comprising of 10-90%w/w GMS (f_2 values > 50, f_1 value < 10).

Formulations A-D and K (Figure 3.6) are characterised by the BP specifications as a conventional immediate release dosage form as at least 75% of the active is released in 45 minutes. Therefore, statistically significant differences between drug release profiles,

using fit factors, cannot be interpreted to mean that the formulation is no longer an immediate release dosage form, as indicated by granules containing 10%w/w, 20%w/w and 30%w/w GMS.

3.3.3.3 $T_{70\%}$ values of GMS:PCM granules and pellets

For each dissolution run, six release profiles were obtained. The standard deviation of the $T_{70\%}$ values obtained from each of these six dissolution profiles was determined (Table 3.6).

Table 3.6 $T_{70\%}$ values and Standard deviations obtained from the pellet and granule release profiles (n=6).

GMS Content (% w/w)	**Granules**	**Pellets**
	$T_{70\%}$±SD (mins)	**$T_{70\%}$±SD** (mins)
30	42.6±11	39.5±2.7
40	35.3±9.9	53.0±4.9
50	36.3±13.7	63.5±5.9
60	42.0±8.8	67.7±6.3
70	66.1±23.5	76.9±3.0
80	83.7±17.6	47.7±7.8
90	41.0±17.6	51.1±2.4

For granules and pellets, calculating the standard deviation and $T_{70\%}$ values for formulations containing less than 30%w/w was not possible as these formulations had released over 70% of the drug from the matrix system before the first UV reading at 10mins (Table 3.6). However, a significant difference can be observed between the $T_{70\%}$

values for the pellets and granules containing at least 30%w/w upwards ($p<0.05$, Two-Way ANOVA). For granules containing up to 70%w/w GMS, $T_{70\%}$ is reached faster than the $T_{70\%}$ of pellets with the same composition of GMS, indicating the extrusion/spheronisation process must be contributing to the additional retardation of drug release from pellets.

In Table 3.6, the SD for pellets was significantly lower than the SD for granules ($p<0.05$, Two-Way ANOVA), indicating that the six drug release profiles obtain for the pellets had less variation between the drug release profiles making pellets more reproducible than granules. The pellet SD was lower because the pellets are more uniform, spherical and compact than the granules, which are characterised as irregular in shape and size and less compact. It is more difficult for the dissolution media to penetrate the pellets than the granules due to the reduction in the diffusional pathways within the matrix (Mehta et al., 2000; Mehta et al., 2002).

As illustrated by Peh and Yuen (1995) and Phajongwiriyathorn (2008), modification of drug release can be achieved by varying the GMS content of the pellets. However, the manipulation of GMS concentration in a binary mixture with paracetamol is not sufficient enough to achieve sustained drug release. As the first time point, taken for 20-30% drug release is not expressed in hours for any of the granule or pellet formulations (Section 1.4). However, as indicated by Phajongwiriyathorn (2008) sustained release profiles can be achieved when an additional excipient is incorporated, such as a tertiary mixture of GMS, paracetamol and DCP.

The extrusion/spheronisation process can also be utilised to decrease the drug release rate (Section 3.3.1.2) and offer reproducibility of the in vitro drug release due to the uniform compaction of the pellets. However, this was still insufficient in achieving sustained drug release in a binary mixture of GMS and paracetamol. Further processing and formulation variables would need to be modified for a sustained drug release rate to be obtained.

3.3.4 Effect of spheronisation time

3.3.4.1 In vitro Release Profiles

The effect of varying spheronisation time on the drug release of paracetamol from pellets is shown in Figure 3.7.

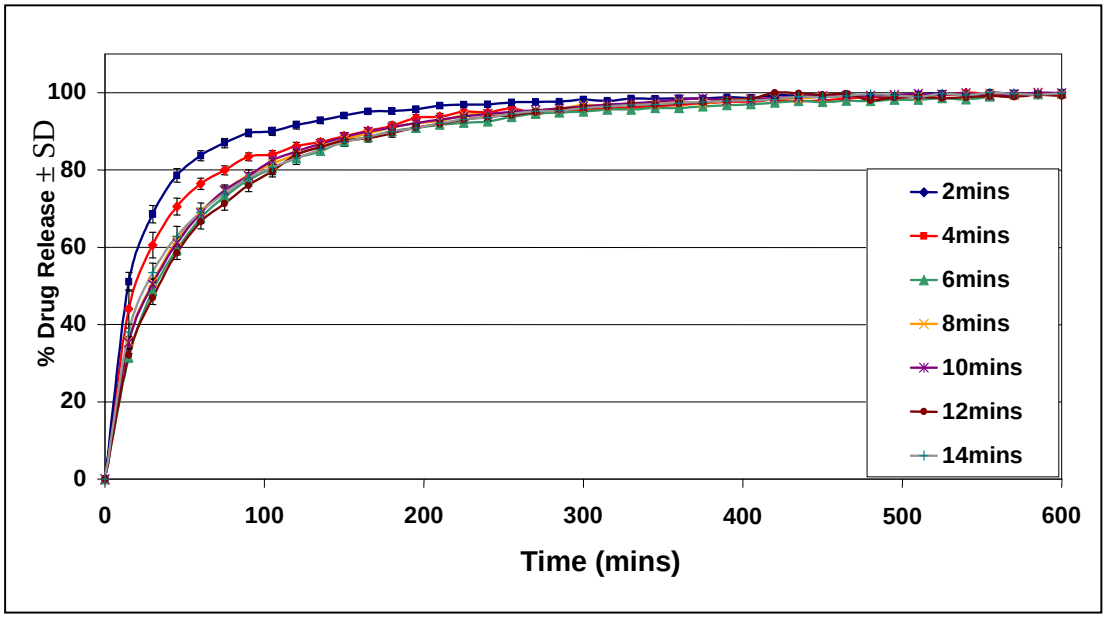


Figure 3.7 Mean Release Profiles of paracetamol from pellets with varying spheronisation times ± SD (n=6).

From Figure 3.7, increasing the spheronisation time from 2 to 6 minutes significantly decreases the drug release rate (f_2 values < 50, f_1 value > 10). When extrudate is spheronised for 2 minutes the pellets exhibited immediate drug release characteristics, when the extrudate is spheronised for at least 4 minutes modified release characteristics were achieved. When the spheronisation time was increased from 6 to 14 mins, there was no further decrease in the drug release and as a result sustained drug release was not achievable by varying the spheronisation time alone. The relationship between the spheronisation time and the mean $T_{70\%}$ are graphically represented in Figure 3.8.

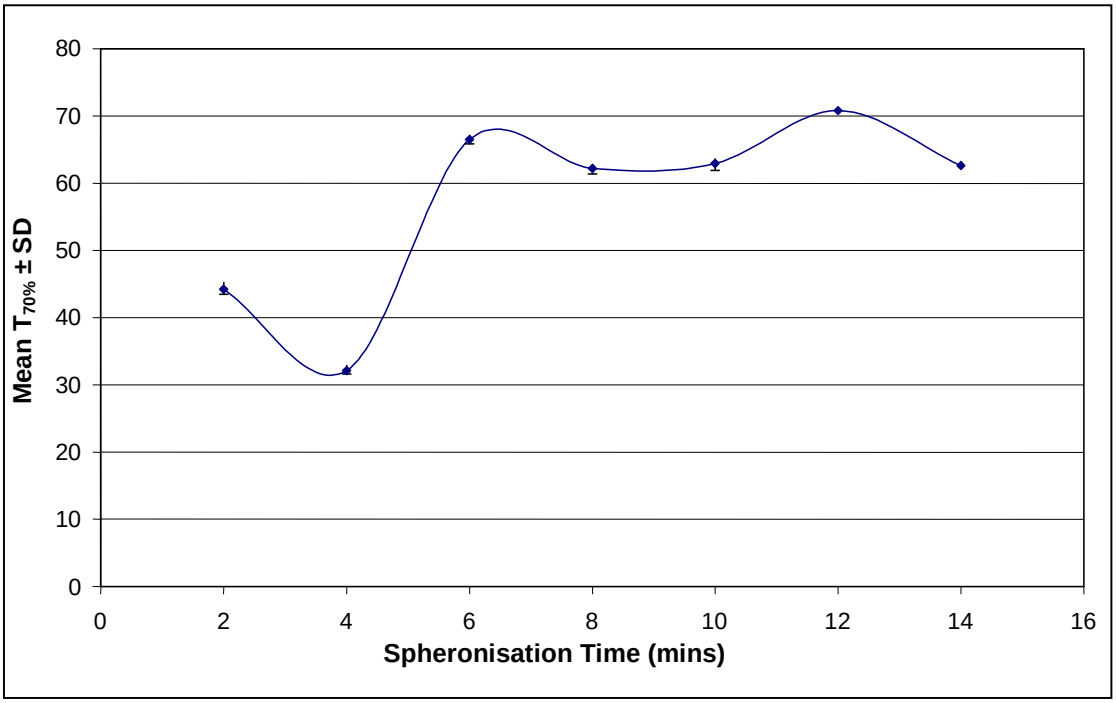


Figure 3.8 Spheronisation time against mean $T_{70\%}$ for paracetamol pellets ± SD (n=6)

Figure 3.8 clearly indicates there is a significant step change of the $T_{70\%}$ values when the spheronisation time increases from 4 minutes to 6 minutes and corresponds to similar

findings by Mehta et al., (2002). Spheronising for longer than 4 minutes significantly increases the time taken for 70% of the drug to be released from the matrix pellets into the dissolution media, decreasing the drug release rate. However, this increase in the $T_{70\%}$ value does not further increase when the pellets are spheronised beyond 6 minutes, no significant difference is found between 6 minutes to 14 minutes $T_{70\%}$ values ($p>0.05$, Two-Way ANOVA).

3.3.4.2 Visual Examination of Pellets

Prior to spheronisation, extrudates appeared irregular in size and shape (not shown). Pellets were visually examined and compared after varying the spheronisation time (Figure 3.9).

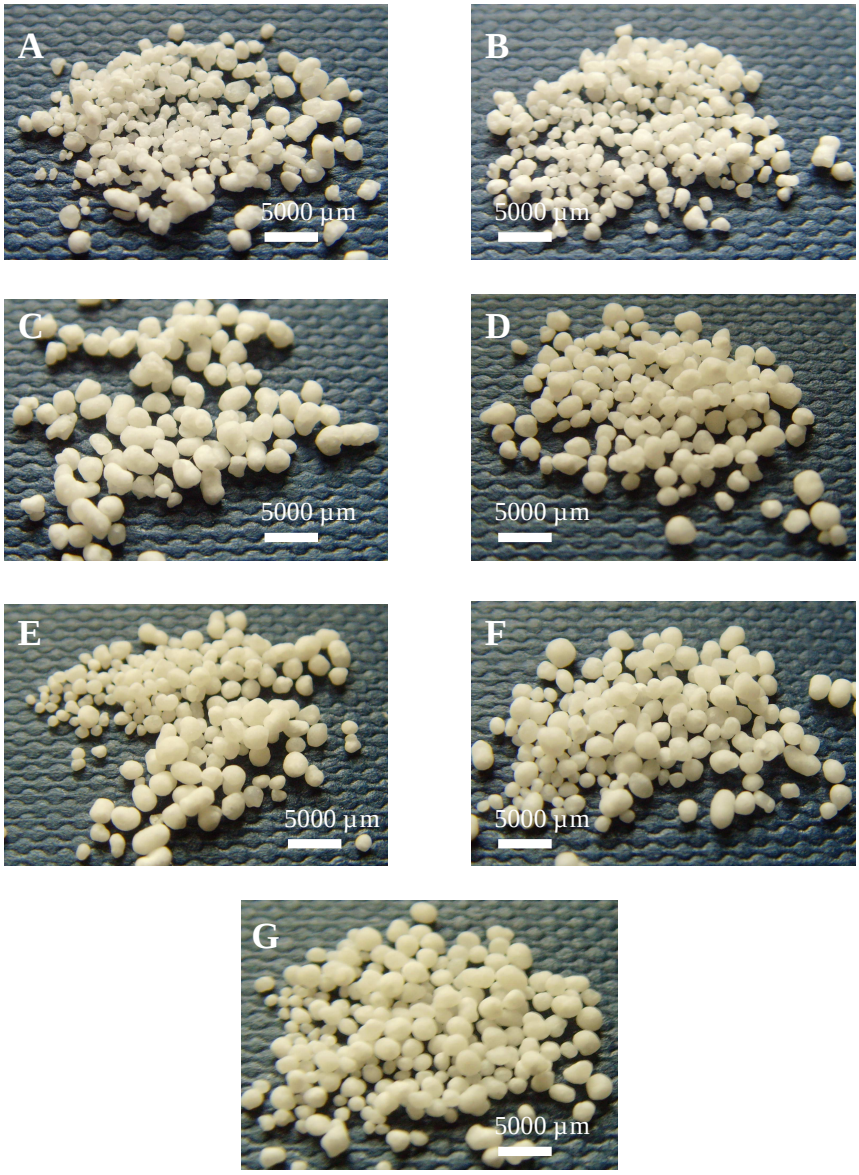


Figure 3.9 Digital photographs of paracetamol pellets produced with varying spheronisation times A) 2 mins, B) 4 mins, C) 6 mins, D) 8 mins, E) 10 mins, F) 12 mins and G) 14 mins (See Section 3.2.4 for process/formulation parameters).

During spheronisation, the rotational and centrifugal forces exhibited on the extrudates led to more spherical-shaped pellets being produced. As the spheronisation time was increased from 2 to 6 mins, the pellet appearance became more rounded and uniform.

Once the spheronisation time reached or exceeded 6 mins, pellets adhered together to form larger dumb-bell and oval shaped agglomerates. Pellet agglomeration continued to become more pronounced as the spheronisation time was increased beyond 6 mins, with 2 or 3 pellets visibly agglomerating together. Similar findings were illustrated by Lee (2003) and Mehta et al., (2000).

In a study by Mehta et al., (2002), densification of the pellets was the predominant mechanism that contributed to decreasing the drug release profiles. Longer spheronisation time produces more compact pellets due to the increased exposure to the rotational and centrifugal forces exhibited. Increased pellet densification makes it more difficult for the dissolution media to penetrate the pellet formulation and sustains drug release. After a defined period of time, the pellets may not be able to compact/densify further and the drug release rate will correlate with the level of densification and not decrease any further.

An optimal spheronisation time can be achieved for a pellet formulation. In this case, spheronising pellets for longer than 6 mins is not productive as the release characteristics do not significantly decrease further and the product may undergo agglomeration or adhere to the spheronising chamber causing product release characteristics to become less reproducible (Mehta et al., 2000; Vervaet et al., 1995). Shorter spheronisation times would also be preferred to enable rapid production of pellets that would be cost effective in the pharmaceutical industry. In addition, the hydrophobic materials and API would not be at risk of any phase transitions that may occur from additional processing stresses.

3.3.5 Effect of pellet particle size

3.3.5.1 Granules

The effect of paracetamol:GMS (40:60) granule particle size on the release rate is shown in Figure 3.10.

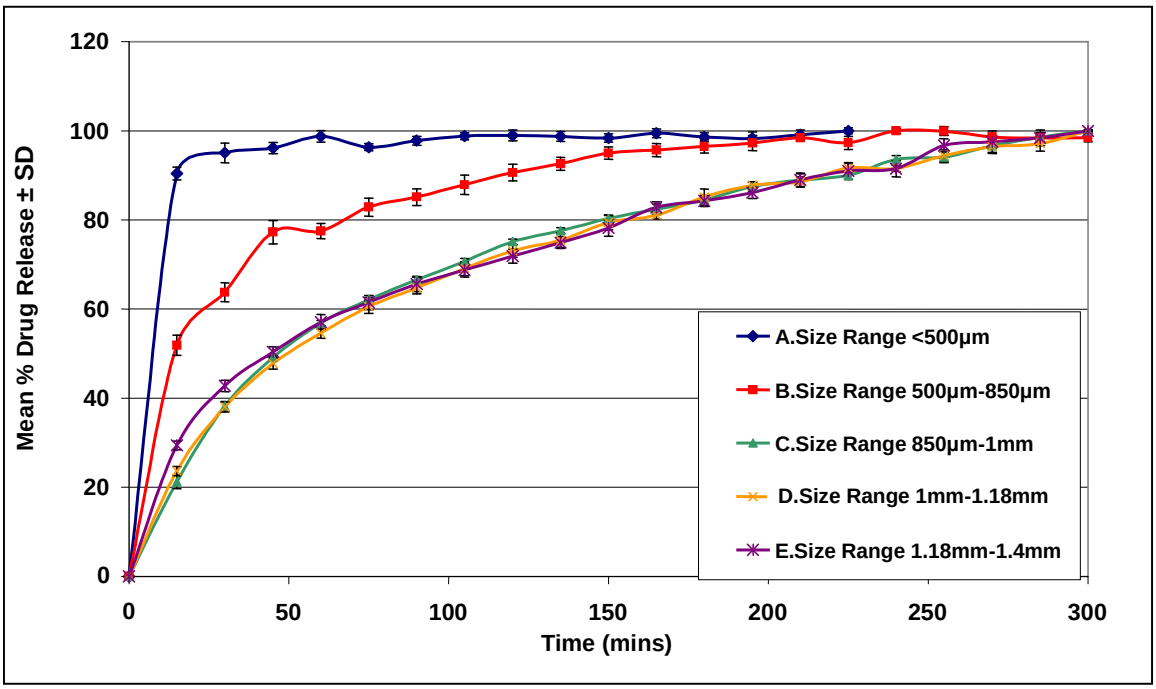


Figure 3.10 Mean release profiles of paracetamol:GMS (40:60) granules with varying size distribution ± SD (n=6).

From Figure 3.10, as the particle size increases from less than 500µm up to 1mm there is a significant decrease in the in vitro release rate (f_2 values < 50, f_1 value > 10), as anticipated by Noyes-Whitney (Qui et al., 2010) where the primary mechanism of drug release from the granules is diffusion (Siepmann et al., 2006).

Increasing the granule size above 850µm increases the diffusional pathway within the granule sufficiently for modified release to be achieved (British Pharmacopoeia, 2012).

However, further increasing the granule size above 1mm did not further prolong the release capabilities of the granules. This indicates the release kinetics for granules 850-1400µm cannot be based on diffusion only (Siepmann et al., 2006). Consideration of the granule shape, surface characteristics and porosity would require further investigation as these may contribute to the granule release performance (Aulton, 2002). Sustained release characteristics could not be achieved with any granule fraction up to 1.4mm in size.

3.3.5.1 Pellets

The effect of paracetamol:GMS (40:60) pellet particle size on the drug release rate is shown in Figure 3.11.

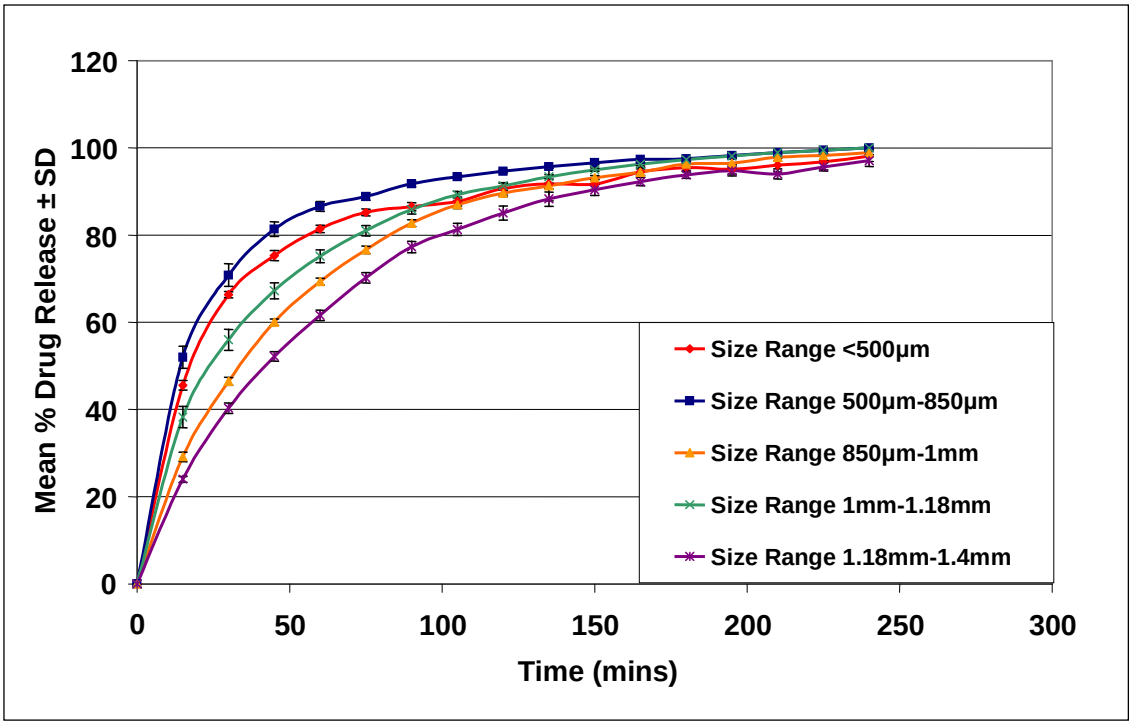


Figure 3.11 Mean release profiles of paracetamol:GMS (40:60) pellets with varying size distribution ± SD (n=6).

Figure 3.11 shows pellets smaller than 850μm have a significantly increased drug release rate compared to the larger pellet size distributions (f_2 values < 50, f_1 value > 10). The release rates of the pellets smaller than 850μm are more reproducible than the granules (figure 3.10) and may be due to the spheronisation process, reducing surface irregularities and matrix densification (Vervaet et al., 1995).

As observed with the granules (figure 3.10), increasing the pellet size greater than 850μm achieved modified release (British Pharmacopoeia, 2012). However, further increasing the pellet size above 1mm did slightly prolong the release capabilities of the pellets (Mehta et al., 2002). This indicates the release kinetics for pellets 850-1400μm cannot be based on diffusion only (Siepmann et al., 2006). Consideration of the pellet surface porosity would require further investigation as this may contribute to the pellet release performance (Aulton, 2002).

The release classifications were the same for both granules and pellets of the same size. The continued decrease in the dissolution rate of the pellets greater than 1.18mm in size indicated the pellet manufacturing process may contribute to the further decrease in release rate. However, despite the pellets being more compact and uniform in shape than granules they do not significantly contribute to the release properties.

Both granules and pellets could not achieve sustained drug release by modulating the particle size alone but it was demonstrated that pellet size can influence the rate of drug

release from an immediate release rate to a modified release rate for both types of formulations (Aulton, 2002; Qui et al., 2010).

As the granules/pellets became larger the rate limiting step in significantly decreasing drug release rates may be associated with the granule/pellet porosity or the manufacturing process (Abdel-Hamid et al., 2011), especially milling as this is common in the production of both granules and pellets (Heng et al., 2006). Thermal analysis of the product should be assessed to determine the stability of the granules and pellets.

3.4 Conclusions

To define the product design space, successful transfer of the extrusion/spheronisation process enabled Sebomin® MR to be reproduced in house. This enabled QbD to be successfully implemented and critical parameters modulated. Release profiles of minocycline HCl and paracetamol wax matrix granules and pellets were utilised to evaluate product performance and the potential development of a sustained release product was also evaluated. Investigated formulation and processing parameters demonstrated an ability for formulation modulation and optimisation to be achieved for either an immediate drug release or modified drug release capability.

The extrusion/spheronisation process improved granule performance by significantly decreasing the drug release rate when formulated into pellets. Pellets with desirable modified release characteristics were produced and reduced batch to batch variability was achieved when compared to drug release profiles of granules.

'In-house' generic minocycline pellets were developed utilising bench scale equipment and exhibit the same release profiles as Actavis Sebomin® MR pellets, despite the extruder screen sizes not being the same. In house the extruder screen was 1mm and during scale-up in Actavis a 1.5mm screen is used. Therefore with this particular formulation the type and size of the extruder screen within the limits tested do not significantly impact on reproducing the drug release profile in house or at Actavis, despite the literature (Harrison et al., 1987; Juppo et al., 1997; Vervaet et al., 1995).

The milling process involved in producing granules and pellets was demonstrated to have a significant impact on product quality. Many parameters associated with milling have been identified to have a significant impact on the products performance characteristics including milling time and type of mill equipment (Mullin, 1996; Phajongwiriyathorn, 2008). Pellets formulated from hand milled granules have a significantly increased drug release rate than pellets formulated from granules that had undergone no hand milling. An increase in milling time or the use of a crude milling system can produce additional heat and stress on wax/drug granules that may lead to polymorphic transition of formulation components (Zhang et al., 2004).

During wax fusion, modulation of the cooling rate for the wax:drug mixture, from 65 to 40˚C, did not appear to effect the drug release rate in the immediate post-manufacture time period. However as with the milling parameters, there is evidence to support that the cooling rate can promote transitional changes in wax based systems and FT-IR, XRPD or

DSC would require to be undertaken over several weeks to identify if there is a long term effect (Phajongwiriyathorn, 2008).

Modulation of the granulation liquid composition directly impacted on product quality. An increase in the ethanol content significantly decreased the drug release rate for both minocycline and paracetamol hydrophobic matrix pellets. This decrease in release rate correlated with an increase in the particle size distribution. Significant differences in the drug release rate and subsequent increase of the particle size could be dependent on the liquid saturation level of the granules (Galland et al., 2005; Mehta et al., 2002; Wan et al., 1993). Therefore the volume of granulation fluid to achieve complete liquid saturation of the granules should be determined and the effect of the ethanol content on the wax-based system investigated.

Modification of GMS concentration of paracetamol pellets produced by extrusion/spheronisation was not sufficient to achieve sustained drug release. However, by incorporating an additional excipient with the GMS and paracetamol could achieve sustained drug release from this wax matrix system (Thomsen et al., 1994).

Increasing the spheronisation time of the pellets led to a decrease in the drug release rate. The rotational and centrifugal forces exhibited on the extrudates led to more densified spherical-shaped pellets being produced. However, once densification of the pellets was optimised there was no further decrease in the drug release rate suggesting that

densification is the primary mechanism controlling these changes (Juppo et al., 1997; Qui et al., 2010).

It is important to determine the optimum time for spheronisation as prolonged spheronisation time may cause agglomeration of pellets (Mehta et al., 2000; Wan et al., 1993). The spheronisation residence time can also have a significant effect on the moisture content of pellets (Hellén et al., 1993b), the effect of moisture content on the wax-matrix pellets would need to be further investigated. Additionally, in wax-based pellets transitional changes may occur due to excess heat and stress on the formulation materials. This further processing could change the drug or excipient characteristics impacting on the overall drug release profile of the product. Thermal analysis studies can be undertaken to determine the compatibility of the formulation components on formulation and processing parameters (Aulton, 2002; Watson, 2005; Freitas & Muller, 1999; Jenning & Gohla, 2000; Phajongwiriyathorn, 2008; Yoshino et al., 1981; Qui et al., 2010).

Pellet size was indicated to effect the rate of the drug release from the pellets (Qui et al., 2010). However, pellet surface and porosity characteristics would need to be further characterised to confirm this observation and take into consideration that even though the granules are the same nominal sieve size it does not mean their surface area size and shapes are the same (Aulton, 2002).

Utilising a QbD approach, the optimal design space for the Sebomin MR formulation was successfully established. From utilising the same hydrophobic matrix pellet system and manufacturing processes it was concluded the optimal performance for this product was modified release. By modulating both manufacturing process parameters and formulation variables of minocycline HCl pellets and paracetamol pellets, the delivery system could not achieve sustained drug release characteristics. The optimal design space for a modified release hydrophobic matrix pellet system, utilising the current formulation and extrusion/spheronisation is outlined in Table 3.7.

Table 3.7 Defined design space to achieve a modified release Sebomin® MR or paracetamol formulation utilising extrusion spheronisation.

Composition Variable	**Optimal Parameters**	**Formulation**	**Drug Load***
GMS Content	40-90%w/w	Paracetamol Pellets	60-10%w/w
Granulation Fluid	56%w/v	Sebomin® MR	85%w/w
Pellet particle size	850-1400µm	Paracetamol Pellets	40%w/w
Process Variable	**Optimal Parameters**	**Formulation**	**Drug Load***
Milling	Scale up - Oscillating mill Bench Scale - manually feed through sieve	Sebomin® MR	85%w/w
Spheronisation	4-14mins	Paracetamol Pellets	10%w/w
Extruder screen	1-1.5mm	Sebomin® MR	85%w/w

***During wax fusion**

Immediate release characteristics could also be achieved, when utilising extrusion spheronisation, by modulating the spheronisation time, milling technique, pellet particle size and GMS content but the optimal design space to achieve this product performance is more restricted (Table 3.8).

Table 3.8 Defined design space to achieve an immediate release Sebomin® MR or paracetamol formulation utilising extrusion spheronisation.

Composition Variable	**Optimal Parameters**	**Formulation**	**Drug Load***
GMS Content	0-30%w/w	Paracetamol Pellets	100-70%w/w
Pellet particle size	<850µm	Paracetamol Pellets	40%w/w
Process Variable	**Optimal Parameters**	**Formulation**	**Drug Load***
Milling	Bench Scale – Hand mill	Sebomin® MR	85%w/w
Spheronisation	2mins	Paracetamol Pellets	10%w/w

***During wax fusion**

In conclusion, to achieve sustained release characteristics a new formulation and/or manufacturing process would be required. In Chapter 4, the development of a hot-melt spray system is undertaken utilising experimental design for process characterisation. Once this is achieved product performance can be assessed utilising QbD and the ability to achieve sustained release characteristics.

5. Development and Characterisation of an Agitated Hot-Melt Spray System

4.1 Introduction

As demonstrated in Chapter 3, extrusion/spheronisation can successfully produce wax matrix pellets and successfully scaled down to reproduce the modified drug release characteristics of Sebomin MR®. Modulation of the various formulation and processing parameters enabled retardation of the pellet drug release but this manufacturing technique could not be utilised to produce wax matrix pellets that satisfy the sustained release specification outlined in the British Pharmacopoeia (2012).

Another disadvantage of this manufacturing method involves the production of hot-melt wax granules, where cooled solidified wax melt must undergo a milling process that can be difficult to reproduce. Publications of milling process variables, including type of milling equipment and milling duration, have demonstrated mechanical and thermal stress may alter the dissolution performance of a product (Mullin, 1996; Phajongwiriyathorn, 2008). Therefore, the development and investigation of an alternative manufacturing technique was undertaken to avoid the problems associated with extrusion spheronisation identified in section 3.3.4.

The main objective in this chapter was to develop and characterise an agitated hot-melt method for the production of GMS granules. Various formulation and process parameters were investigated in a design of experiments. In addition to the design of experiments, sprayed granules were characterised based on using the GMS hydrophobic matrix system

to determine whether the hot-melt spray system was robust, reproducible and the stability of the sprayed GMS granules evaluated. Spraying drying was not considered for this study as solvents or water were not utilised in the hydrophobic system.

4.2 Methods

A hot-melt approach was utilised in the development of producing wax granules from an air-assisted spray technique (Section 2.3.4). Preliminary formulation development comprised of glyceryl monostearate only, in order to determine granule quality, reproducibility and stability. Formulation manufacture and analytical techniques are summarised in Section 4.2.

4.2.1 Characterisation of sprayed GMS granules

GMS sprayed granules were produced utilising a hot-melt spray technique at 80ºC (Section 2.3.4). The resultant GMS granules underwent particle size (Section 2.4.2.1), DSC (Section 2.4.5.2), XRPD (Section 2.4.6) and SEM (Section 2.4.7.4) analyses. All batches used for DSC analysis were stored at 4, 25, 37 and 45ºC and monitored for 108 days.

4.2.2 The effect of adjustable spray gun components

A number of ‘one variable’ experiments were undertaken to determine whether certain manufacturing factors had an effect on the resulting characteristics of GMS wax granules. The batch size processed was kept constant at 65g. The manufacturing factors investigated are summarised in Table 4.2.

Table 4.2 Manufacturing variables investigated in production of a 65g batch of GMS granules.

Manufacturing Factor	**Variables**		
Adjustment Screw (controls spray rate)	Closed (2.49m/s)*	Mid-way (2.57m/s)*	Open (2.57m/s)*
Adjustment Knob (controls air flow rate)	Closed (1.20m/s)*	Mid-way (1.99m/s)*	Open (2.06m/s)*
Butterfly Nozzle (controls spray pattern)	Vertical Pattern	Circular Pattern	Horizontal Pattern

*Flow rates determined via an anemometer utilising sprayed water to represent low viscosity liquids. The spray gun was operated at 230v with a 1mm nozzle.

All GMS granule formulations were produced utilising the agitated hot-melt spray system operated at 80ºC (Section 2.3.4). The resultant GMS granules were analysed by particle size analysis (Section 2.4.2.1).

4.2.3 The evaluation of formulation and manufacturing variables in the production of wax granules utilising experimental design

Statistical experimental design (Section 2.4.1) was utilised to characterise various formulation and manufacture parameters associated with the development of wax granules utilising an agitated hot-melt spray system. Design of experiments was the chosen method of characterisation as it enables a number of variables to be investigated

simultaneously utilising a systematic structure. It also enables determination of any interactions that may occur between these variables which would not be detected utilising a conventional 'trial and error' approach.

Utilising a two factorial design of experiments, four spray formulation variables were investigated (Table 4.2).

Table 4.2 Factors investigated in the fractional factorial experimental design.

Factors	Low Level	Centre Point	High Level
A. Spraying temperature above wax melting point (^{o}C)	10	20	30
B. Wax Type	Witepsol (Glycerides C10-C18: Castor Oil 95:5%w/w) (1)	Hydrogenated Castor Oil (2)	Glyceryl Monostearate (Imwitor 900K) (3)
C. Voltage (v) (Modulates air pressure of spray gun)	170 (1.99m/s)*	200 (2.15m/s)*	230 (2.33m/s)*
D. Nozzle size (mm)	1	2	3

*Flow rates determined via an anemometer utilising sprayed water to represent low viscosity liquids and fitted with a 1mm nozzle.

The following experiments were conducted in a randomised order provided by the computer package (Table 4.3).

Table 4.3 Experimental design order of experiments.

Run	Factors			
	A	**B**	**C**	**D**
1	10	3	170	3
2	10	1	170	1
3	30	3	230	3
4	30	1	230	1
5	20	2	200	2
6	20	2	200	2
7	30	3	170	1
8	10	1	230	3
9	20	2	200	2
10	30	1	170	3
11	20	2	200	2
12	10	3	230	1
13	20	3	200	2
14	20	3	200	2
15	20	1	200	2
16	20	2	200	2
17	20	2	200	2
18	20	2	200	2

Four response factors were chosen to characterise the resultant granules, these included particle size determination utilising sieve analysis and laser diffraction (Mastersizer) techniques (Section 2.4.2.2), bulk tap density (Section 2.4.2.3) and angle of repose (Section 2.4.2.4). Stat-ease®, design expert computer software enabled ANOVA statistical determination.

4.3 Results and Discussion

4.3.1 Characterisation of sprayed GMS granules

The PSD of sprayed GMS granules are shown in Figure 4.1.

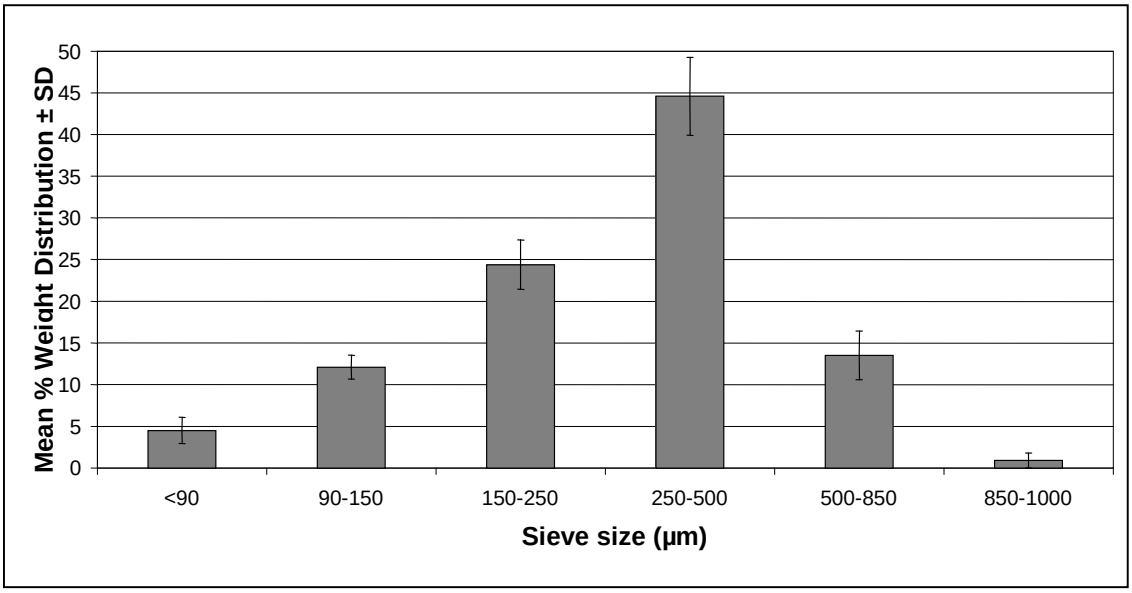


Figure 4.1 Particle size distribution of sprayed GMS granules (n=3)

The particle size distribution of the sprayed granules (Figure 4.1) was Gaussian in nature with the prevalent particle size being within the 250-500µm size range.

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the sprayed GMS. The DSC profiles of sprayed GMS granules monitored are shown in Figure 4.2-4.4.

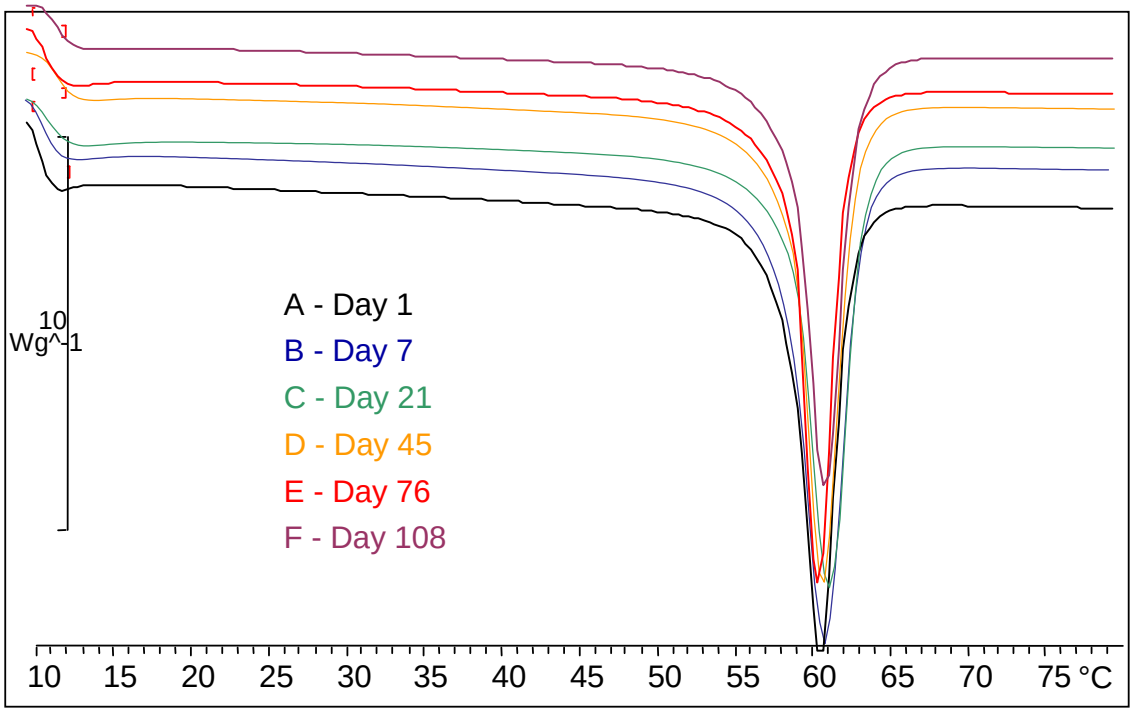


Figure 4.2 Effect of storage at 4^{o}C on DSC profiles of sprayed GMS granules (scale bar = heat flow [10 watts per gram]).

From figure 4.2, there were no significant changes in the DSC profiles of the sprayed GMS after prolonged storage at 4^{o}C. The endotherms have a broad melting range, between 55^{o}C and 63^{o}C, for the sprayed GMS. As GMS comprises of a mixture of monoglycerides, diglycerides, triglycerides and long chain C_{18} fatty acids, it melts over a range of temperatures associated with these components.

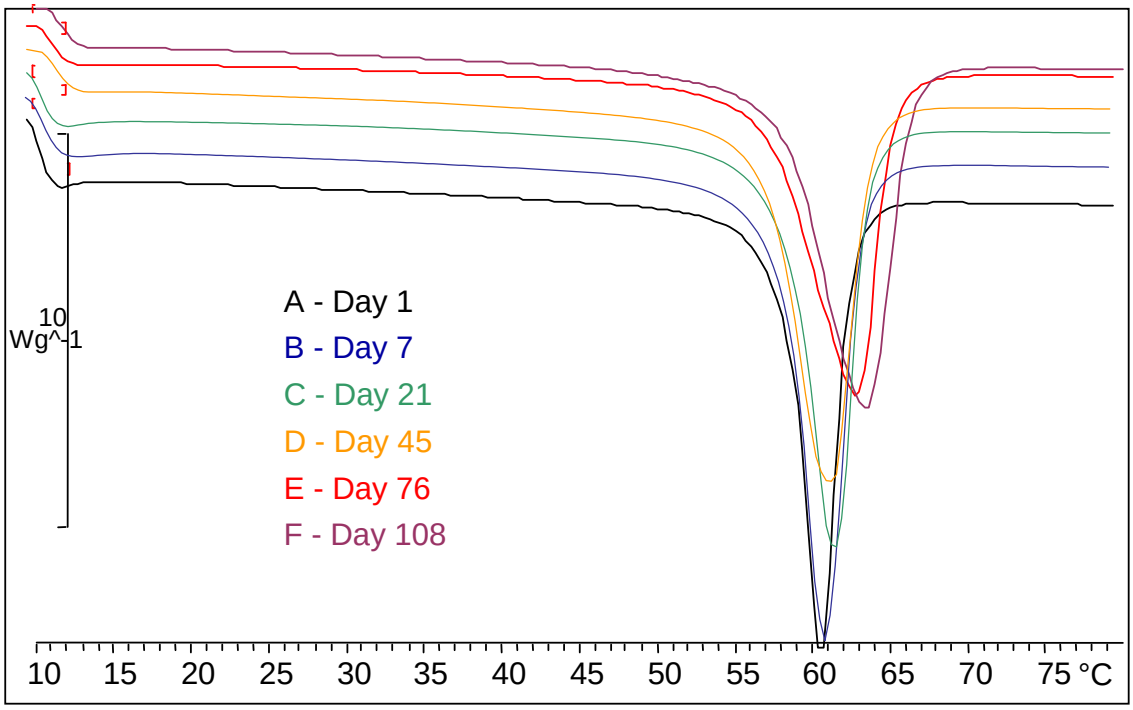


Figure 4.3 Effect of storage at room temperature on DSC profiles of sprayed GMS granules (scale bar = heat flow [10 watts per gram]).

In Figure 4.3, prolonged ambient storage of the sprayed GMS has led to a slight upward trend in the peak melting temperature followed by a broadening of the endotherm melting range. This thermal change correlates to the conversion of the GMS from the unstable α-polymorphic form to the stable β- polymorphic form of GMS (Cornish, 1968; Yajima et al., 2002).

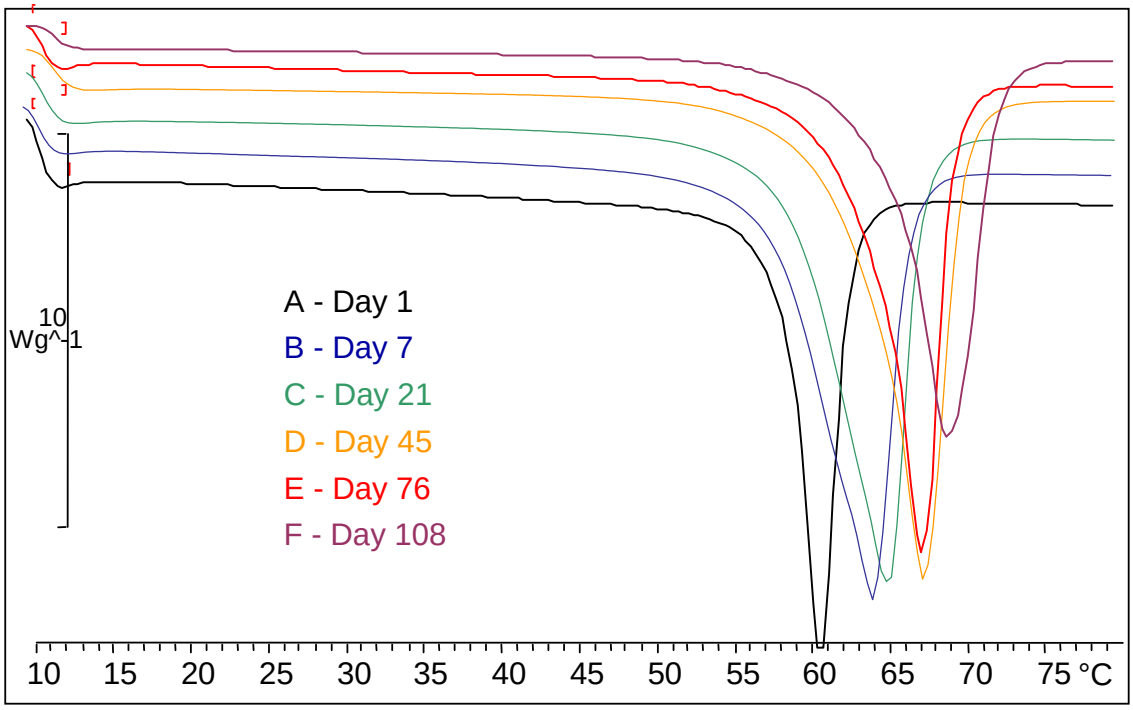


Figure 4.4 Effect of storage at 37˚C on DSC profiles of sprayed GMS granules (scale bar = heat flow (10 watts per gram)).

At 37^{o}C storage (figure 4.4), the GMS endotherm further broadens and significantly shifts to a higher temperature with prolonged storage of the sprayed GMS. This suggests higher temperature storage accelerates the thermal changes ongoing in the sprayed GMS compared to the lower storage temperatures. By day 108 the thermal changes appear to be ongoing and not complete as the endotherm melting temperature is still increasing. A similar trend was observed for monoacid triglycerides and tristearin during ageing or melting (Garti et al., 1982; Whittam & Rosano, 1975).

As indicated previously, the thermal changes observed may relate to the transformation of sprayed GMS from the unstable α-form to a more stable β-form of GMS

(Phajongwiriyathorn, 2008; Yajima et al, 2002). These accelerated stability results indicate the transformation of the GMS from the α-form to the β-form may not be complete, the final ratio of β-form GMS is unknown.

To further confirm the thermal changes exhibited in section 4.3.1, scanning electron micrographs of the sprayed GMS granules were undertaken (figure 4.5).

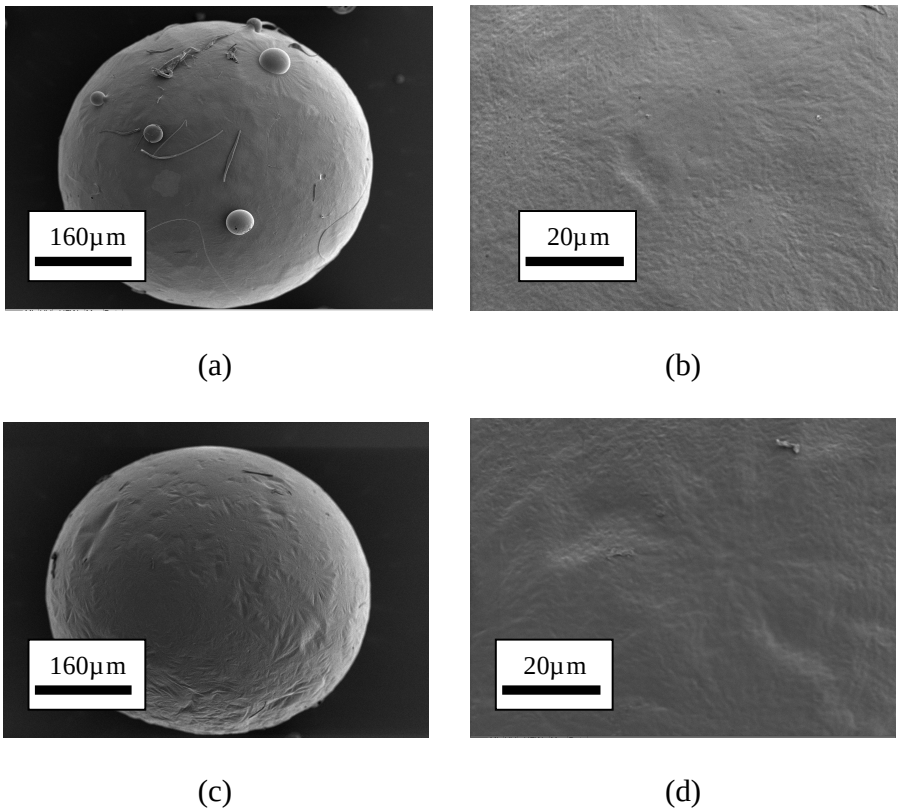


Figure. 4.5 SEM images of GMS sprayed granules 2hrs post manufacture at a magnification of (a) x250 and (b) x2000. SEM images of GMS sprayed granules 30hrs post manufacture at a magnification of (c) x250 and (d) x2000.

Sprayed GMS granules (Figure 4.5) were smooth and spherical and exhibited better flow properties post-spraying than the GMS powder. Post 2 hours manufacture, they appeared

as non-aggregated, compact microparticles with no cracks observed (Figure 4.5a-b). The smooth homogeneous surface corresponds to the α-form of GMS observed by Garti and Sato (1988). The surface of the sprayed GMS granules 30 hours post manufacture, is not as smooth as the surface of the GMS granules 2 hours post-manufacture, where the surface has a slightly rougher texture (Shimpi et al., 2004). Suggesting there may be a transition occurring from the α-form to β-form of GMS, XRPD was undertaken as evidence to support this observation in Figure 4.7.

X-ray powder diffraction (XRPD) was used to determine the crystalline state of GMS both as a raw material and as a hot-melt and sprayed mixture and are shown in Figures 4.6 and 4.7.

Patterns were collected from the same samples and held on the instrument between data collections this eliminated changing diffracting volumes from causing differences in the diffractogram.

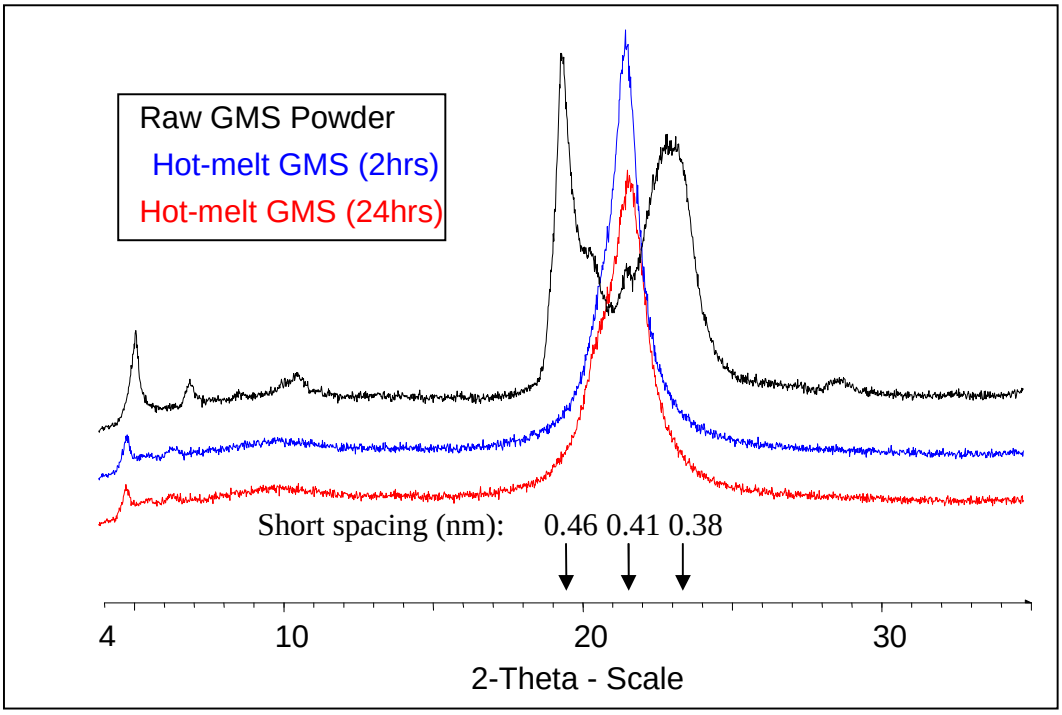


Figure 4.6. Diffractograms of hot-melt GMS over 24hrs

From Figure 4.6, GMS raw powder has two distinct peaks at 2θ angles of ~19.5º (0.46nm) and 23.5º (0.38nm) which corresponds to the β-form of GMS identified by Yajima et al (2002). However, for hot-melt GMS there is only one distinct peak at 2θ angles of ~21.5º (0.41nm) corresponding to the α-form of GMS (Garti & Sato, 1988; Yajima et al, 2002). This indicates that melting and cooling of GMS has a significant effect on the crystal packing within the GMS lattice. In addition, after 24 hours the peak intensity of the hot-melt GMS decreases, indicating there maybe a further physical transformation of GMS (Phajongwiriyathorn, 2008).

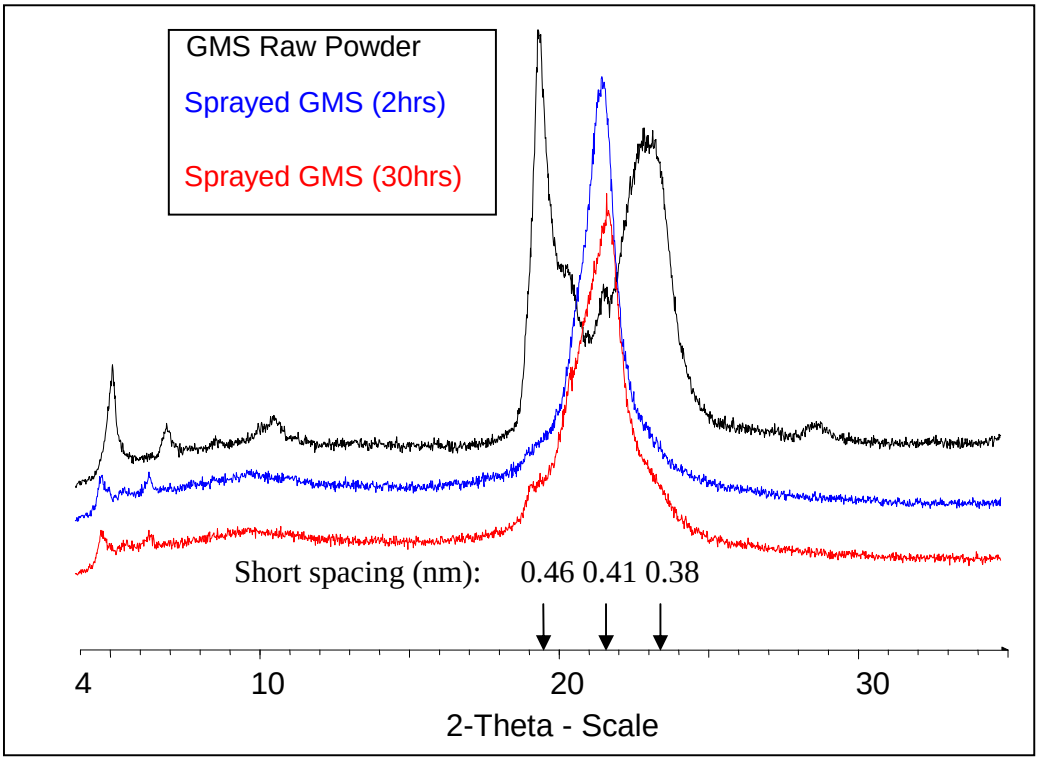


Figure 4.7 Diffractograms of sprayed GMS over 30 hours

From Figure 4.7, the sprayed GMS exhibits one main distinctive peak at 2θ angles of ~21.5º (0.41nm) indicating the α-form of GMS but also has two shoulder peaks corresponding to the β-form of GMS. This suggests that the sprayed GMS comprises primarily of the α-form of GMS but has begun to exhibit polymorphic changes indicating that GMS is reverting back into the more stable β-form. This transition becomes even more pronounced after 30hrs and is characterised by a decrease in the primary peak and an increase in the shoulder peak intensities.

4.3.2 The Effect of adjustable spray gun components

4.3.2.1 Effect of the Adjustment Screw (Flow rate)

The PSD of sprayed GMS granules are shown in Figure 4.8.

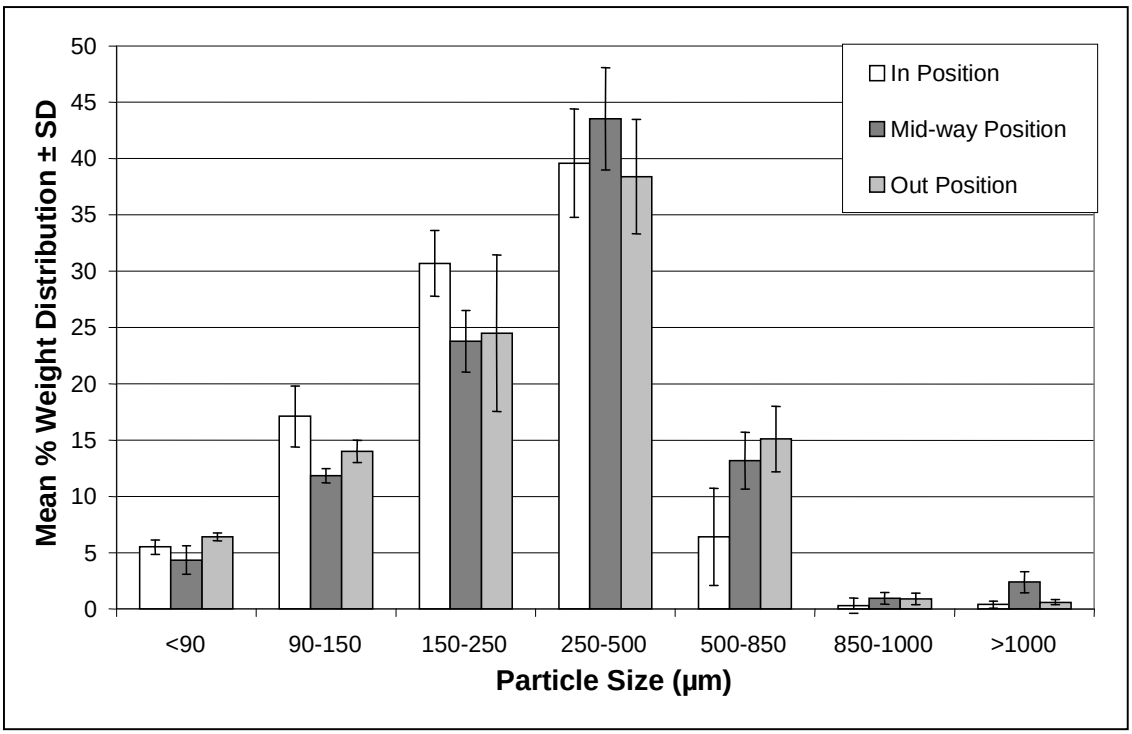


Figure 4.8 Particle size distribution of sprayed GMS granules when adjusting the quantity being sprayed (n=3)

From Figure 4.8, there is no significant difference (2-way ANOVA; $p>0.05$) in the particle size distribution of GMS granules when the adjustment screw position is altered on the spray gun. This indicates the quantity of molten wax being atomised from the spray gun does not have an impact on the resultant granule distribution size.

4.3.2.2 Effect of the Adjustment Knob (Air pressure)

The PSD of sprayed GMS granules are shown in Figure 4.9.

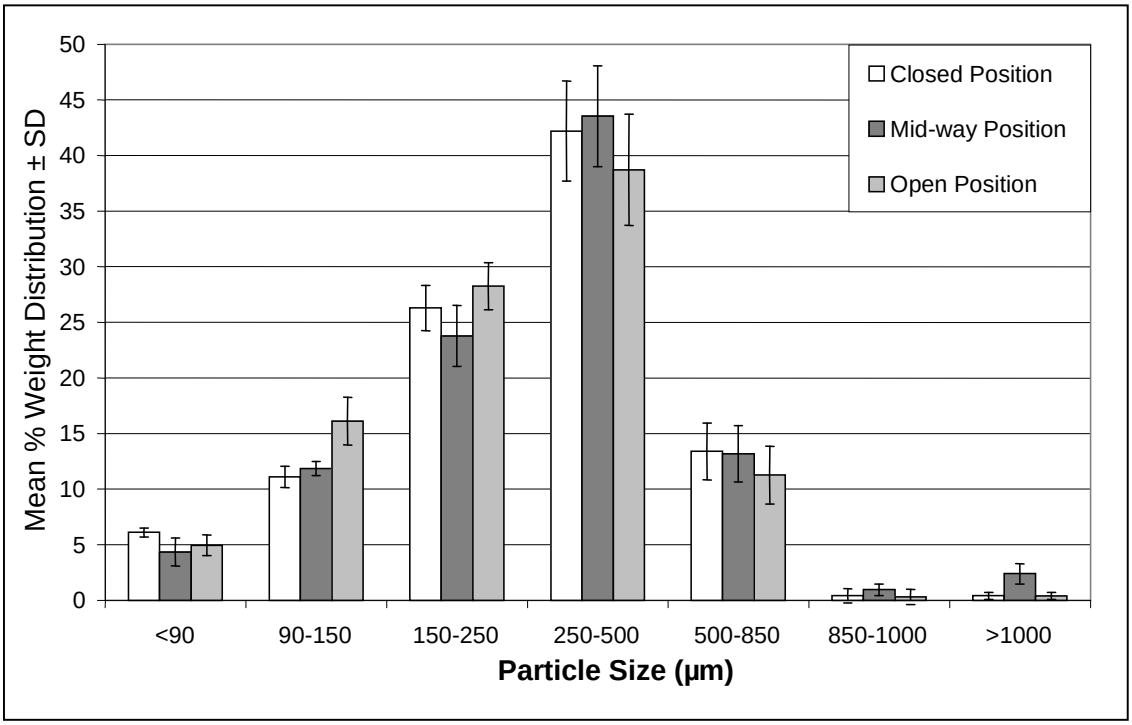


Figure 4.9 Particle size distribution of sprayed GMS granules when adjusting the spray gun flow rate (n=3)

From Figure 4.9, there is no significant difference (2-way ANOVA; $p>0.05$) in the particle size distribution of GMS granules when the adjustment knob position is altered on the spray gun. This indicates that increasing or decreasing the flow directed through the spray gun does not have an impact on the resultant granules size.

4.3.2.3 Effect of the Butterfly Nozzle (Spray pattern)

The PSD of sprayed GMS granules are shown in Figure 4.10.

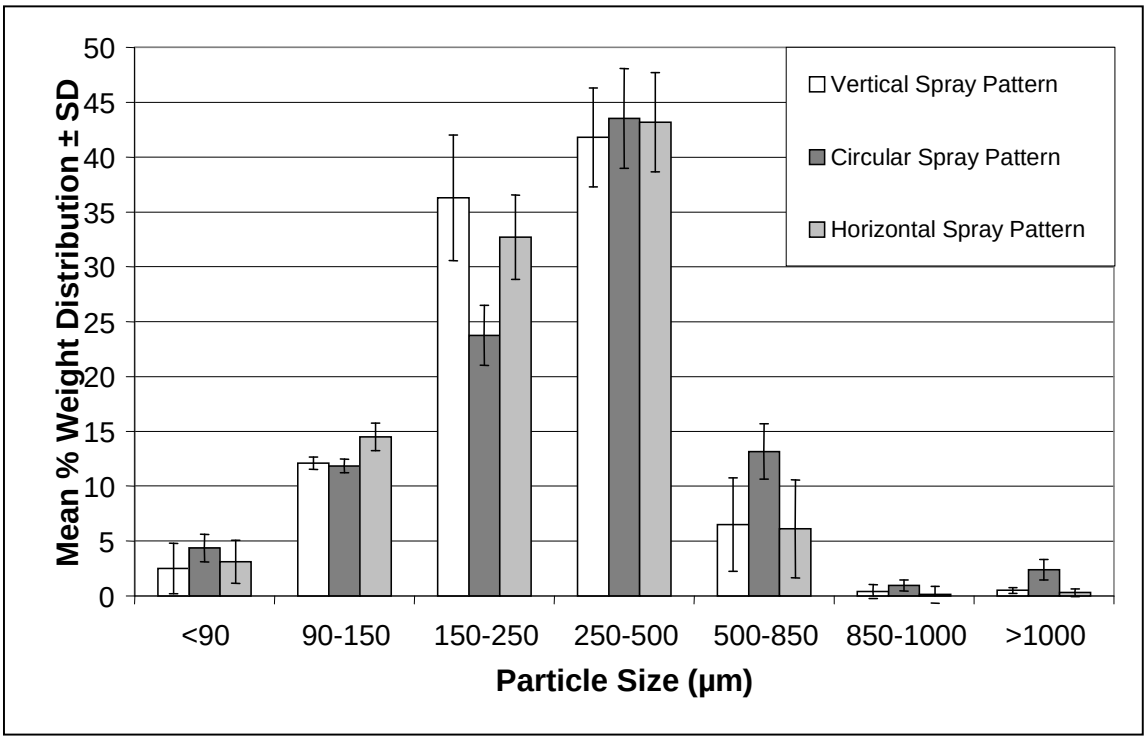


Figure 4.10 Particle size distribution of sprayed GMS granules when altering the spray pattern (n=3)

From Figure 4.10, there is no significant difference (2-way ANOVA; $p>0.05$) in the particle size distribution of GMS granules when the butterfly nozzle is altered on the spray gun. This indicates that the spray pattern chosen on the spray gun does not have a significant impact on the resultant granules size.

4.3.3 The evaluation of formulation and manufacturing variables in the production of wax granules utilising experimental design

The experimental factors and responses and the corresponding results for the factorial design are illustrated in Table 4.4.

Table 4.4 Experimental design output

Run	A	B	C	D	Sieve Analysis Mean PS (µm)	Mastersizer d(0.5) ±SD (µm) (n=1)	Mastersizer Span Value (n=1)	Bulk Tap Density (100 taps)
1	10	3	170	3	437.5	459.6	2.3	0.59
2	10	1	170	1	280	252.0	2.0	0.62
3	30	3	230	3	265	256.5	1.4	0.66
4	30	1	230	1	250	234.8	2.3	0.64
5	20	2	200	2	300	324.0	2.2	0.74
6	20	2	200	2	312.5	230.0	1.4	0.71
7	30	3	170	1	260	246.3	1.0	0.67
8	10	1	230	3	180	162.8	2.2	0.53
9	20	2	200	2	300	372.3	2.6	0.70
10	30	1	170	3	291	294.7	1.6	0.65
11	20	2	200	2	300	236.3	1.3	0.68
12	10	3	230	1	250	258.5	0.9	0.66
13	20	3	200	2	315	378.9	2.5	0.7
14	20	3	200	2	300	372.3	2.3	0.7
15	20	1	200	2	333	230.0	1.5	0.7
16	20	2	200	2	300	242.2	2.6	0.71
17	20	2	200	2	260	238.1	1.5	0.71
18	20	2	200	2	350	359.7	2.4	0.71

The results from the experimental design are discussed below.

The PSD of sprayed wax granules are shown in Figure 4.11.

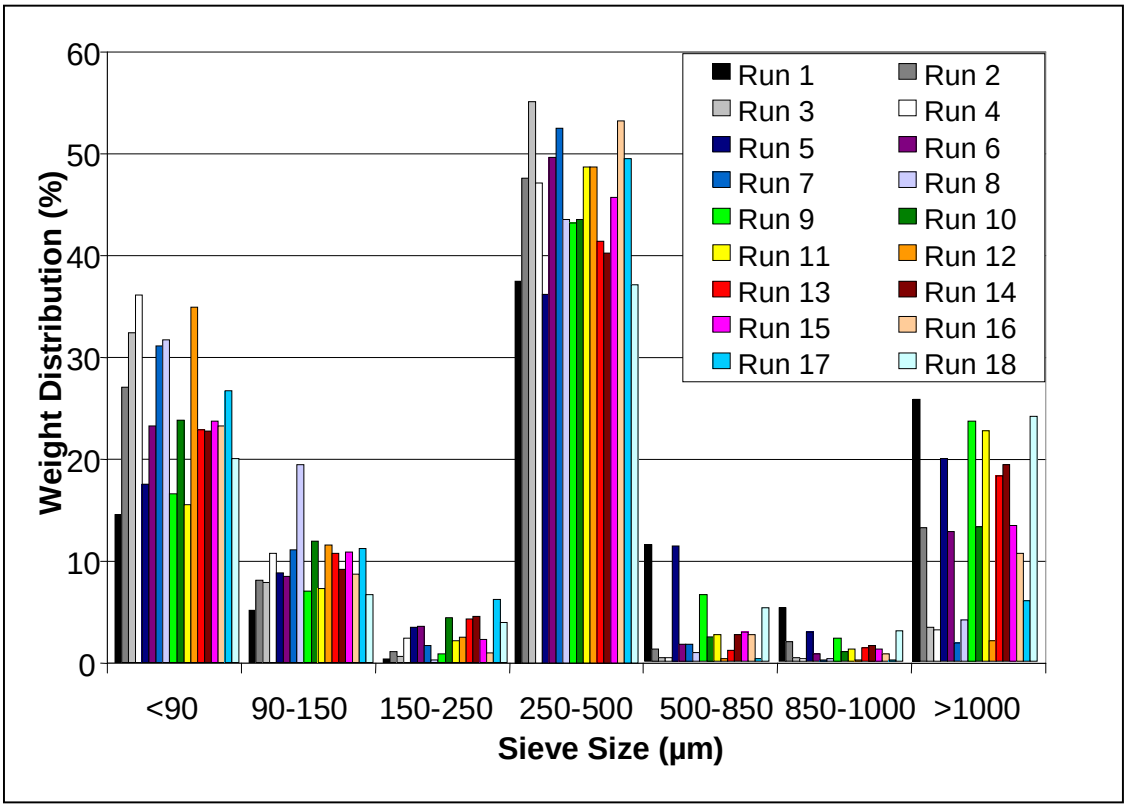


Figure 4.11 Particle size distribution of all sprayed granule formulations produced for the design of experiments (n=1).

From Figure 4.11, there appears to be no significant difference in the particle size distribution of the various batches of sprayed granules (Two-way ANOVA; $p>0.05$). The distribution is not Guassian in nature, indicating the data is not normally distributed. The data has a comb distribution indicating the bar range may be too narrow and is slightly skewed to the left. The most prevalent size fraction is 250-500µm which correlates with the preliminary sprayed GMS study (Figure 4.1).

Three populations of particle size distribution are observed in figure 4.11. The effect could be attributed to the spray gun nozzle design as a direct correlation has been documented between nozzle type and the resultant particle size (Nuyttens et al., 2007; Spray systems Co, 2009). Due to the nature of spray congealing the optimal nozzle design should also be temperature controlled to maintain the temperature at the nozzle orifice to improve the particle size uniformity (Mashke et al., 2007). An air-assisted external mixing butterfly nozzle (figure 4.12) requires further characterisation to determine its robustness and reproducibility on heating. The 'butterfly' shape may promote greater heat loss rates due to its larger surface area and the continuous flow of air at the nozzle orifice may also reduce the nozzle temperature, impacting the temperature at which atomisation is taking place. This may be contributing to the various PSD populations obtained during the DOE.

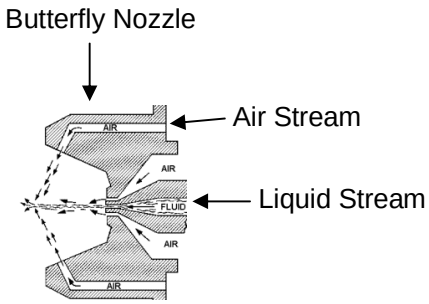


Figure 4.12 Illustration of an air-assisted external mixing nozzle.

Potential issues with particle shape were eliminated by GMS SEM images (figure 4.5) confirming the sprayed material to be spherical and not irregular in shape. However, sieve openings can be unequal in size and again prolonged shaking would impact on amount of particles passing through. Complete sorting of a given size range is rarely

achieved which is why it is important to standardise the sieving procedure due to the Weibull distribution (Allen, 1997; Aslan et al., 1998).

The angle of repose was also calculated for the 18 formulations (Figure 4.12).

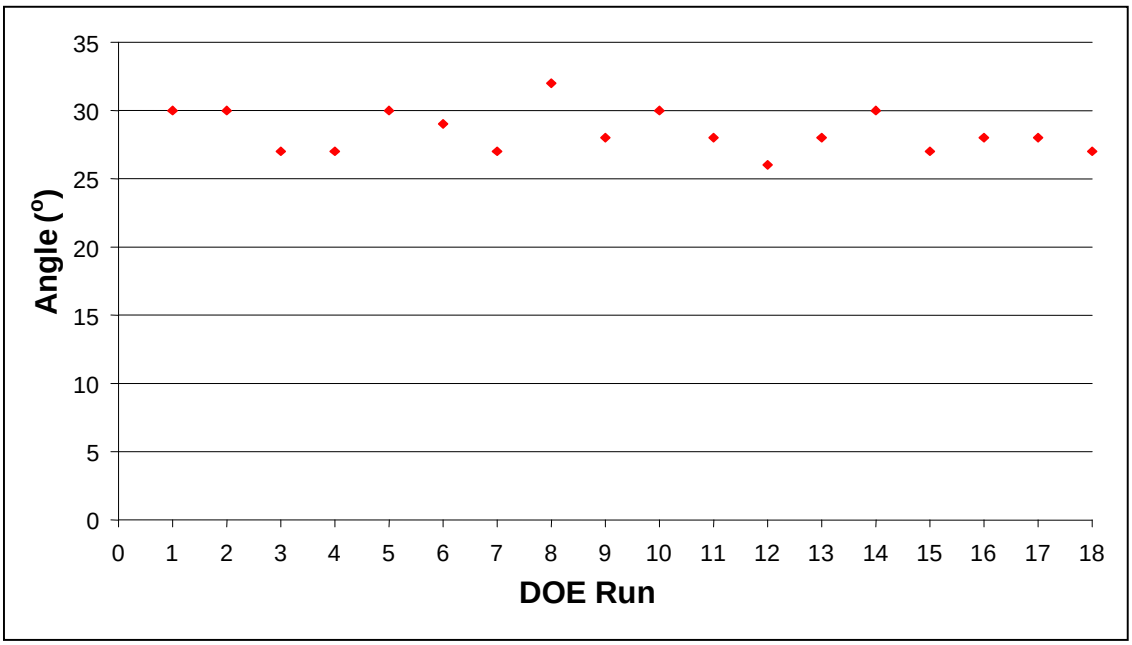
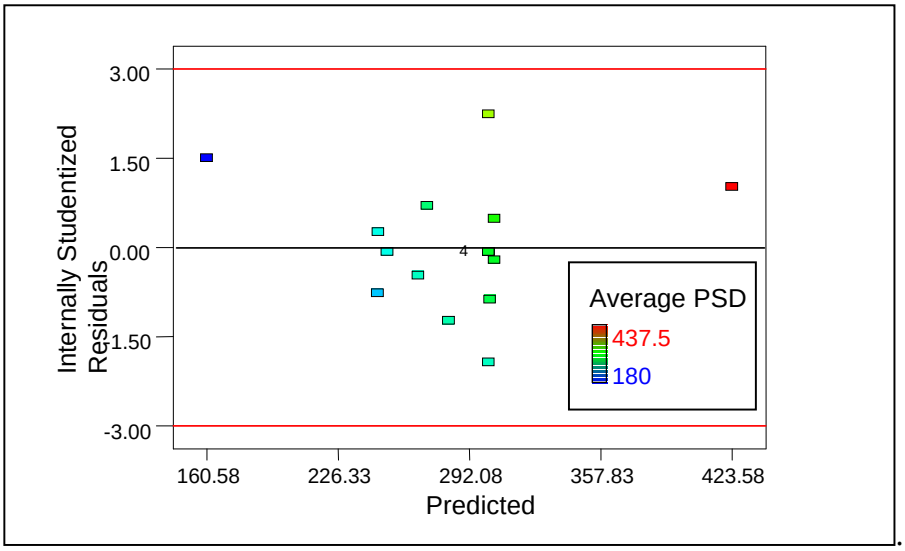


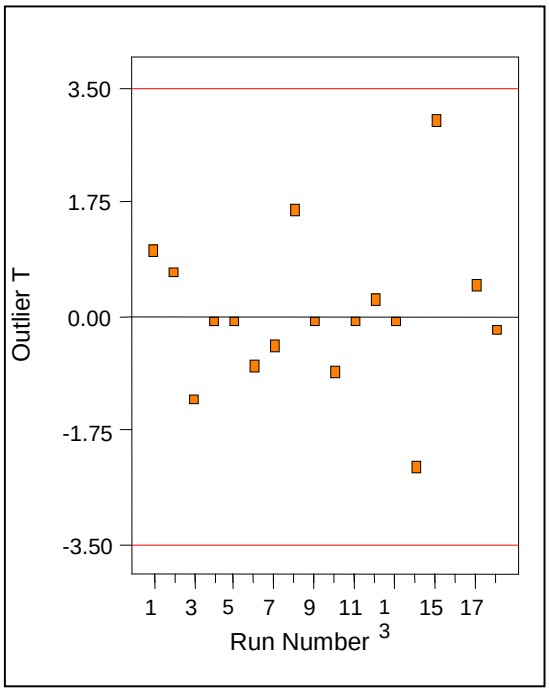
Figure 4.13 Scatter plot illustrating the angle of repose for the granules manufactured during the design of experiments

No significant difference was determined from the results of figure 4.13 (Two-way ANOVA; $p>0.05$), indicating the factors investigated in the design of experiments did not affect the flow properties of the resultant GMS granules.

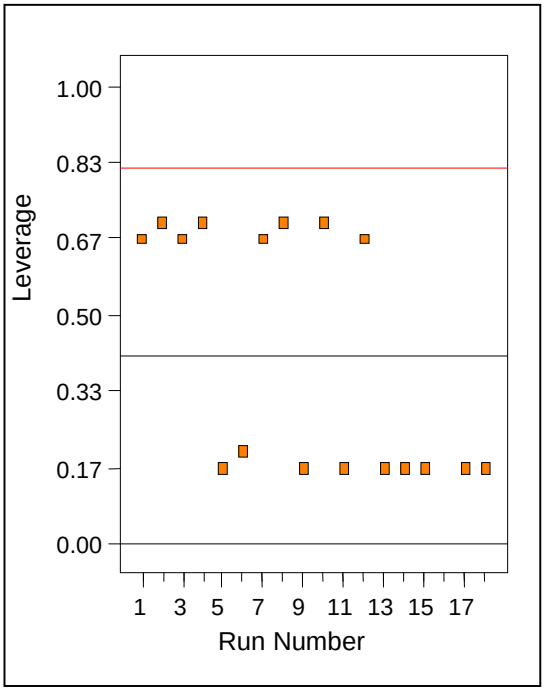
Utilising the experimental response data in figure 4.4, the following graphical diagnostics were obtained in figure 4.14


3.00
1.50
0.00
-1.50
-3.00
Internally Studentized Residuals
4
Average PSD
437.5
180
160.58
226.33
292.08
357.83
423.58
Predicted

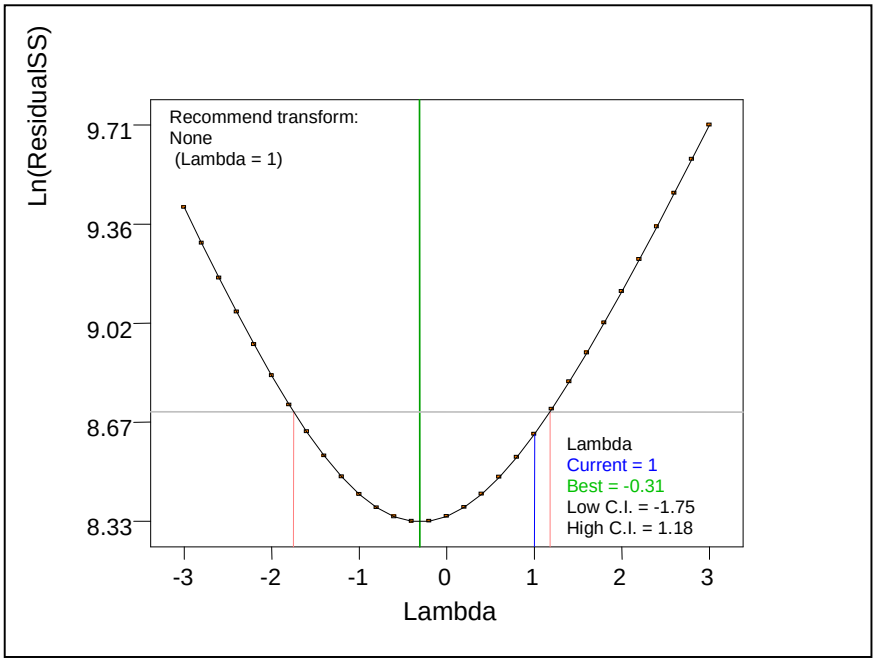
(a)


3.50
1.75
0.00
-1.75
-3.50
Outlier T
1
3
5
7
9
11
1
15
17
Run Number
3

(b)


1.00
0.83
0.67
0.50
0.33
0.17
0.00
Leverage
1
3
5
7
9
11
13
15
17
Run Number

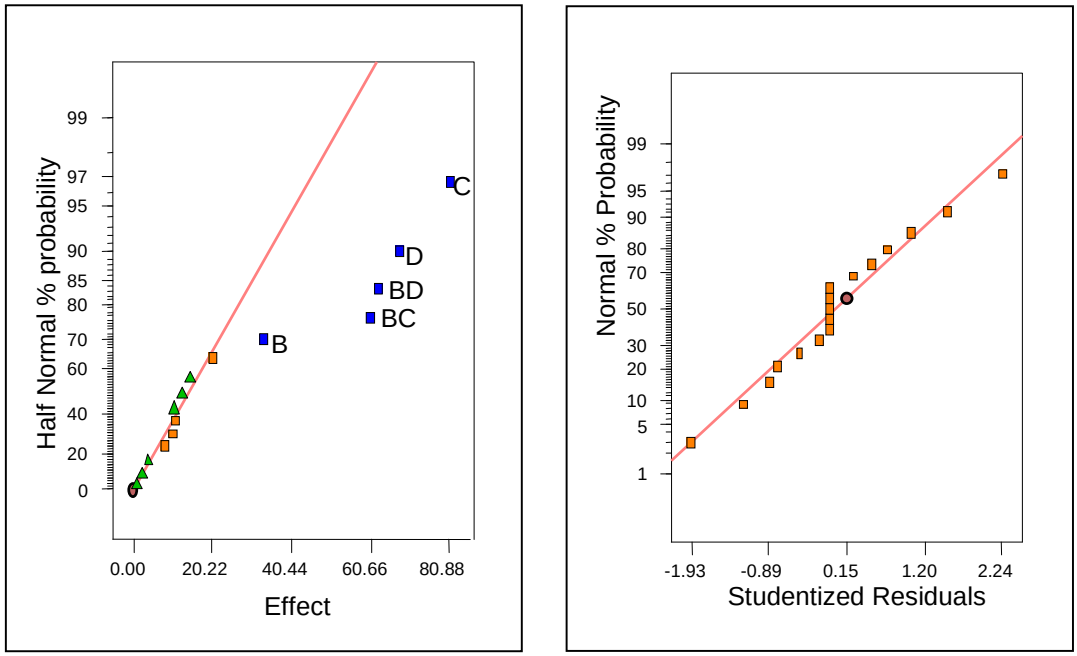
(c)



(d)

Figure 4.14 Validation of model for sieve analysis response factor: studentised residuals versus predicted values (a); outlier T plot (b); leverage plot (c); box-cox plot for power transforms (d).

From Figure 4.14a, there is an even spread of studentised residuals representing a constant error. The outlier T plot (Figure 4.13b) demonstrates that there were no outliers as all the values were within the range -3.50 to 3.50. Figure 4.14c represents the degree of leverage associated with each run. As none of the data points are close to 1 the model is not influenced by any individual runs. The box-cox plot (Figure 4.14d) indicates that no transformation is required to improve statistical analysis, as the range from the minimum to the maximum confidence interval is not greater than 3 (Stat-ease).



(a) (b)

Figure 4.15 Half normal (a) and normal (b) percentage probability plots for sieve analysis

The half normal probability plot (Figure 4.15a) obtained for the sieve analysis response factor indicates two experimental factors significantly impact on the resulting particle size of the sprayed wax granules. These factors include the voltage (C) and nozzle size (D). In addition, interactions where also identified between factors BC and BD (figure 4.16-4.17). The analysis of variance data for the response factor; average PSD (sieve analysis) is represented in Table 4.5.

The normal probability plot (Figure 4.15b) demonstrates that the sieve analysis data follows a straight line. This indicates that no abnormalities were found within the data set and the residual values were normally distributed (Gardiner & Gettinby, 1998).

Table 4.5 ANOVA results for response factor: Sieve analysis mean value

Analysis of variance table						
Source	Sum of Squares	DF	Mean Square	F-value	P-value	
Model	39417.38	5	7883.48	14.09	0.0003	***Significant***
B	2227.78	1	2227.78	3.98	0.0739	*Not Significant*
C	13081.53	1	13081.53	23.38	0.0007	***Significant***
D	9296.22	1	9296.22	16.62	0.0022	***Significant***
BC	7411.53	1	7411.53	13.25	0.0045	***Significant***
BD	7906.53	1	7906.53	14.13	0.0037	***Significant***
Curvature	2672.42	1	2672.42	4.78	0.0537	*Not significant*
Residual	5594.97	10	559.50			
Lack of Fit	1399.13	4	349.78	0.50	0.7382	*Not significant*
Pure Error	4195.83	6	699.31			
Cor Total	47864.76	16				

From Table 4.5, the model is statistically significant and the lack of fit is not significant relative to the pure error which indicates the ANOVA model fits the data and is suitable for statistical analysis. Voltage (C), nozzle diameter (D) and interactions between wax type-voltage (BC) and wax type-nozzle diameter (BD) are the statistically significant factors that impact upon the mean particle size of the resulting sprayed GMS granules (p-value < 0.05).

The voltage directly controls the speed the air fan rotates and draws air into the spray system, impacting the air flow rate (table 4.2). The results confirm there is a direct correlation between the air flow rate and the resultant sprayed particle size. Due to the interaction with the wax type the extent of the change will be dependent on the type of wax system utilised. Further work would need to be undertaken to define the mechanisms

contributing in the different wax types. Initial review of the formulation parameters would include viscosity, surface tension and wax composition.

No significant curvature was identified, indicating the response at the centre point correlates to the average responses of all factorial runs. This indicates a linear relationship exists between the mean centre point and all other mean factor points within the experimental design. No model/data set adjustments are required due to nonlinearity (O'Brien & Wang, 1996).

From figure 4.15a, the increase of the temperature between 10-30^{o}C above the waxes melting temperature (factor A) had no significant effect on the response factors for the sprayed wax granules produced. Increasing the temperature of a liquid can decrease the viscosity and surface tension, high surface tension and viscosity can reduce the spray angle of the material and increase the particle size produced (Juslin et al., 1995; Lefebvre, 1989; Maschke et al., 2007). However, in this instance the viscosity and surface tension of the waxes must be low as increasing the temperature did not significantly decrease the particle size of the sprayed material.

The wax type also has no significant effect on the particle size when modulated independently to other factors (Table 4.5). This may also relate to a non-significant difference between the wax viscosities and surface tensions at these temperatures. The waxes would behave in a similar manner during spraying and yield similar particle size distributions.

The interaction effect of BC and BD on the average particle size distribution (PSD) is illustrated in Figure 4.16.

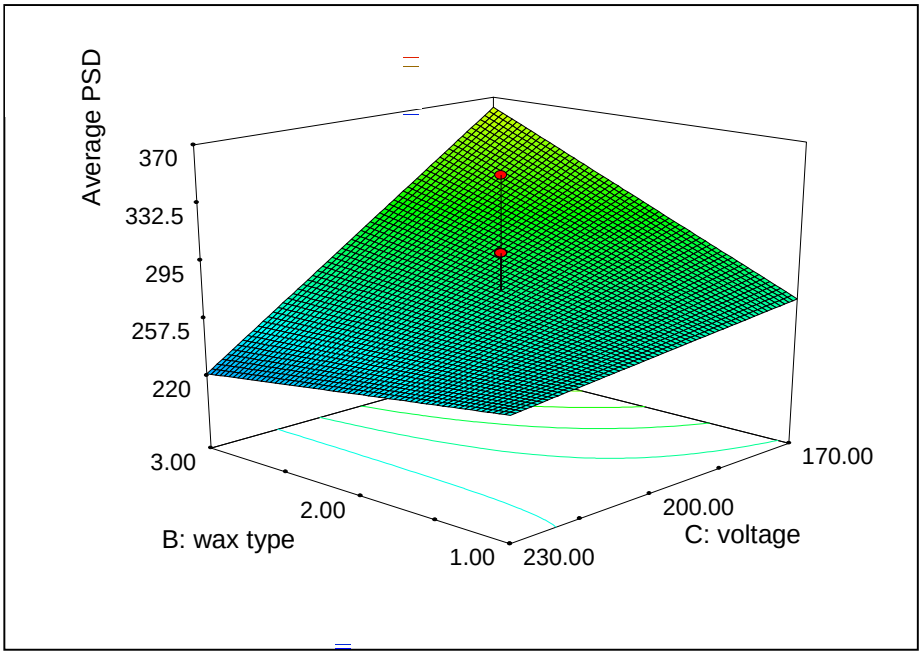


Figure 4.16 Effect of experimental factors on the sieve analysis response factor: voltage and wax type interaction plot.

The 3D surface plot of the interaction identified between wax type and voltage has a linear relationship with the mean particle size of the sprayed waxes (figure 4.16). When modulating only the wax type incorporated into the spray system there was no significant effect on the resultant particle size. However, if the wax type and the voltage were simultaneously modulated in the spray system there is a significant effect on the resultant particle size of the sprayed wax.

It appears as the voltage of the spray system is decreased the average particle size of the sprayed wax increases, although the extent to which it is increased is also dependent on the type of wax being sprayed. The voltage directly controls the speed the air fan rotates and draws air into the spray system, impacting the air flow rate. An increase in the air flow rate would build pressure at the spray nozzle opening, enabling a greater rate of atomization and production of a finer spray with a smaller average particle size (Ilic et al., 2009; Lefebvre, 1989; Tajber et al., 2009; Zhang & Youan, 2010). Extremely low voltages would cause a slow flow rate and a 'spluttering' effect would be observed with larger particles produced.

Molten wax solutions may behave differently under varying pressures and are dependent on physical properties of the wax and chemical composition (Cusimano & Becker, 2006; Ilic et al., 2009).

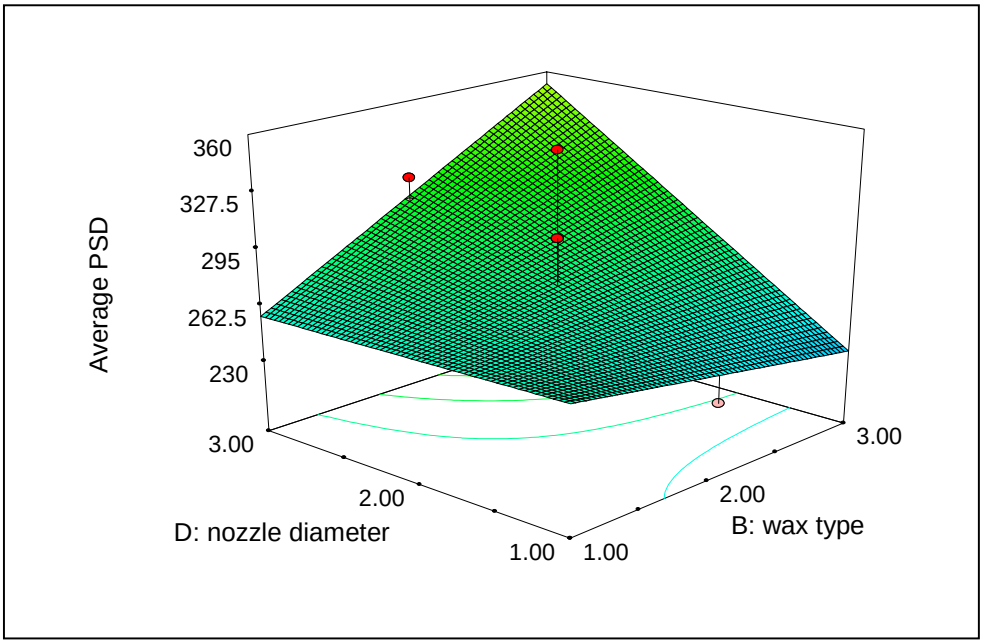


Figure 4.17 Effect of experimental factors on the sieve analysis response factor: nozzle diameter and wax type interaction plot.

In Figure 4.17, the average PSD appears to increase as the nozzle size of the spray system is increased, although the extent of this increase is again dependent on the type of wax being sprayed. The smaller the nozzle size the greater the pressure at the nozzle opening during atomization of the molten wax, as a result this energy causes the bulk liquid to be further broken up into finer particles and leads to a smaller average PSD (Lefebvre, 1989).

Varying molten wax solutions have been demonstrated in literature to have a significant effect on the resultant sprayed particles, as well as nozzle size (Cusimano & Becker, 1968; John & Becker, 1968). The mean diameters and volume-surface diameters of the sprayed material yielded were affected and a direct impact on the dissolution rates of

sprayed material incorporating drug was reported due to the physical properties of the wax and the wax chemical composition.

Three of the experimental responses did not fit a model that would satisfy the ANOVA, these responses included the Mastersizer d(0.5), span value and bulk tap density (Table 4.6-4.8).

Table 4.6 ANOVA results for response factor: Mastersizer d(0.5)

Analysis of Variance table						
Source	Sum of squares	DF	Mean square	F-value	p-value	
Model	0.00	0				
Curvature	85.87	1	85.87	0.015	0.9031	*Not significant*
Residual	83961.78	15	5597.45			
Lack of Fit	71046.31	9	7894.03	3.667	0.0639	*Not significant*
Pure Error	12915.47	6	2152.58			
Cor Total	84047.65	16				

From Table 4.6, the model source has no calculated values indicating the ANOVA model does not fit the Mastersizer d(0.5) data, therefore statistical analysis of the experimental variables for this response factor was not possible.

Table 4.7 ANOVA results for response factor: Mastersizer span value

Analysis of Variance table						
Source	Sum of squares	DF	Mean square	F-value	p-value	
Model	0.00	0				
Curvature	0.11	1	0.11	0.931	0.3498	*Not significant*
Residual	1.75	15	0.12			
Lack of Fit	1.32	9	0.15	2.035	0.1999	*Not significant*
Pure Error	0.43	6	0.07			
Cor Total	1.86	16				

From Table 4.7, the model source has no calculated values indicating the ANOVA model does not fit the Mastersizer span value data, therefore statistical analysis of the experimental variables for this response factor was not possible.

Table 4.8 ANOVA results for response factor: bulk tap density

Analysis of Variance table						
Source	Sum of squares	DF	Mean square	F-value	p-value	
Model	0.00	0				
Curvature	0.01	1	0.01	7.513	0.0152	*Significant*
Residual	0.03	15	0.00			
Lack of Fit	0.03	9	0.00	9.564	0.0062	*Significant*
Pure Error	0.00	6	0.00			
Cor Total	0.04	16				

From Table 4.8, the model source has no calculated values indicating the ANOVA model does not fit the bulk tap density data, therefore statistical analysis of the experimental variables for this response factor was not possible.

Table 4.9 Experimental design output for centre point experiments

Run	**A**	**B**	**C**	**D**	**Sieve Analysis Mean PS (µm)**	**Mastersizer d(0.5) (µm) (n=1)**	**Mastersizer Span Value (n=1)**	**Bulk Tap Density (100 taps)**
5	20	2	200	2	300	324	2.218	0.74
9	20	2	200	2	300	242.2	2.569	0.7
11	20	2	200	2	300	281.2	1.317	0.68
16	20	2	200	2	300	242.2	2.569	0.71
17	20	2	200	2	260	238.1	1.472	0.71
18	20	2	200	2	350	359.7	2.355	0.71

By looking at the centre point data from the design of experiments (Table 4.9), the d(0.5) and span value results obtained using laser diffractrometry (Mastersizer) have high variability and no matter how many more experiments had been carried out no statistical model would have satisfied this data. The Mastersizer d(0.5) could differentiate between the various size fractions utilising isopropyl alcohol as the dispersion media, however the d(0.5) values were significantly higher than mean sieve analysis result obtained by manual sieving. This initially suggests the Mastersizer experimental protocol was not adequate in analysing the particle size of the sprayed granules and an alternative dispersion system may need to be developed.

When developing the method to utilise a light scattering technique, an important parameter used in the calculation of the particle size (Mie theory) is the refractive index of the particle and dispersion medium. If the dispersion medium is not optimised for the particles being analysed or an estimated refractive index was utilised for the wax, the estimated optical properties may not be truly representative of the sample, in accordance with Stokes equation (Roach, 2003; Smith & Mullins, 2000). However, the effect of the optical properties on the particle size distribution for particles greater than 100µm has been shown to be negligible (Wedd, 2003). From figure 4.11, approximately 30% of the sprayed material is below 100 µm which could significantly impact the mean values calculated.

Particle size analysis via laser diffraction has a further limitation as both the Mie and Fraunhofer theory assumes the particle is spherical in nature. The SEM results (Section

4.3.1) confirmed sprayed GMS material to be spherical in nature but the slight solubility of GMS in IPA may have impacted on this assumption. Visually assessing the GMS samples post analysis would identify whether the particle shape has been impacted due to the chosen dispersion medium. Non-spherical particles have been documented to produce inaccurate results utilising laser particle sizing techniques (Roach, 2003; Xu & Guida, 2003). Other possible limitations for the inconsistent laser diffraction analyses include secondary scattering, the particle surface not being optimal or different degrees of aggregation being exhibited under test conditions, all of which increase in error when measuring particles smaller than 50 µm, (ISO 13320-1, 1999).

The bulk tap density results do not vary much between batches for any of the experiments undertaken in the experimental design. This indicates that the shape of the particles formed is reproducible and this response is factor independent explaining the non-significance of the models with which the data was fitted.

4.4 Conclusions

An agitated hot-melt spray system can be used to produce spheroid and smooth GMS granules. The thermal properties of the GMS granules changed on storage, XRPD confirmed this was due to a polymorphic transformation of the GMS from unstable α-form to the stable β-form with time. The surface physical characteristics were also altered in association with the polymorphic transformation which was dependent on the storage time and conditions. Complete conversion to the more stable polymorph was not achieved during the time period investigated as both polymorphs were detectable in the

thermogram, the recrystallisation rate was increased under accelerated temperature conditions (Windberg et al., 2009).

DSC, XRPD and SEM were useful techniques in detecting polymorphic transformations within the sprayed GMS granules (Garti & Sato, 1988; Laine et al., 1988; Sutanata et al., 1994c; Yajima et al., 2002). Both hot-melt and sprayed GMS samples show evidence of polymorphic transformation and suggest, when monitored for over 24hrs, that the polymorphic form will revert back to its more stable β-form of GMS with more time (Grant, 1999). Both sprayed and hot-melt GMS formulations appeared to be a mixture of the α- and β-form of GMS polymorphs with the α-form still the most predominant polymorph present in the mixture 30 hours post-manufacture (Yoshino et al., 1984). In my samples, complete transformation of GMS to the β-form is unknown however, sprayed GMS continued to exhibited transformation from the α-form to the β-form of GMS after 108 days.

When monitored up to 24 hours post-manufacture, sprayed GMS appeared to exhibit a faster transition rate from the α-form to the β-form compared to the hot-melt GMS formulation. Variation in the annealing temperature of both manufacturing techniques could contribute to this occurrence (Phajongwiriyathorn, 2008; Yajima et al., 2002). During wax fusion, the molten wax is cooled from 80^{o}C to room temperature when transferred directly into the hard gelatin capsules. During hot-melt spraying the cooling rate is faster and the granules solidified quicker due to the large surface area of granules

being produced from atomisation and exposure of the granules to carbon dioxide post-spraying on descent.

For wax-based matrix systems, polymorphic transitions can impact the dissolution properties of the wax. For example, phase transitions, changes in physical structure or chemical composition can increase the drug release rate (Shimpi et al., 2004; Sutanata et al., 1994a; Sutanata et al., 1994b) whereas decreased rates of drug release from wax matrix formulations have been observed upon ageing of the formulation during storage (Freitas & Muller, 1999; Jenning & Gohla, 2000; Phajongwiriyathorn, 2008; Yoshino et al., 1981). To prevent these occurrences, fast transition to the most stable polymorphic form of the wax component is considered advantageous for prolonged storage of the final product.

In the case of GMS, the β-form of GMS is considered more stable as it has a higher melting point, higher density and is a poorer foaming and wetting agent than the α-form. Therefore it would be anticipated that aged GMS formulations would have a slower drug release rate than fresh GMS formulations. Optimal transformation conditions can be determined by heat treatment development to transform the GMS to its most stable form (Phajongwiriyathorn, 2008; Yajima et al., 2002). In addition, the type of drug incorporated can have an effect on the physicochemical properties of a GMS based matrix formulation and shall be investigated in Chapter 5.

Stress testing can be undertaken, increasing the temperature in 10^{o}C increments above 40^{o}C to determine whether the rate of polymorphic transition further increases. However, consideration to the melting point of GMS would be needed as the melting point is at 60^{o}C. A further study could involve storing sprayed GMS at 50^{o}C/75RH at T0, T3 and T6 months (Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, 2009). Spraying other glycerides for use as a hydrophobic matrix could be undertaken to characterise their recrystallisation behavior, the literature indicates chain-length may have a significant impact on the rate of polymorphic transformation. Tristearin, with a long fatty acid chain, is able to achieve complete transformation to the stable β-form within 48hours in accelerated storage conditions (Windberg et al., 2009). A greater understanding of the solid-state behavior of glycerides both during storage and processing via a hot-melt spray system enables predictable dosage forms to be developed and minimises undesirable changes.

Initial investigations of the hot-melt spray system involved a one factor at a time (OFAT) approach to determine any effect of modulating the adjustable parameters of the spray gun on the atomisation process and the resultant particle size distribution. The adjustable components would impact the air pressure, liquid flow and the alignment of the spray.

From the study, the modulation of spray gun parameters had no significant effect on the particle size and was considered an unusual observation. The literature documents the correlation between spray system variables such as pressure and liquid flow rate impacting on the quality of atomisation and its effect on the particle size distribution of

the spray (Ilic et al., 2009; Lefebvre, 1989; Tajber et al., 2009; Zhang & Youan, 2010). It may be the variation between the spray gun settings was not sufficient for a significant difference in comparison to the publications. Alternatively these factors may not be of significance modulated independently. As a result, a design of experiments was developed to investigate the remaining parameters and determine whether interactions between factors may have a significant effect on the particle size of the sprayed GMS.

Design of experiments proved to be a useful tool in determining the importance of factors on the manufacturing process and resultant sprayed granules. The experimental design enabled relationships between response factors and variables to be established, as well as interactions to be determined. The significant individual factors affecting the spray system included the voltage and nozzle diameter. Interactions were observed between factors including the wax type-voltage and wax type-nozzle diameter.

The identification of factor interactions highlighted the importance of experimental design in the formulation development. In OFAT experiments, wax type would have been dismissed as not significant in the modulation of the particle size, however, when in combination with other factors it has a significant impact and requires consideration for formulation optimisation.

Viscosity and surface tension have been identified to significantly impact on the particle size. However, these variables do not need to be considered for a single component molten wax system, as the viscosities are low. Consideration of viscosity and surface

tension will be needed during the development of sprayed delivery systems comprising of two or more materials, as some excipients can thicken liquids and directly impact product performance (Attwood & Florence, 2008). High viscosity liquids can have a narrower spray angle when compared to water or lower viscosity liquids (Maschke et al., 2007; Nuyttens et al., 2007).

Not all response factors chosen for the design of experiments were successful due to the large variation with the data set or due to factor independence. The experimental design also highlighted the lack of correlation between the laser diffractometry method and sieving method in sizing the sprayed granules. Both particle sizing methods could differentiate between various size fraction but high variablility of the d(0.5) values were observed from the experimental data. The determinations are correct in accordance with the procedures but limitations of each method used to analyse the sprayed material results in different particle size distributions being obtained.

A confirmatory technique that could be utilised during the development of particle size analysis includes image analysis (Arasan et al 2011) or a microscopic method. However, both these methods depend on a reliable dispersion technique and are time consuming in comparison to laser diffraction and sieving techniques.

This indicated the importance of further method development for the Mastersizer to improve the accuracy of the particle size measurements, an inaccurate analytical method for particle size analysis has serious implications due to the direct correlation to

dissolution via the Nernst-Brunner and Levich modification of Noyes-Whitney (Passerini et al., 2010; Sheng et al., 2008). A validated Malvern Mastersizer method would be extremely useful not only for formulation and analysis optimisation but during routine maintenance of the spray nozzle performance both at bench scale and commercial manufacture (Nuyttens et al., 2007) and finished product testing.

The mean yield of sprayed GMS granules obtained for hot-melt spray system was 80%. Through continuous improvement a more efficient and economic process could be developed to improve the total yield. For example, the spray chamber could be placed above the spray system with a heated jacket to enable controlled and consistent heating. A gravitational feed system could be developed into the spray gun to minimise residue waste in the spray chamber.

Potentially the rate-limiting steps for the hot-melt spray system would be the small batch size achievable with the current spray chamber. To achieve scale up of a hot-melt spray system the sprayed product characteristics at bench scale would need to be replicated at a commercial scale. Additionally, an intermediate scale and commercial scale spray system would be desirable with similar equipment components which correspond to regulatory requirements.

Critical parameters include nozzle type, fluid flow rate, atomisation pressure on spray pattern uniformity, drop size and velocity (Spray systems Co®, 2009). The type and size of nozzle being used would be the primary consideration as there are a variety of nozzle

sizes and styles that may function in different ways (Passerini et al., 2010; Nuyttens et al., 2007). The nozzle size simply can not be scaled up as this would alter the PSD of the sprayed material, impacting on product quality and consistency. Several of the same size air-assisted external mixing nozzles would have to be mounted and aligned via a heated fluid line. The alignment of the nozzles must also be parallel to optimise spraying capacity. Spray drying and spray congealing techniques have overcome such issues and are scaled up successfully (Maschke et al., 2007; Passerini et al., 2010; Nuyttens et al., 2007).

Other products could also be developed utilising the hot-melt spray system and commercially produced on a larger scale. Formulation considerations to achieve this would include viscosity, surface tension and specific gravity characterisation of the materials and whether they are heat stable (Chapter 5). In addition, the type of organic solvents, metals, corrosive and abrasive materials that may be incorporated in the formulation and passed through the hot-melt spray system may require specially designed nozzles.

During this PhD research, only GMS sprayed granules were investigated for polymorphic transitions. Sprayed GMS granules could be further developed into tablets, capsules, pellets with the addition of API and possible further excipients. This opportunity to further characterise the sprayed material and determine its physicochemical properties is reported in Chapters 5 and 6. For future work, the investigation of other sprayed wax matrix systems could be investigated (Chapter 8).

5. Characterisation and Compatibility of Water Soluble and Insoluble Model Drugs Incorporated into Sprayed Material

5.1 Introduction

The effect of various formulation processing factors impacting upon the performance of the agitated hot-melt spray system was determined in Chapter 4 and indicated that the system was robust and capable of producing high quality GMS pellets. However, an important parameter that also needed to be investigated was the effect of different types of drugs on the resultant properties of the sprayed GMS pellets and the compatibility of the different formulation components. Additionally, the ability of the hot-melt spray system to achieve sustained release sprayed material using a GMS-based wax matrix system must also be determined.

The main objective of this study was the production and characteristion of a sustained-release hydrophobic matrix pellet drug delivery system, achieved utilising a hot-melt agitated spray system. Incorporation of paracetamol and ibuprofen (log *P* values 0.33 and 3.6 respectively) into the sprayed material enabled investigation of relatively hydrophilic and hydrophobic model drugs within the GMS matrix system, characterising their behaviour during atomisation and the effect on in vitro drug release from the final sprayed products.

5.2 Methods

During method development, the API PSD was evaluated due to the 1mm nozzle diameter of the spray gun and the PSD of GMS granules (Section 4), all actives utilised with this spray system were required to be less than 500 microns. From figure 5.1, the particle size distribution of paracetamol powder indicated that the drug particles were too large, with 84.2% between 500-1000 microns, as a result a size reduction technique was performed. Ibuprofen powder in contrast did not require size reduction as the PSD was significantly smaller than that of paracetamol.

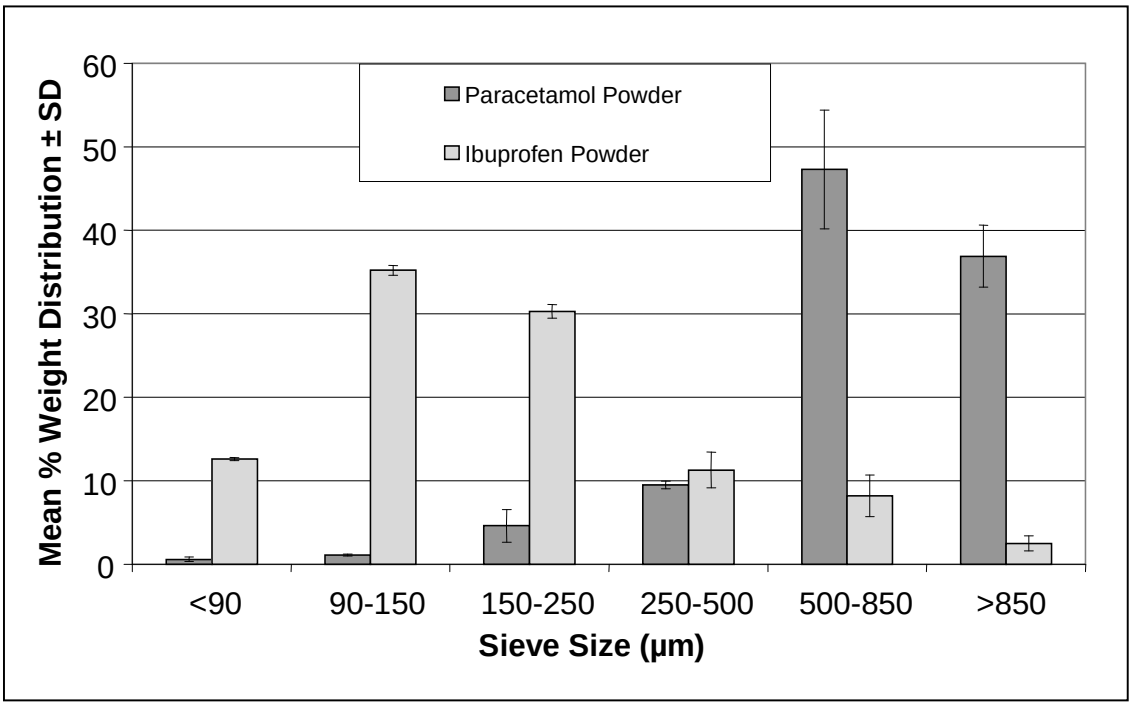


Figure 5.1 Particle size distribution of paracetamol and ibuprofen powders (n=3)

Formulation manufacture and analytical techniques are summarised in Section 5.2. All batches were stored at room temperature and monitored for 24 hours.

5.2.1 Investigation of a Sprayed Paracetamol Solid Dispersion

5.2.1.1 Characterisation of a size reduction technique on paracetamol raw powder.

Size reduction of paracetamol powder was undertaken by ball milling (Section 2.3.2). A comparison between unmilled and ball-milled paracetamol powder was analysed by particle size analysis (Section 2.4.2.1), DSC (Section 2.4.5.2) and FT-IR (Section 2.4.3.1).

5.2.1.2 Characterisation of a sprayed ball-milled paracetamol GMS formulation

GMS sprayed material with 90% GMS and 10% paracetamol were produced at 80ºC (Section 2.3.4). Prior to spraying, a two phase liquid suspension is produced between the GMS and paracetamol due to the drug physicochemical properties (melting point, 170˚C; log *P* values 0.34), as a result agitation of the spray system was required.

Sprayed material was produced comprising of varying paracetamol particle size fractions ranging between 53-250 microns (Table 5.1).

Table 5.1 GMS sprayed granule formulations containing various size fraction of paracetamol.

Formulation	**Paracetamol Particle Size (microns)**
A	150-250
B	90-150
C	75-90
D	53-75

The resultant material was analysed utilising the following analytical techniques (Table 5.2).

Table 5.2 Analytical techniques utilised in the characterisation of GMS sprayed material comprising of ball-milled paracetamol.

Analytical Technique	**Method Information**
PSD	Section 2.4.2.1
DSC	Section 2.4.5.2
Dissolution	Section 2.4.4
HSM	Section 2.4.7.3

5.2.2 Investigation of a sprayed ibuprofen GMS formulation

A size reduction technique was not required for ibuprofen powder as fractionation of the powder particles enabled sufficient ibuprofen particles within the desired range of 50-250 microns to be collected (Section 2.4.2.1).

5.2.2.1 Effect of ibuprofen concentration on sprayed GMS material

Sprayed material incorporating GMS and ibuprofen were produced at 80ºC (Section 2.3.4). Prior to spraying, a one phase liquid solution is formed between the GMS and ibuprofen due to the drug physicochemical properties (melting point, 70˚C; log *P* value 3.7). Agitation of the system was not required but was utilised to standardise the methodology as used in Section 2.3.4 for the paracetamol sprayed material.

Six formulations of varying ibuprofen concentrations were produced (10, 25, 35, 45, 50, 75, 100 %w/w) and analysed by DSC (Section 2.4.5.2) and HSM (Section 2.4.7.2).

5.2.2.2 Effect of initial ibuprofen particle size

GMS sprayed granules with 90% GMS and 10% ibuprofen were produced at 80ºC (Section 2.3.4) using ibuprofen of varying particle size fractions (Table 5.3).

Table 5.3 GMS sprayed formulations containing various size fraction of ibuprofen.

Formulation	**Ibuprofen Particle Size Fraction (microns)**
Ibu A	150-250
Ibu B	90-150
Ibu C	53-90

The resultant formulations were analysed utilising various analytical techniques (Table 5.4).

Table 5.4 Analytical techniques utilised in the characterisation of GMS sprayed material comprising of ibuprofen

Analytical Technique	**Method Information**
PSD	Section 2.4.2.1
DSC	Section 2.4.5.2
Dissolution	Section 2.4.4

Analytical Technique	Method Information
HSM	Section 2.4.7.3
Scanning Electron Microscopy	Section 2.4.7.4
Polarised Microscopy	Section 2.4.7.2
XRPD	Section 2.4.6

5.3 Results and Discussion

5.3.1 Investigation of a Sprayed Paracetamol GMS Formulation

5.3.1.1 Characterisation of ball milling on paracetamol raw powder particle size.

The results of the ball-milled and unmilled paracetamol are shown in Figure 5.2

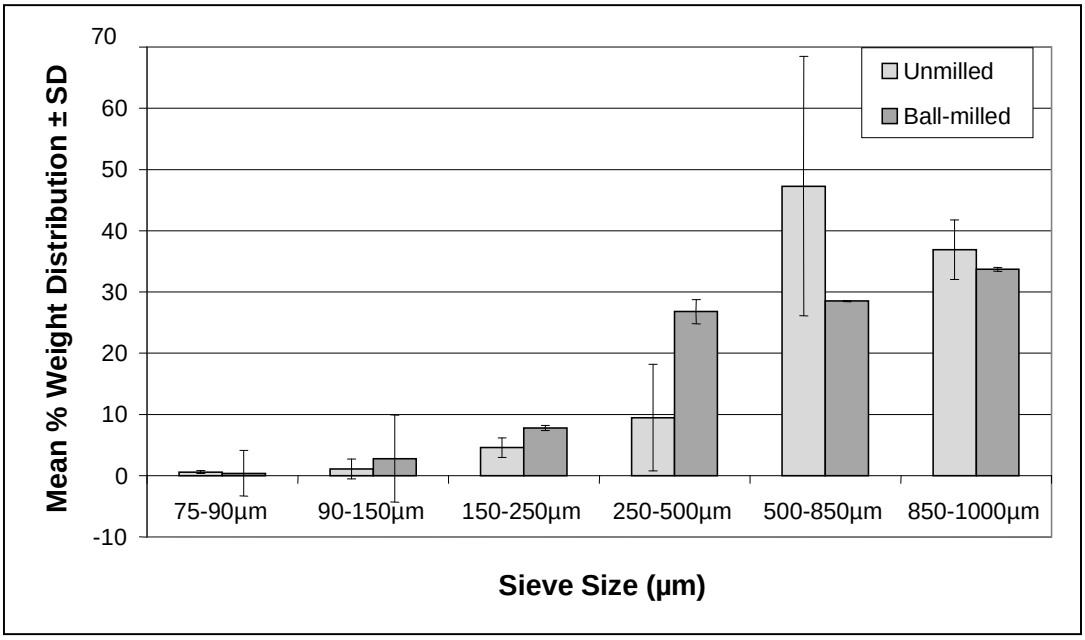


Fig. 5.2 Particle size distribution of milled and unmilled paracetamol powder

From Figure 5.2, the amount of paracetamol powder that is less than 500 microns increased when the paracetamol was ball-milled. This indicates that ball-milling was successful in reducing particle size of paracetamol.

The DSC profiles of the unmilled and milled paracetamol powders are shown in Figure 5.3.

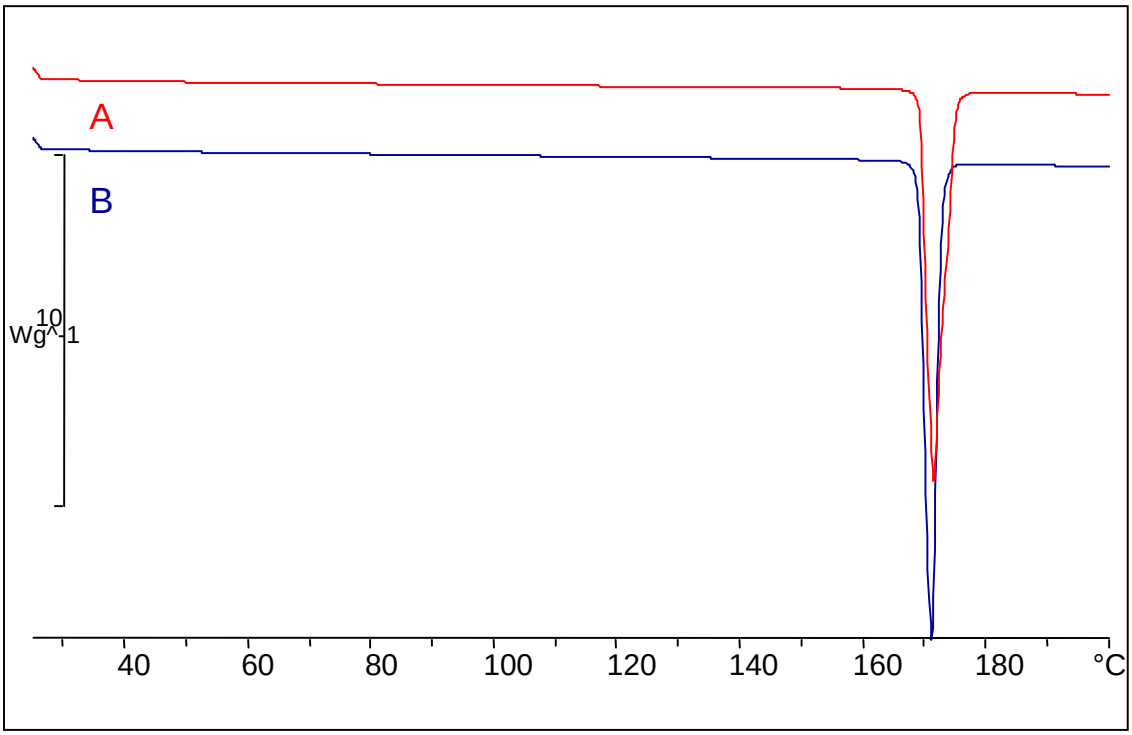


Fig. 5.3 DSC profiles of paracetamol powders (A) Unmilled (B) Ball milled (scale bar = heat flow (10 watts per gram)).

DSC analysis (Figure 5.3) indicated no significant shifts in the endotherms for the two paracetamol powders and thermal stability of the ball-milled paracetamol. Milled paracetamol was characterised with a melting point of 171^{o}C (figure 5.3) and would

correlate to polymorph form I (Giordano et al., 2002). Confirmation of the polymorphic form could be undertaken via XRPD.

The FT-IR spectra of unmilled and ball-milled paracetamol are shown in Figure 5.4.

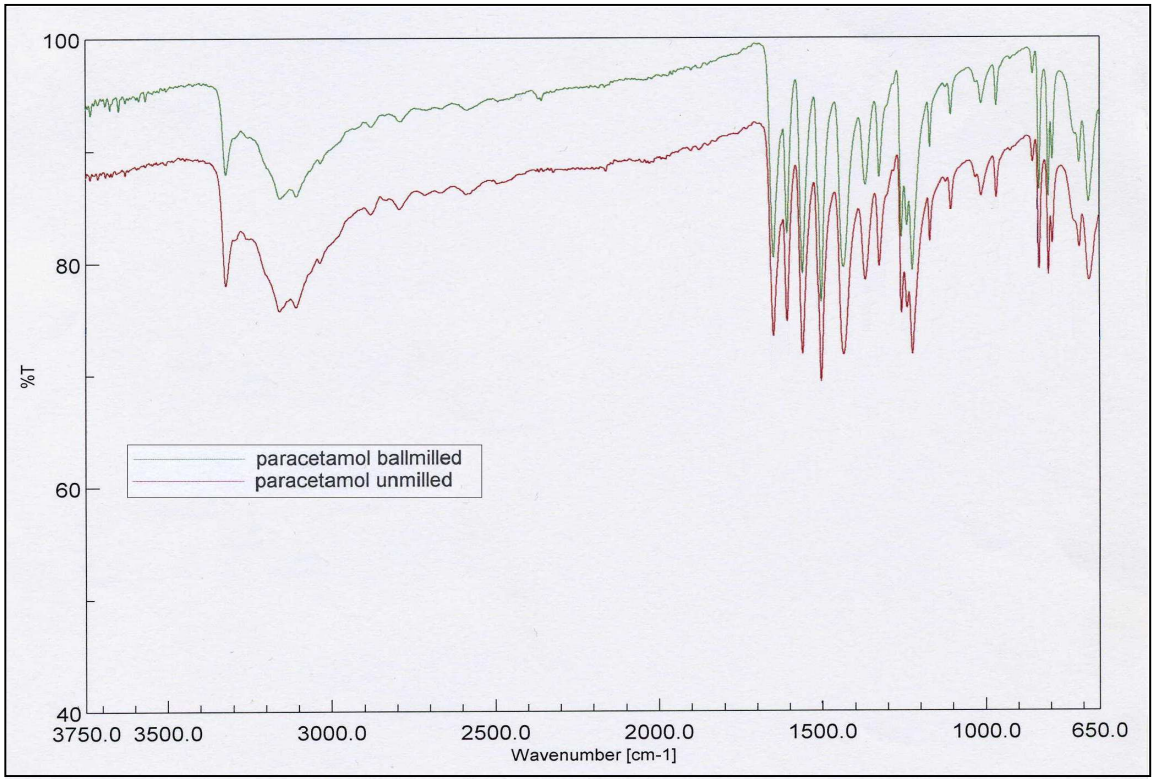


Figure 5.4 FT-IR spectra of unmilled and ball-milled paracetamol.

The FT-IR spectra of the unmilled and ball-milled paracetamol exhibited no changes pre- and post-milling. This further confirms the thermal stability of the ball-milled paracetamol.

5.3.1.2 Effect of initial paracetamol particle size on sprayed GMS material

The results of the effect on ball-milled paracetamol particle size on GMS material are shown in Figure 5.5.

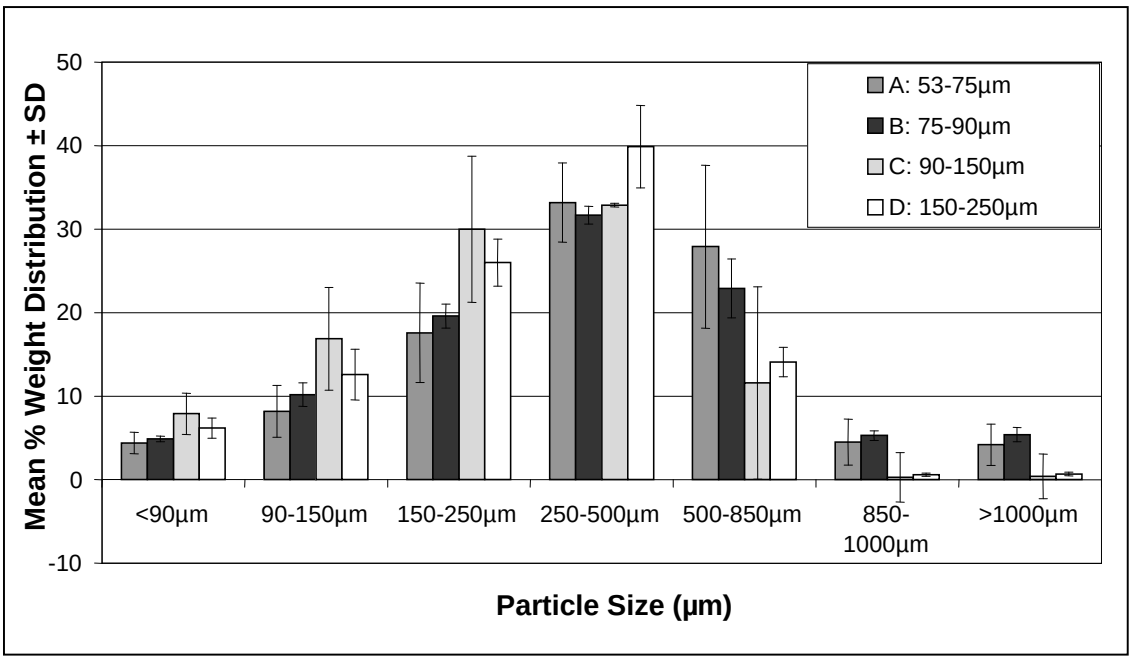


Figure 5.5 Particle size distribution of sprayed GMS material with varying paracetamol particle size fractions (n=3).

For all four batches of sprayed paracetamol material the majority of the resultant material were within the 250-500µm size range (Figure 5.5). Statistical comparison of the PSD obtained for the four paracetamol batches indicated there was no significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed material was independent of drug particle size.

The DSC profiles of the paracetamol-GMS sprayed granules incorporating various drug particle size fractions are shown in Figure 5.6.

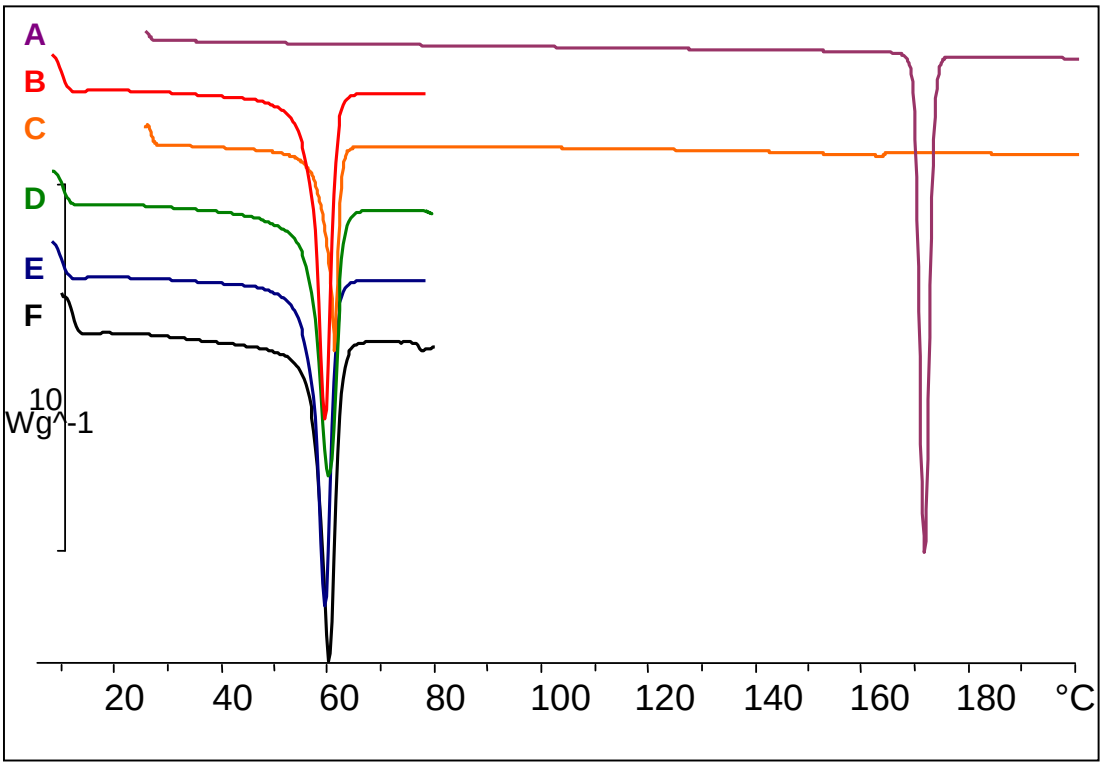


Fig. 5.6 DSC profiles of individual components and sprayed binary paracetamol mixtures incorporating varying initial paracetamol particle size fractions (A) Paracetamol powder, (B) GMS powder, (C) PCM 150-250µm, (D) PCM 90-150µm, (E) PCM 75-90µm and (F) PCM 53-75µm (scale bar = heat flow (10 watts per gram)).

DSC analysis (Figure 5.6) indicated no significant shifts in the endotherms for the GMS component in the four different binary mixtures containing paracetamol of different particle size fractions. This indicated thermal stability of the GMS component in the binary mixtures. The paracetamol form present in the mixtures would need to be confirmed via XRPD.

The release profile of paracetamol of varying size from the GMS matrix is shown in Figure 5.7.

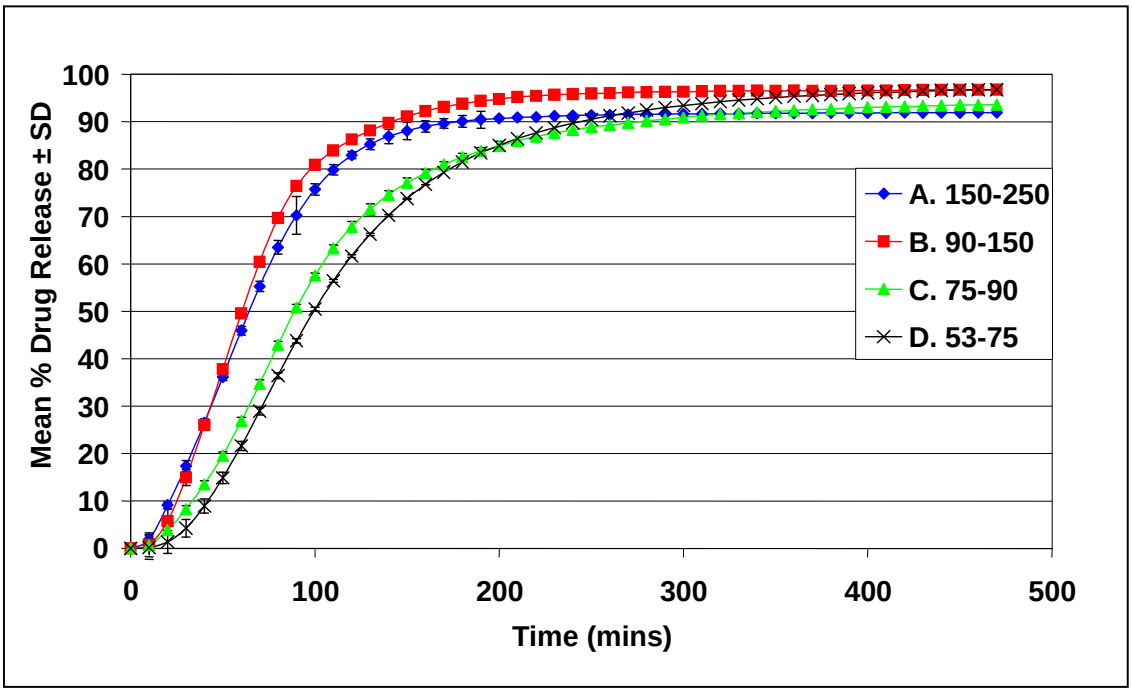


Figure. 5.7 Mean release profiles of sprayed paracetamol GMS formulations with varying paracetamol particle size (n=6)

Mean drug release profiles for paracetamol sprayed material (Figure 5.7) indicate that as the particle size of the active ingredient within the material decreases below 90µm the rate of drug release significantly decreases (f_2 value < 50). The decrease in dissolution rate may be due to smaller particles having a more effective barrier/coverage with GMS than larger particles of paracetamol. This enables a thicker layer of GMS to surround the smaller individual drug particles and due to the hydrophobic nature of the wax a more effective diffusional barrier is produced decreasing the drug release rate (Dredan et al.,

1996; Gandhi et al., 1999). This suggests the drug release mechanism of paracetamol from the GMS sprayed matrix is primarily controlled by diffusion at small particle sizes.

The drug release profiles obtained for 10:90 %w/w GMS-paracetamol sprayed mixtures do not exhibit immediate release or sustained release properties (refer to section 1.4) but are characteristic of modified release (refer to section 1.4). The dissolution profiles from were fitted to the Korsmeyer-Peppas, zero order and Higuchi models (Section 1.1.1.3). The correlation coefficients of the different mathematical models are included in Table 5.5.

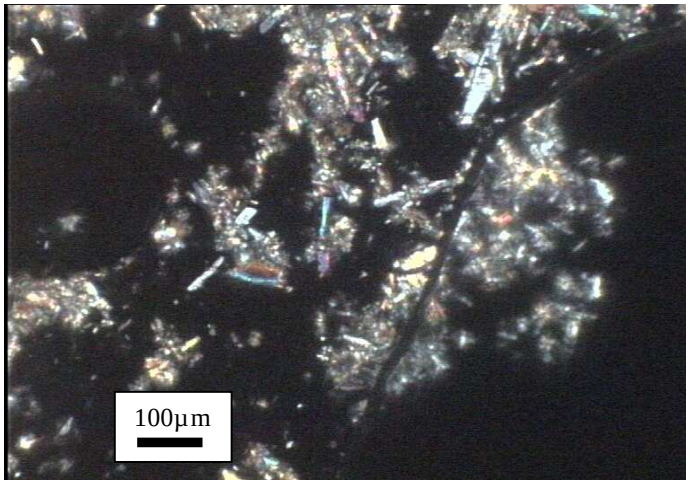
Table 5.5 Correlation coefficients of the different mathematical models applied to the paracetamol sprayed granules.

PCM sprayed granules	Korsmeyer-Peppas model			Zero order model		Higuchi model	
	r^2	N	K_K	r^2	K_0	r^2	K_H
A	0.721	1.3691	1.977	0.5315	0.137	0.729	4.15
B	0.6785	1.6093	1.072	0.5305	0.1457	0.6721	5.54
C	0.8079	1.9474	0.380	0.7018	0.1765	0.8554	5.04
D	0.8033	2.5051	0.080	0.753	0.198	0.8847	5.55

From the three models, the model that best represents the mechanism of drug release from the sprayed GMS granules is the Higuchi model. The correlation coefficient for this model is closest to the value of 1, indicating that the primary mechanism of drug release is diffusion. However, as the particle size of the paracetamol sprayed granules increases

the correlation coefficient value decreases and indicates that another mechanism of drug release may be contributing.

The results of the effect on ball-milled paracetamol particle size on GMS material are shown in Figure 5.8.

A. 

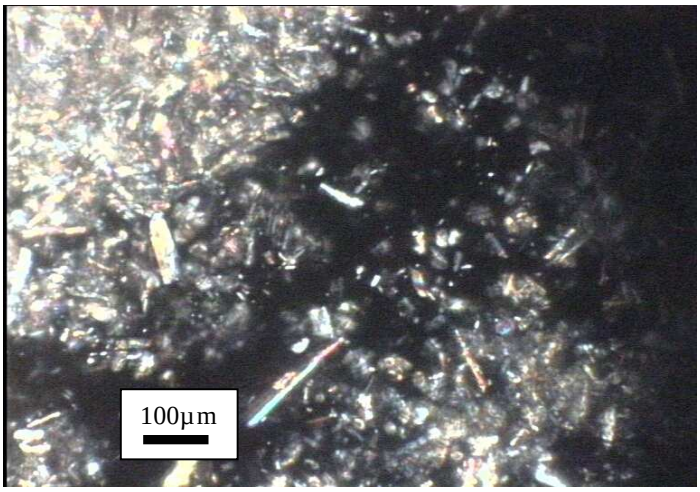
B. 

Fig. 5.8 Hot stage polarising photomicrographs at 65^{o}C of paracetamol-GMS sprayed granules (A) 0-90µm ball-milled paracetamol and (B) 90-150µm ball-milled paracetamol at a x25 magnification.

The photomicrographs (Figure 5.8) illustrated the sprayed paracetamol material at 65ºC when the GMS had become molten and the ball-milled paracetamol suspended within the wax. The microscopic images indicated that the individual ball-milled paracetamol particles are crystalline in nature. In addition, there appears to be larger areas of molten GMS in the image when the particle size fraction incorporated into the granules is less than 90µm (A). The paracetamol particles greater than 90µm (B) have a smaller area of molten GMS present between the paracetamol particles.

This observation may correspond to the in vitro release results (Figure 5.7) and confirms an increased diffusional GMS barrier has formed around the smaller paracetamol particles and has led to a decreased dissolution rate if a size fraction of less than 90µm is used.

5.3.2 Investigation of a sprayed ibuprofen GMS formulation

5.3.2.1 Effect of ibuprofen concentration on sprayed GMS material

The DSC profiles for the ibuprofen-GMS sprayed granules produced with different ibuprofen concentrations are shown in Figure 5.9.

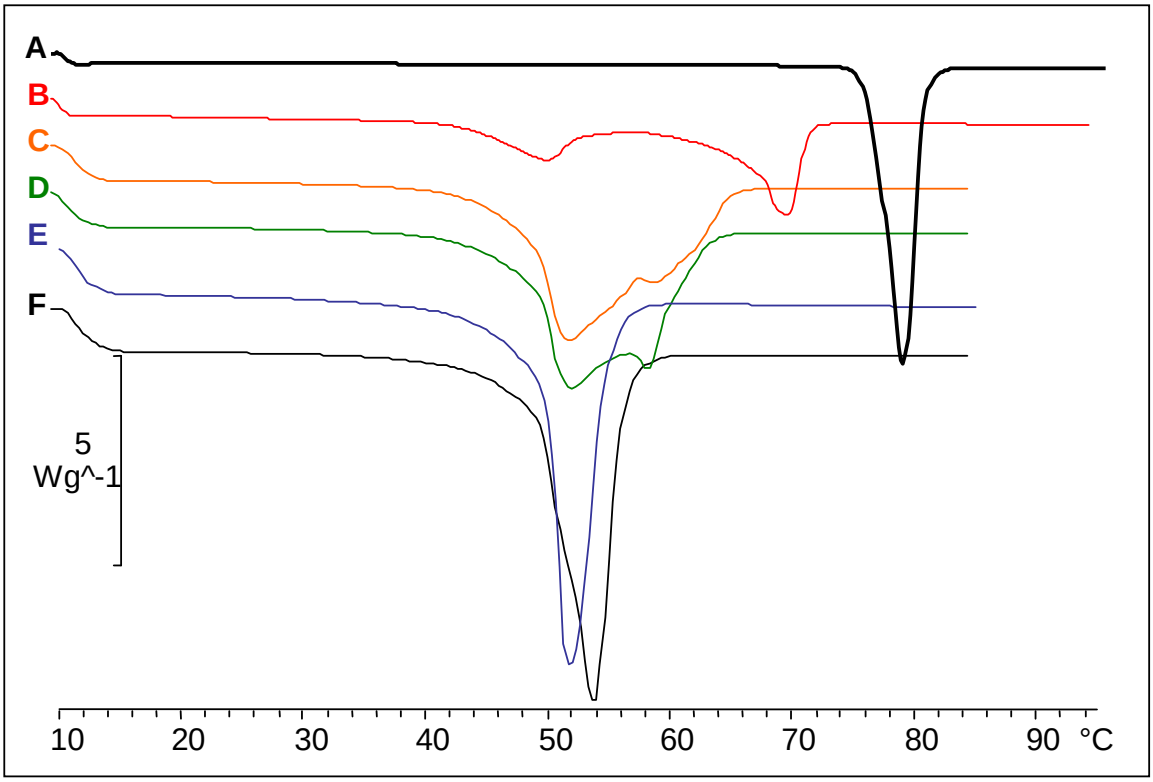
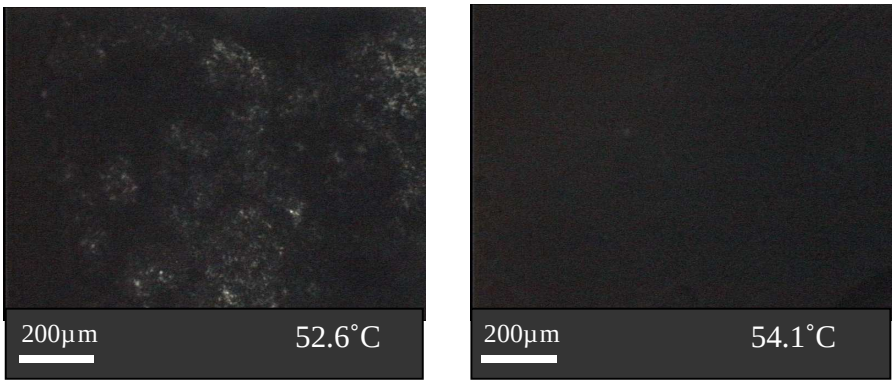


Fig. 5.9 DSC profiles of ibuprofen-GMS sprayed material with varying ibuprofen concentrations, (A) 100%w/w, (B) 75%w/w, (C) 50%w/w, (D) 45%w/w, (E) 35%w/w and (F) 25%w/w (scale bar = heat flow (5 watts per gram)).

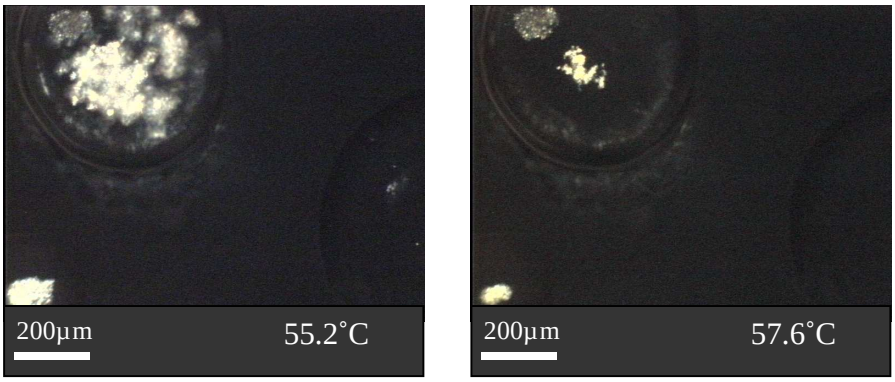
From figure 5.9, the absence of the drug peak in the Ibuprofen-GMS granules containing up to 35%w/w ibuprofen indicates potential ibuprofen solubilisation during melting or a strong interaction with the GMS and the ibuprofen, present either in an amorphous form or as a solid solution within the GMS matrix (Kapsi et al., 2001; Passerini et al., 2001). The new thermal peaks at 52 and 54^{o}C indicates the melting of the ibuprofen-GMS solid solution (Passerini et al., 2002). The slight upward trend in the endothermic peak for the 25%w/w ibuprofen mixture (54^{o}C), was possibly due to the larger quantity of excipient present in the mixture than for 35%w/w ibuprofen mixture (Passerini et al., 2002).

For ibuprofen-GMS granules containing 45%w/w ibuprofen and above, two endotherms can be observed which suggests the presence of both ibuprofen crystals and the GMS/Ibuprofen solid solution, indicating possible saturation of the solid solution (Lira et al., 2007). XRPD or hyper- DSC could be utilised to determine additional information.

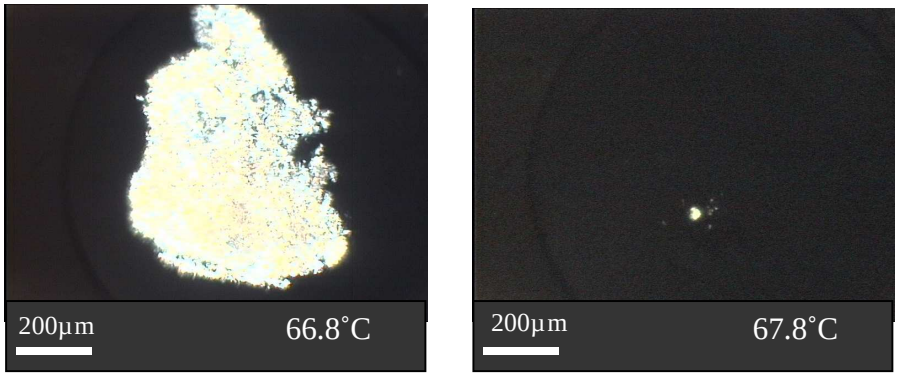
The results of the microscopy for the ibuprofen-GMS sprayed granules produced with different ibuprofen concentrations are in Figure 5.10.



25%w/w Ibuprofen



50%w/w Ibuprofen



75%w/w Ibuprofen

Fig. 5.10 Hot-Stage Microscopy of sprayed ibuprofen-GMS mixtures produced with different ibuprofen concentrations at x10 magnification.

In the 25%w/w mixture of ibuprofen-GMS, no ibuprofen crystals were observed suggesting that the ibuprofen had completely dissolved in the GMS matrix and formed a solid solution. Therefore, absence of the drug endotherm (Figure 5.9) is due to formation of a solid solution and not amorphisation (Passerini et al., 2001).

HSM revealed for mixtures comprising of 50%w/w and 75%w/w ibuprofen that not all the ibuprofen crystals could be dissolved in the melted GMS at the same temperature that is was achieved for the 25%w/w ibuprofen-GMS mixture. At a temperature of ~55^{o}C the ibuprofen dissolves in the GMS to form a solid solution until the GMS becomes fully saturated with ibuprofen.

For the mixtures with at least 50%w/w, the volume of GMS has decreased than for the 25%w/w ibuprofen mixture and at 55^{o}C no further ibuprofen can be dissolved in the GMS. However, when the temperature is increased it enables a supersaturated solution of

GMS-ibuprofen to be created and by 58°C and 68°C (50%w/w and 75%w/w ibuprofen-GMS mixtures, respectively) all ibuprofen is dissolved in the GMS. These HSM observations correspond to the DSC findings and the presence of two peaks for both of these binary Ibuprofen-GMS mixtures.

5.3.2.2 Effect of initial ibuprofen particle size on sprayed GMS material

The results of the particle size distribution for the ibuprofen-GMS (10:90%w/w) sprayed mixture incorporating various drug particle size fractions are in Figure 5.11.

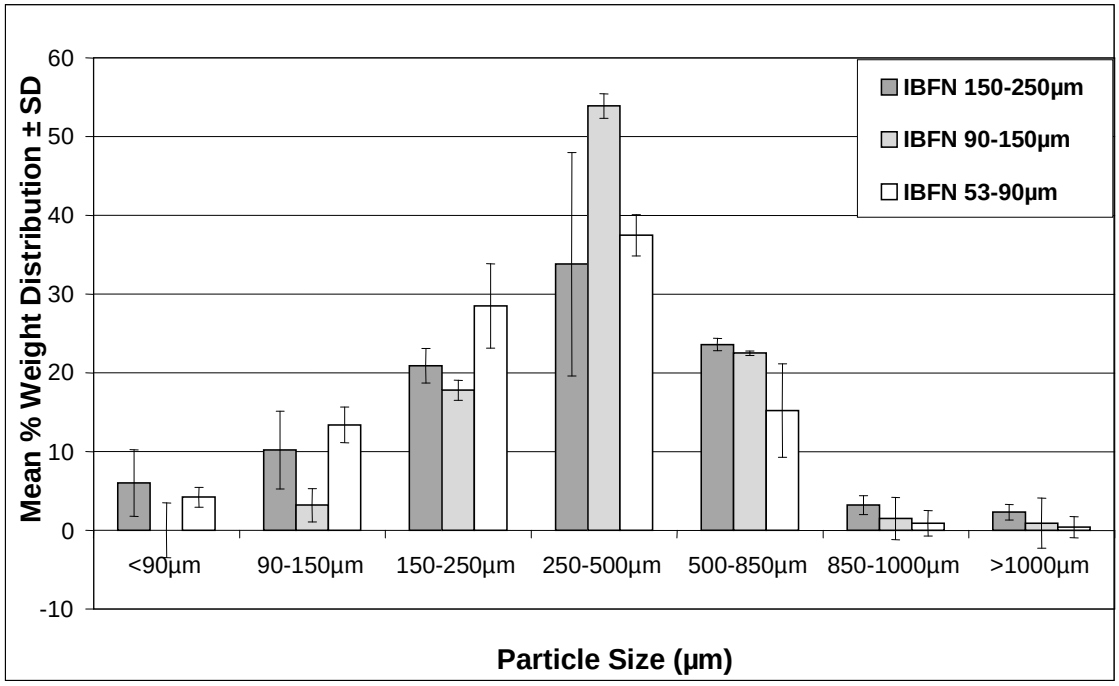


Fig. 5.11 Particle size distribution of sprayed GMS material with varying ibuprofen particle size fractions (n=3)

For all three batches of sprayed GMS material the majority of the resultant particles were within the 250-500µm size range (Figure 5.11). Statistical comparison of the PSD

obtained for the three ibuprofen batches indicated there was no significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed material is independent of initial ibuprofen drug particle size. This is anticipated as the ibuprofen forms a solid solution with GMS and is molecularly dispersed.

The DSC profiles of 10:90%w/w ibuprofen-GMS sprayed material incorporating various drug particle size fractions at 2hrs and 24hrs post manufacture are shown in Figure 5.12-5.13, respectively.

DSC analysis (Figure 5.12) indicated that the endotherms shifted left for the three different binary mixtures containing ibuprofen of different particle size distributions in comparison with the raw GMS and ibuprofen powder, with individual endotherms exhibiting a significant decrease in drug/excipient melting endotherms, indicating a strong drug-wax interaction (Mura et al., 1998).

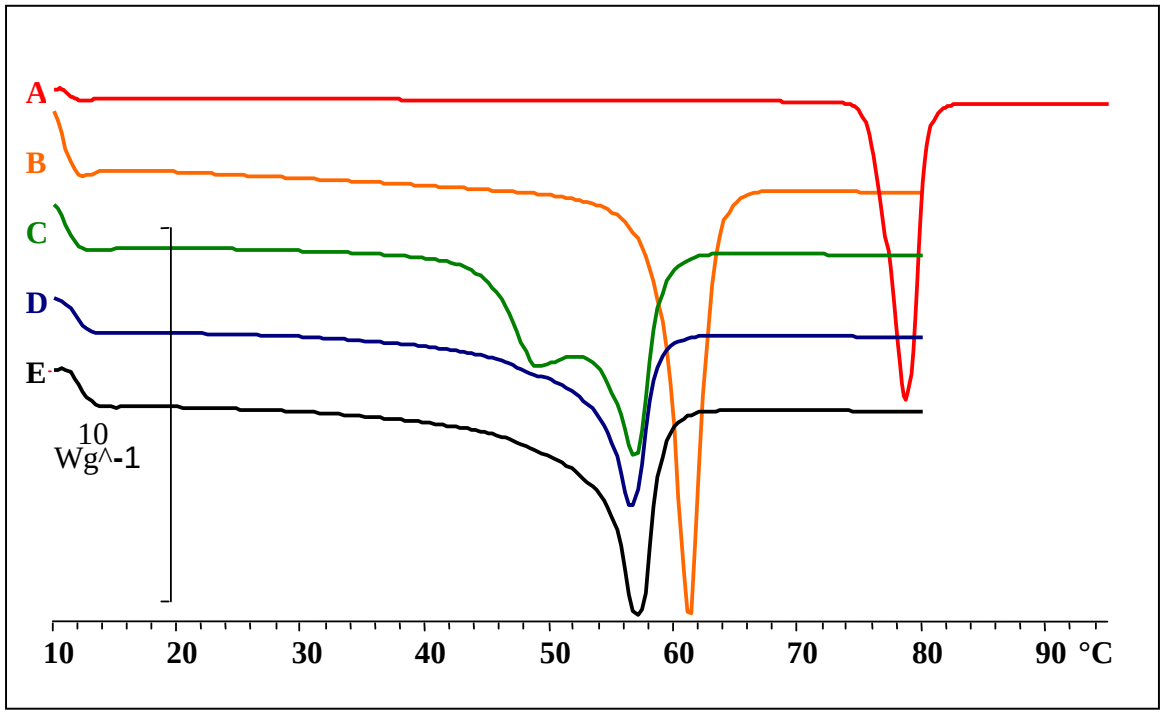


Fig. 5.12 Effect of ibuprofen particle size on the DSC profiles of 10:90%w/w sprayed ibuprofen-GMS mixtures, 2hrs post manufacture. (A) Ibuprofen powder, (B) GMS powder, (C) IBFN 150-250µm, (D) IBFN 90-150µm and (E) IBFN 53-90µm (scale bar = heat flow (10 watts per gram)).

Granules, 2hrs post manufacture (Figure 5.12), comprised of ibuprofen powder with particle sizes of 53-90µm, 90-150µm or 150-250µm exhibited endotherms at 57^{o}C (single), 48^{o}C (one broad endotherm with a slight shoulder) or two endotherms at 48^{o}C and 57^{o}C, respectively. This is an unusual observation as the ibuprofen is molecularly dispersed in the GMS for all formulations and therefore should exhibit similar thermal properties.

The single endotherm at ~57^{o}C indicates the formation of solid solution between the ibuprofen and GMS. The endotherm is exhibited at a slightly higher temperature than observed in figure 5.7 due to the increased volume of GMS present (Passerini et al., 2002).

The endotherm exhibited at approximately 47^{o}C cannot be representative of crystalline ibuprofen as this would be expressed at a higher temperature as illustrated in Figure 5.9 and no known ibuprofen polymorphs have been discovered (Potthast et al., 2005). However, GMS can form different polymorphs, α-form and β-form, and exhibit different melting points (Yajima et al., 2002). In Chapter 4, it was identified that sprayed GMS was forming both the α-form and β-form of GMS. Therefore, it is possible to suggest that the two endotherms at 47^{o}C and 57^{o}C are both solid solutions formed between the ibuprofen and GMS and that each endotherm represents a different GMS polymorphic form. To confirm which endotherm indicates which GMS polymorph solid solution would have to be confirmed by XRPD (Section 5.3.2.2).

From initial review, the results from figure 5.12 indicate the initial ibuprofen particle size has a significant effect on the formation of one or two endotherms, despite a solid solution being formed. These results are unusual and may be spontaneous but should be evaluated further to determine if the initial particle size of a drug could impact the rate of crystallisation in a solid solution, there is currently no literature available to support this. Alternatively, the single endotherm may be a reflection of the melting point of the mixed material of the sprayed GMS post 2 hours and the shoulders that are present in the larger

ibuprofen particles may be some undissolved ibuprofen crystals that are acting as a nucleation point. These observations would indicate the agitation speed or time is not optimised for larger ibuprofen particles and would require further analysis utilising XRPD and HSM (refer to 5.3.2.2).

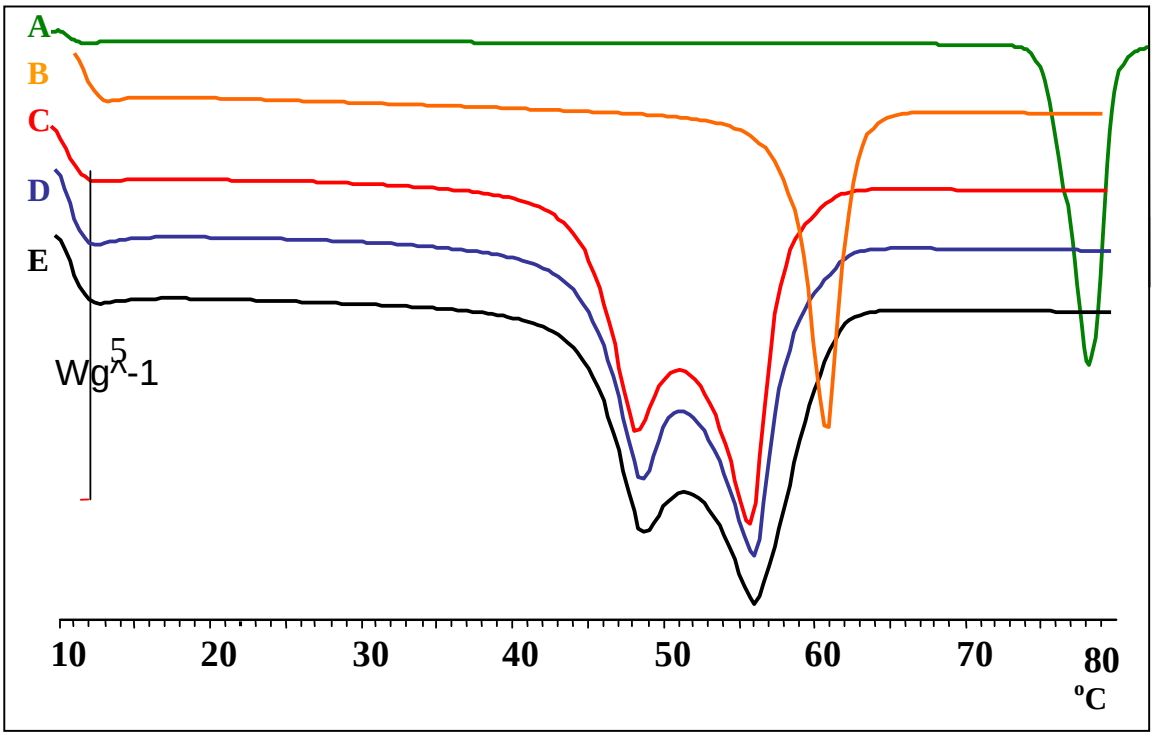


Fig. 5.13 Effect of ibuprofen particle size on the DSC profiles of sprayed 10:90%w/w ibuprofen-GMS solid solutions, 24hrs post manufacture. (A) Ibuprofen only, (B) GMS only, (C) IBFN 150-250µm, (D) IBFN 90-150µm and (E) IBFN 53-90µm (scale bar = heat flow (5 watts per gram)).

Sprayed binary mixtures 24hrs post manufacture (Figure 5.13), comprised of ibuprofen powder with particle sizes of 53-90µm, 90-150µm or 150-250µm exhibited two endotherms at 48°C and 57°C, respectively. This suggests that 24hrs post-manufacture all

the 10:90%w/w ibuprofen-GMS sprayed mixtures have similar thermal properties, unlike the samples 2hrs post-manufacture (Figure 5.12).

The change 24 post-manufacture, indicates sprayed binary mixtures containing ibuprofen smaller than 150µm have also undergone a transition. This may indicate either two GMS polymorphs are present within the solid solution (Eldem et al., 1991; Sutananta et al., 1994a) or the undissolved ibuprofen crystals have partially crystallised out of the solid solution with time (Iervolino et al., 2001; Kamble et al., 2004; Oladiran & Batchelor, 2007; Sutananta et al., 1994c). Whether the transition is complete or would continue beyond 24 hours post manufacture is unknown and would require further studies to be undertaken. For further clarification of the above observations analysis utilising XRPD and HSM would be required (refer to 5.3.2.2).

In order to clarify the findings described in Sections 5.3.2-5.3.3, X-ray powder diffraction (XRPD) was used to determine the crystalline states of ibuprofen and GMS both as raw materials and within binary sprayed mixtures.

The XRPD obtained for the ibuprofen raw powder (Figure 5.20) confirms the drug is a racemic mixture, the crystalline nature of the drug is characterised by the numerous sharp and intense peaks at 2θ angles of ~12.4º, 13º, 14º, 14.5º, 18.7º, 19.1º, 19.7º and 20.3º (Dudognon et al., 2008; Stahly et al., 1997).

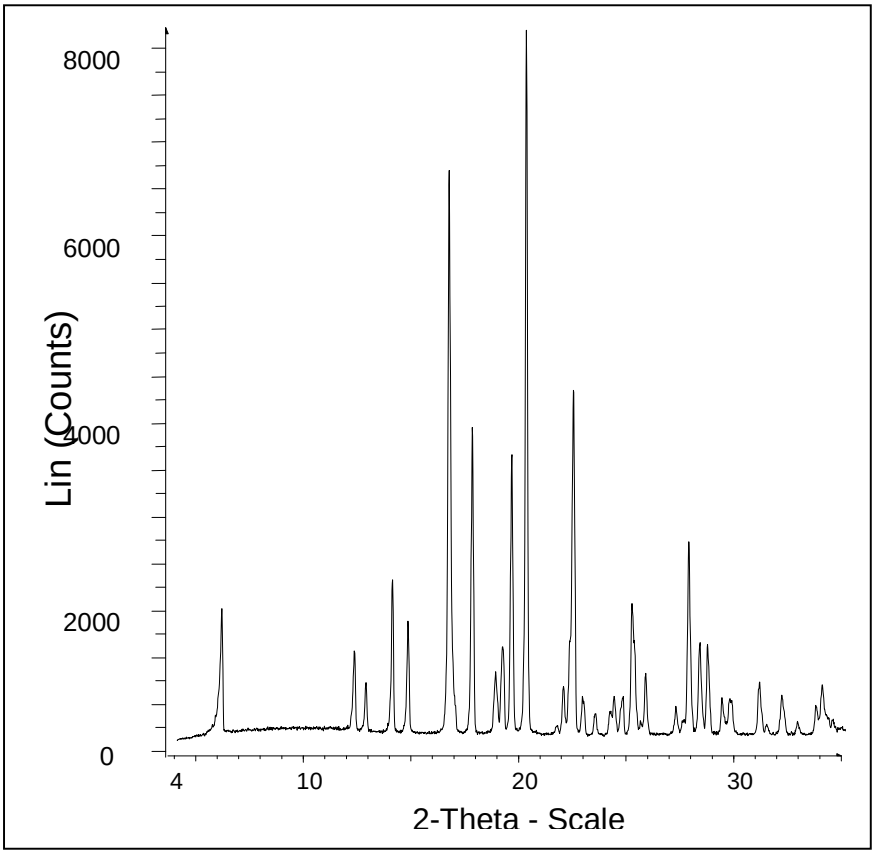


Figure 5.14 XRPD of raw ibuprofen powder

The comparison of X-ray diffractograms of 10:90%w/w ibuprofen-GMS mixtures containing different ibuprofen particle sizes after processing into hot-melt sprayed granules at 80^{o}C are shown in Figure 5.15.

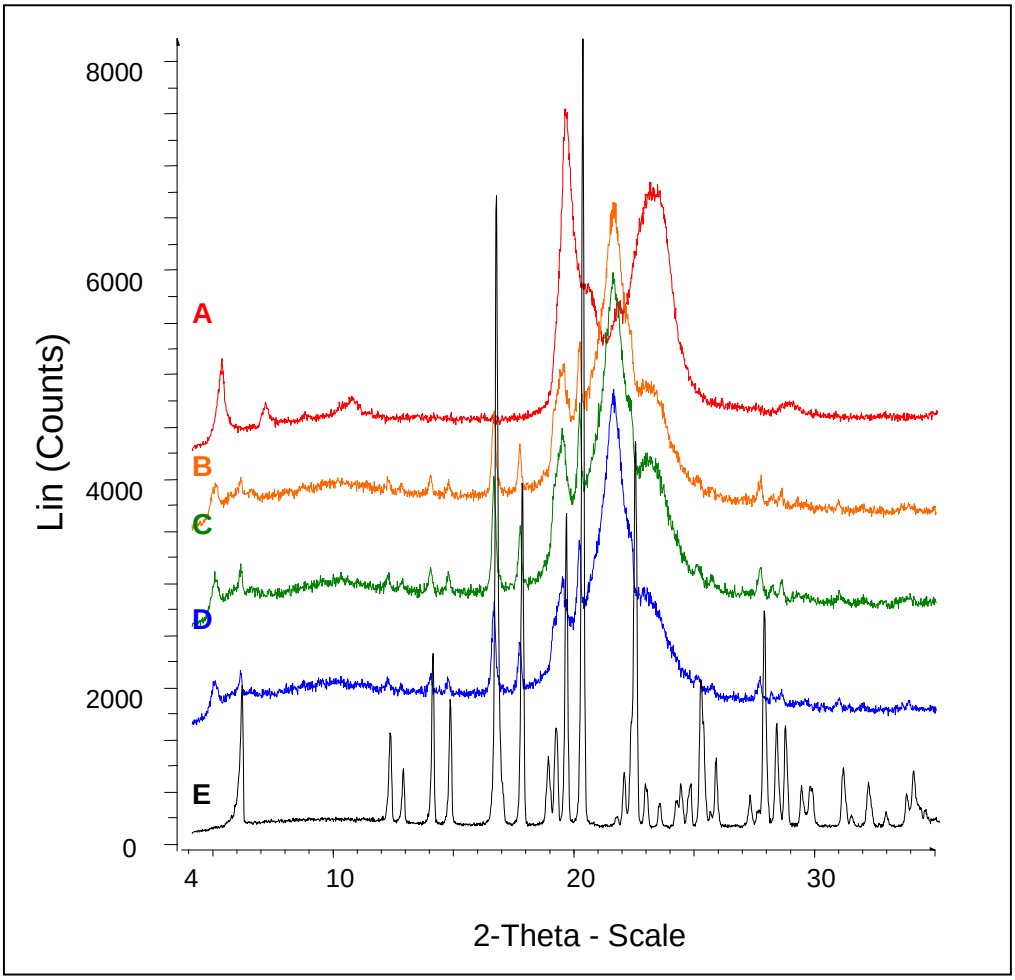


Figure 5.15 Ibuprofen-GMS sprayed granules containing various particle sizes of ibuprofen, 24hrs post manufacture. (A) GMS powder only, (B) 53-90µm IBFN, (C) 90-150µm IBFN, (D) 150-250µm IBFN and (E) Ibuprofen powder only

From figure 5.15, the XRPD of the sprayed binary mixtures show similar features to the diffraction patterns obtained for the raw powders of GMS and ibuprofen. In all sprayed mixtures the characteristic peaks of the drug are present indicating that the ibuprofen within the mixtures is crystalline, peak intensity may be attenuated due to the lower drug content in the mixtures than the raw powder diffraction sample (Passerini et al., 2002).

Every ibuprofen-GMS mixture has three broad peaks or shoulders at 2θ angles of ~19.5º, 21º and 23.5º characteristic to both the α- and β-form of GMS (Yajima et al., 2002) and indicates that both polymorphs are present in the wax-drug granules.

This confirms 24 hours post-manufacture, the two endotherms exhibited in Figure 5.13 are representative of ibuprofen and GMS mixtures, one mixture comprising of the α-form of GMS and ibuprofen and the second endotherm comprising of the β-form of GMS and ibuprofen.

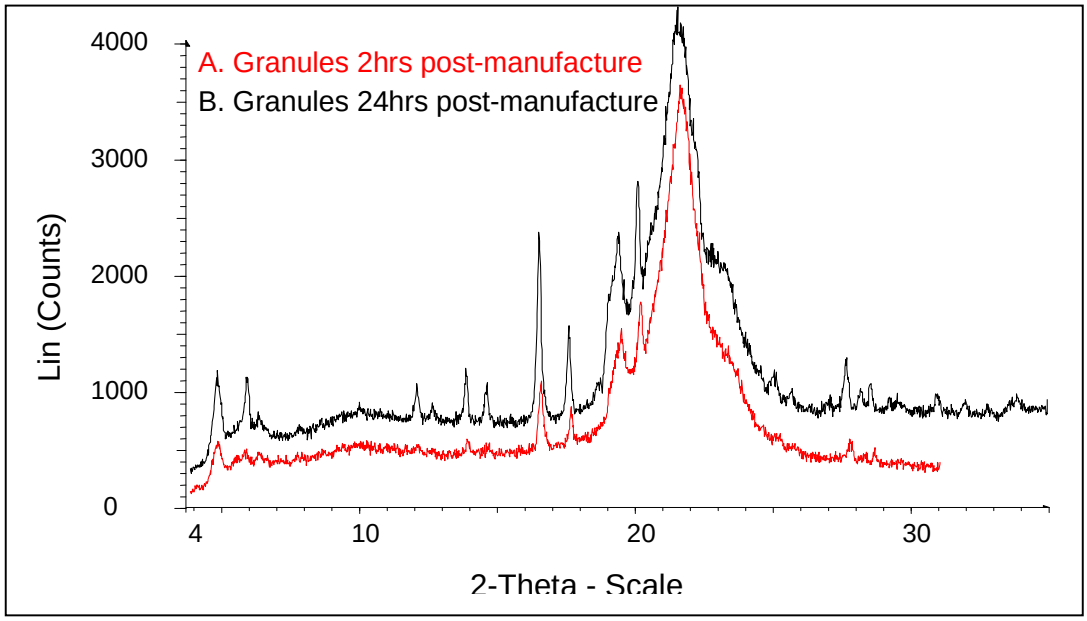


Figure 5.16 10/90 %w/w Ibuprofen-GMS sprayed material containing 53-90μm ibuprofen monitored over 24hrs.

In Figure 5.16, 2 hours post-manufacture the sprayed ibuprofen-GMS mixture exhibits one main distinctive peak at 2θ angles of ~21.5º (0.41nm) indicating the α-form of GMS but also has two shoulder peaks corresponding to the β-form of GMS. This suggests that

the sprayed GMS comprises primarily of the α-form of GMS but has begun to exhibit polymorphic changes indicating that GMS is reverting back into the more stable β-form.

The diffractograms for the smallest ibuprofen particle size fraction (0-90μm) changed after time. After 24hrs manufacture, the GMS polymorphic transition became even more pronounced with an increase in the ~19.5º and 23.5º peaks (stable β-form) and a decrease in the 21.5º primary peak intensities (α-form). In addition, all peak intensities significantly increased and the background slightly reduced being consistent with crystallisation of ibuprofen within the sample held on the diffractometer.

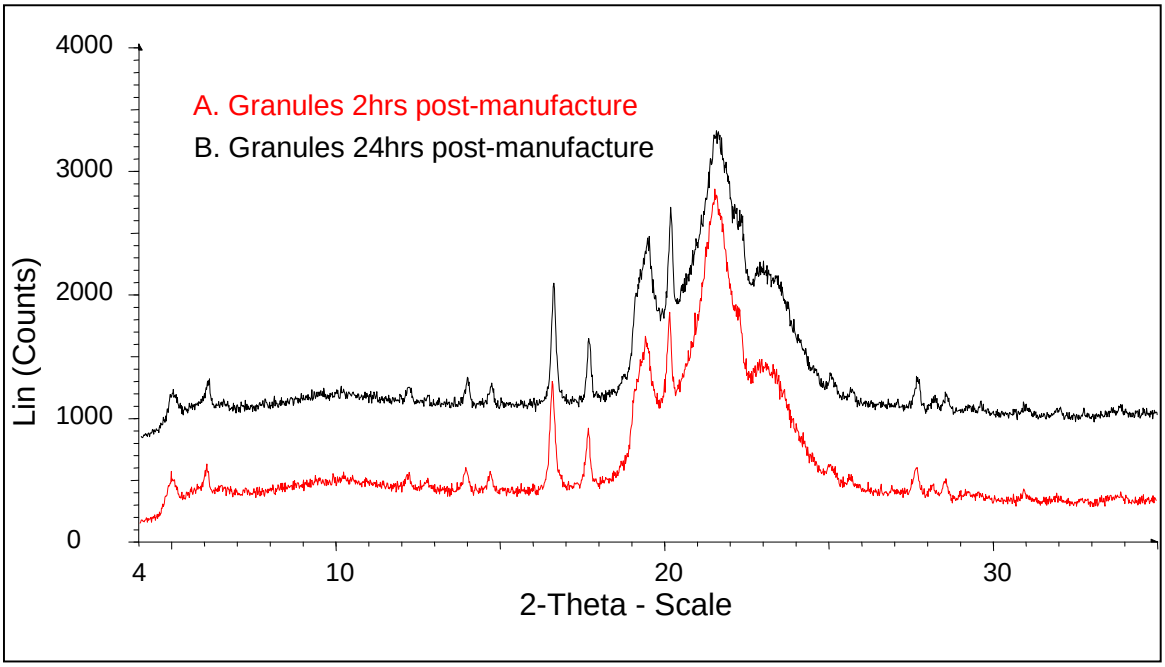


Figure 5.17 10:90 %w/w Ibuprofen-GMS sprayed material containing 90-150μm ibuprofen monitored over 24hrs.

From figure 5.17, all peak intensities increased and the background slightly reduced. The observed increase was not as significant as for the figure 5.16 but is still consistent with some crystallisation of ibuprofen within the sample held on the diffractometer. Additionally, once the sample was held 24 hours at room temperature, a slight intensity reduction of the main GMS peak (~21 degrees) indicates the GMS transition is ongoing in the mixture from the α-form of GMS to the β-form of GMS.

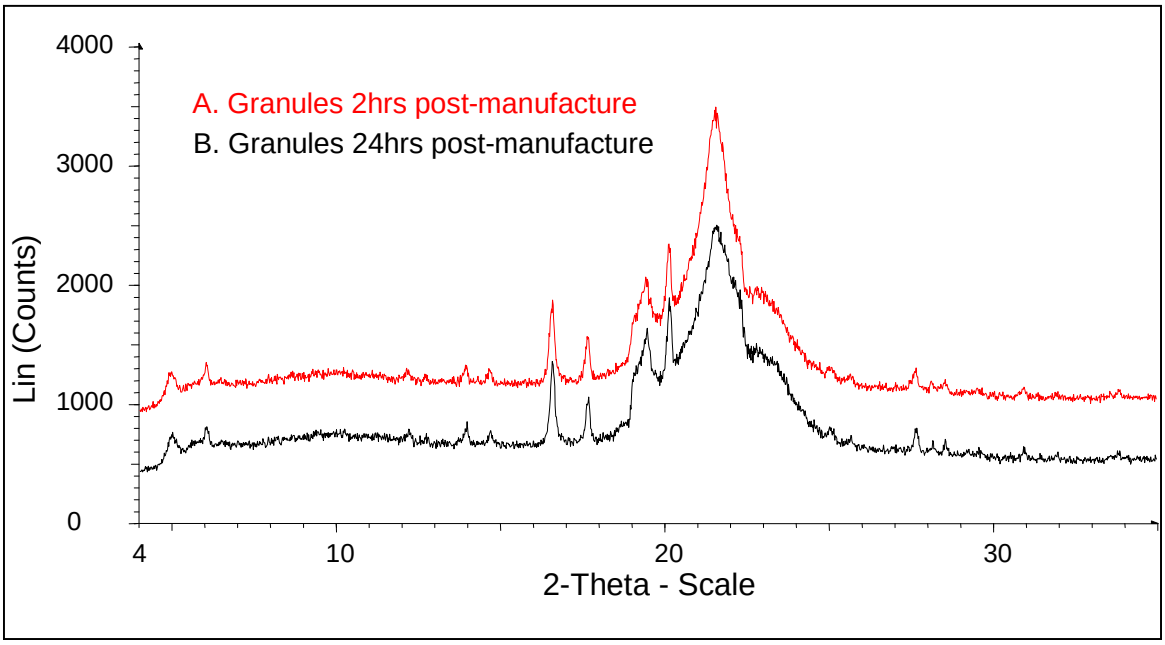


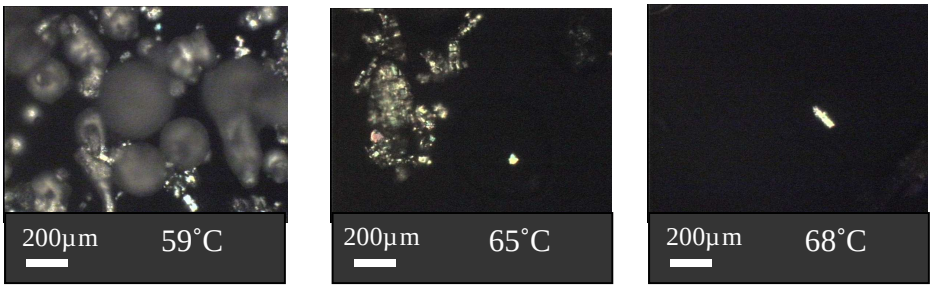
Figure 5.18 10:90 %w/w Ibuprofen-GMS sprayed material containing 150-250µm ibuprofen monitored over 24hrs.

From figure 5.18, there were no significant changes in the diffraction peaks arising from the presence of crystalline ibuprofen. However, in each sample after 24 hours at room temperature, the intensity of the main GMS peak at approximately 21 degrees is slightly reduced. Indicating there is a GMS transition ongoing within the sprayed mixture from

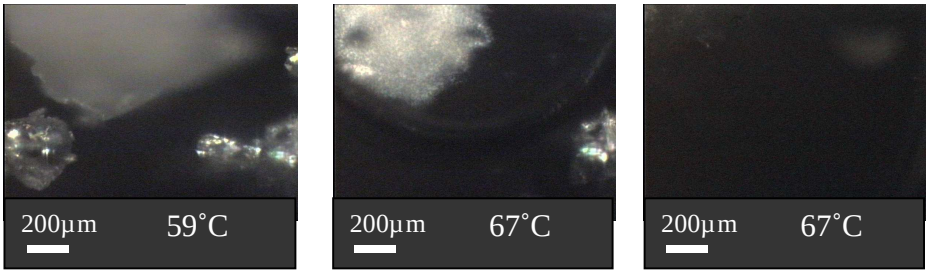
the α-form of GMS to the β-form of GMS and the amount of the α-form is decreasing from 2 hours post-manufacture.

From the XRPD and DSC results, the further crystallisation of ibuprofen, 24 hours post-manufacture, confirms the possibility that not all the ibuprofen is in a solid solution. The remaining undissolved ibuprofen crystals in the GMS mixture are acting as a nucleation point and as a result, further crystallisation of ibuprofen is occurring with time. From the XRPD results the rate of ibuprofen crystallisation within the sprayed samples appears to be linked with the initial ibuprofen particle size incorporated with the GMS. The larger the initial ibuprofen particle size the faster the ibuprofen crystallisation occurs. These observations could be visually confirmed by undertaking a microscopy investigation (section 5.3.2.2.4 – 5.3.2.2.6).

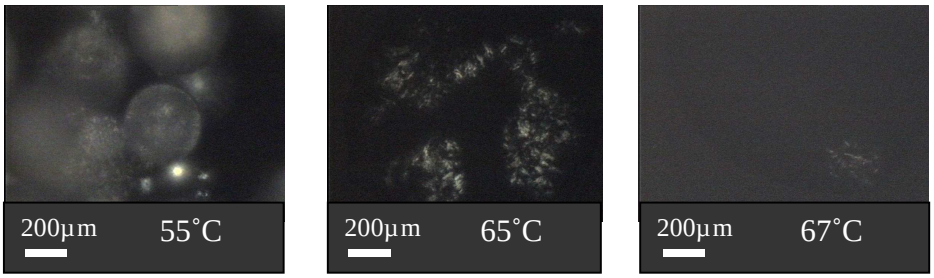
Polarised light microscopy and HSM were used simultaneously in order to visually determine the nature of the physical changes associated with the ibuprofen-GMS sprayed mixtures. Microscopic images were taken between the temperature range of 50 to 75ºC (Figure 5.19).



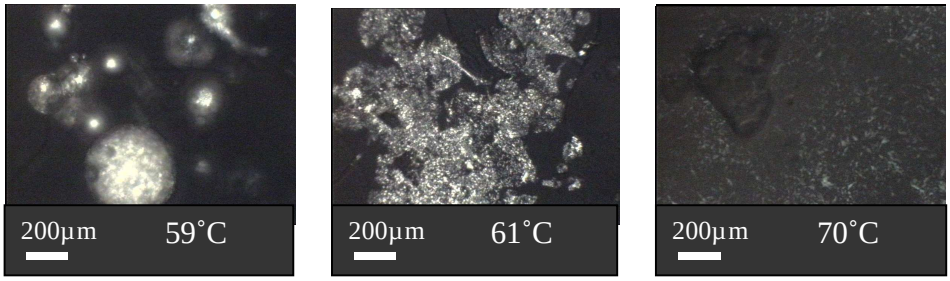
GMS and IBFN Powders admixed



IBFN 50-90µm granules



IBFN 90-150µm granules



IBFN 150-250µm granules

Figure 5.19 HSM images of ibuprofen-GMS sprayed material (10:90 %w/w) at x10 magnification.

From figure 5.19, only the β-form GMS is present in the GMS and ibuprofen powders admixed as it has not be hot-melt sprayed, this is confirmed as the GMS is melting at 59^{o}C. If the α-form was present the melting temperature of the GMS would be lower at approximately 47^{o}C (Yajima et al., 2002). When the ibuprofen-GMS sprayed material is compared to the admixed material, the GMS is also melting at 59^{o}C indicating the presence of the β-form GMS within these mixtures. The presence of the α-form of GMS would be observed if some of the GMS began to melt at the lower temperature of approximately 47^{o}C and although for the IBFN 90-150µm GMS granules there is evidence of some GMS melting at a lower temperature (55^{o}C) it is difficult to determine from the HSM when both polymorphs are present in the same mixture.

HSM (Figure 5.19) revealed that ibuprofen powder less than 90µm is not visible in the molten GMS by 67^{o}C and has formed a solid solution with the ibuprofen. This was also observed for the admixed material and 90-150µm ibuprofen:GMS sprayed material, the majority of ibuprofen was no longer visible prior to reaching the drugs melting point (69^{o}C) indicating the drug has dissolved in the GMS to form a solid solution.

The sprayed material manufactured using ibuprofen powder from the 150-250µm size range remained visible in the molten wax until 71^{o}C, which is beyond the drugs melting point. For ibuprofen particles greater than 90µm a complete solution may not have been formed with the molten GMS prior to the drug starting to melt. This may account for the trend observed in the theromogram at 2hrs post manufacture.

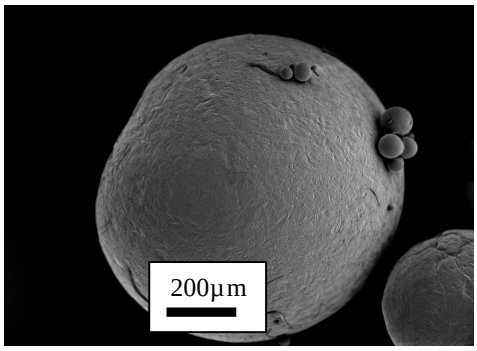
Ibuprofen particles larger than 90µm would require a longer stirring time to enable a complete solid solution to be achieved. If a proportion of undissolved ibuprofen encapsulated in the GMS is molecularly dispersed under a metastable state, both a solid solution and solid dispersion would co-exist. For a metastable molecular dispersion, the proportion may act as a crystallisation centre promoting crystal growth. Partial recrystallisation of the drug in the matrix will be observed as the molecules crystallise under storage (Dubernet et al., 1991), as illustrated in the DSC and XRPD results.

The relationship between initial drug particle size and the formation of a solid solution or a solid dispersion could lead to interactions that may be detrimental to the dissolution performance of the systems. A dissolution study was undertaken in section 5.3.2.2.

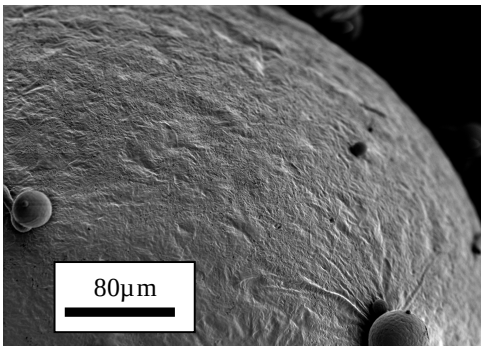
As observed in figure 5.10, high drug loading can cause the GMS to become saturated and ibuprofen can no longer be dissolved in the GMS unless a supersaturated solution can be formed. Formation of a completely saturated solution could not be determined visually as the ibuprofen would melt at 70^{o}C. If the molecularly dispersed ibuprofen exceeds the saturation value of the polymer, a proportion of undissolved ibuprofen encapsulated in the GMS may be molecularly dispersed under a metastable state. This would also result in partial recrystallisation of the drug in the matrix will be observed as the molecules crystallise under storage (Dubernet et al., 1991).

The scanning electron micrographs of the ibuprofen-GMS sprayed granules incorporating various drug particle size fractions at 2hrs and 24hrs post manufacture are shown in Figure 5.20-5.21, respectively.

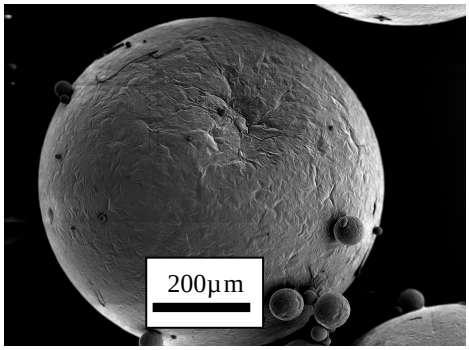
Visual inspection indicated the resulting sprayed material were spheroid with a smooth surface, granules appeared compact while uniform in size and shape. However, some of the sprayed material appeared to have smaller spheroidal particles (10-20µm) adhered to their surface and were observed on all sprayed batches.



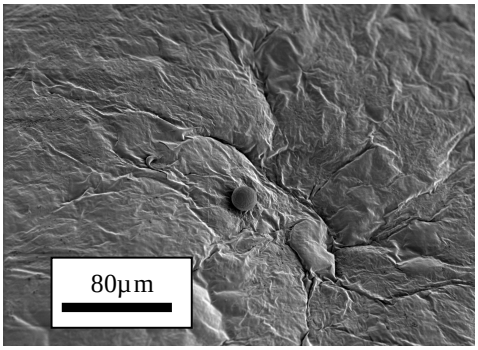
(1a)



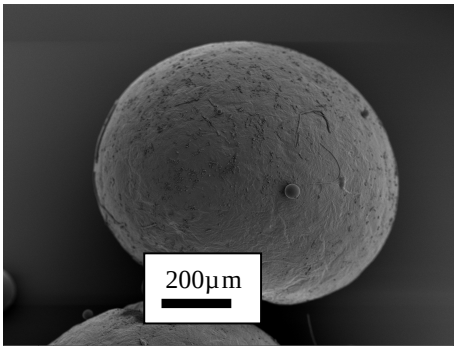
(1b)

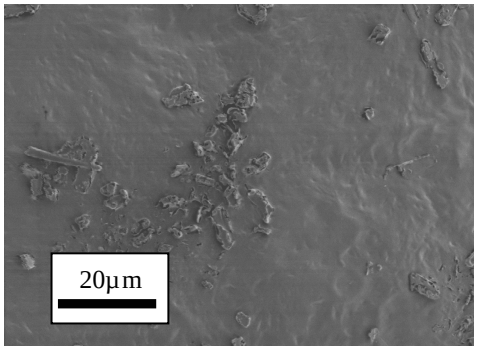


(2c)



(2b)

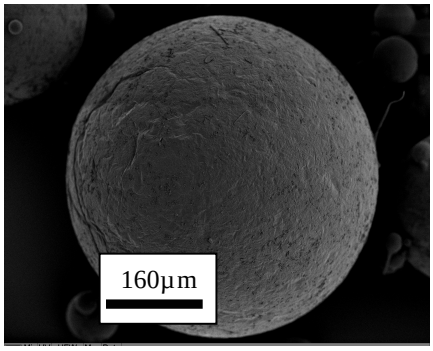




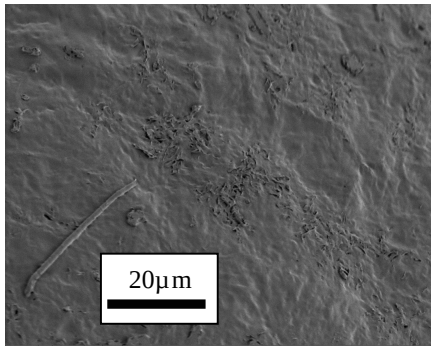
(3a) (3d)

Figure 5.20 SEM images of ibuprofen-GMS sprayed granules (10:90 %w/w), 2hrs post manufacture (1) 53-90µm ibuprofen, (2) 90-150µm ibuprofen, (3) 150-250µm ibuprofen at a magnification of (a) x140, (b) x500, (c) x200 and (d) x2000.

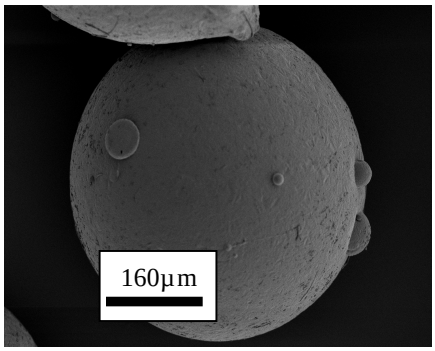
From Figure 5.20, at higher magnification ibuprofen crystals could be seen on the granule surface of the sprayed granules incorporating ibuprofen particles 150-250µm (3d). However, granules incorporating ibuprofen smaller than 150µm (1b and 2b) did not exhibit any ibuprofen crystals on its surface 2hrs post manufacture. In addition, for all sprayed ibuprofen-GMS granules the surface can be characterised as smooth, homogenous with some small, cracked crystalline domains that is characteristic of the α-form of GMS (Garti & Sato, 1988).



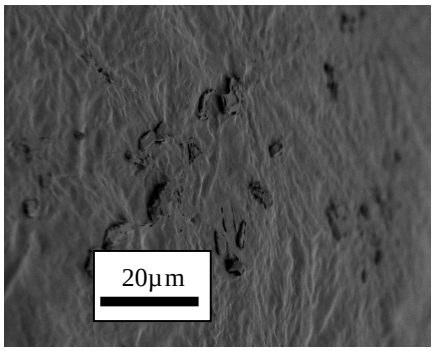
1(a)



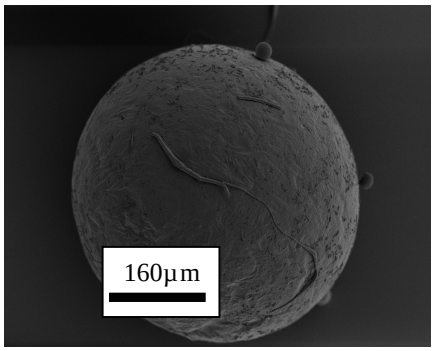
1(b)



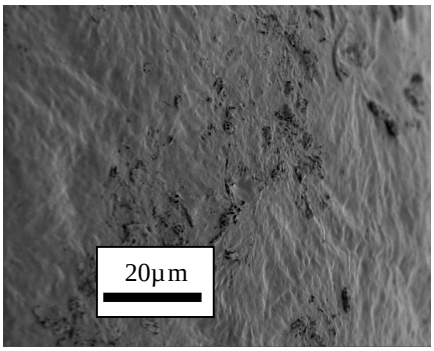
2(a)



2(b)



3(a)



3(b)

Figure 5.21 SEM images of ibuprofen-GMS sprayed material (10:90 %w/w) 24hrs post manufacture (1) 53-90µm ibuprofen, (2) 90-150µm ibuprofen, (3) 150-250µm ibuprofen at a magnification of (a) x250 and (b) x2000.

When sprayed material was visually assessed 24hrs post manufacture (Figure 5.21), ibuprofen crystals could be seen on the surface of all the sprayed granules (1b, 2b and 3b). Indicating that ibuprofen particles smaller than 150μm crystallise out of the sprayed granules 24hrs post manufacture.

The surface characteristics appear smooth which correlate to the presence of the α-form of GMS, even though the β-form of GMS is also present in the solid solution the α-form is the most prevalent 24hours post-manufacture. Upon storage of the samples, it may be expected for the GMS surface characteristics to become rougher in appearance (Garti & Sato, 1988; Eldem et al., 1991; Phajongwiriyathorn, 2008; Sutananta et al., 1994a).

Polarised microscopy was used to monitor 10:90%w/w ibuprofen-GMS sprayed material comprising of 0-90μm ibuprofen. The resultant photomicrograph was obtained at room temperature, 2 hrs and 48hrs post manufacture in Figure 5.22-5.23.

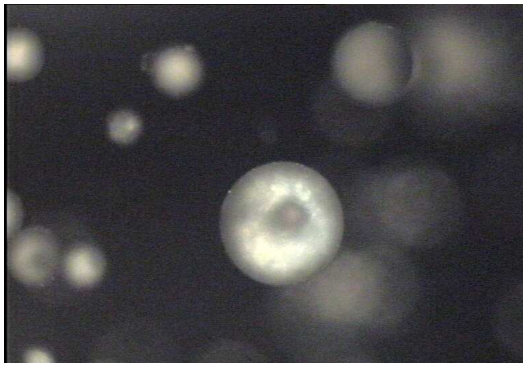


Figure. 5.22 Polarised photomicrograph of material formed from sprayed ibuprofen-GMS mixture, comprising of 53-90µm ibuprofen, 2hrs post manufacture at x10 magnification.

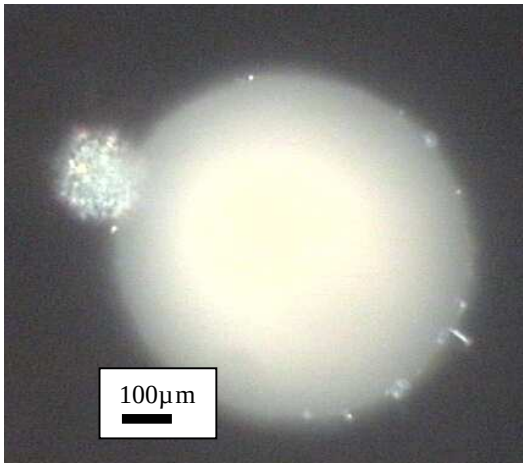


Figure. 5.23 Polarised photomicrograph of material formed from sprayed ibuprofen-GMS mixture, comprising of 53-90µm ibuprofen, 48hrs post manufacture at x25 magnification.

From figure 5.22-5.23, the polarised photomicrograph indicates crystallisation of ibuprofen from the sprayed ibuprofen-GMS granule at 48hrs post-manufacture (Figure 5.22) which was not present 2hrs post manufacture (Figure 5.23). This visually confirms when incorporating ibuprofen particles smaller than 90µm the ibuprofen becomes a solid

solution with the GMS and takes longer to crystallise out of the solid solution than for ibuprofen of a larger particle size that may not have formed a complete solid solution.

The effect of initial distribution of ibuprofen particle size on the resultant drug dissolution rate from sprayed GMS material is shown in figure 5.24.

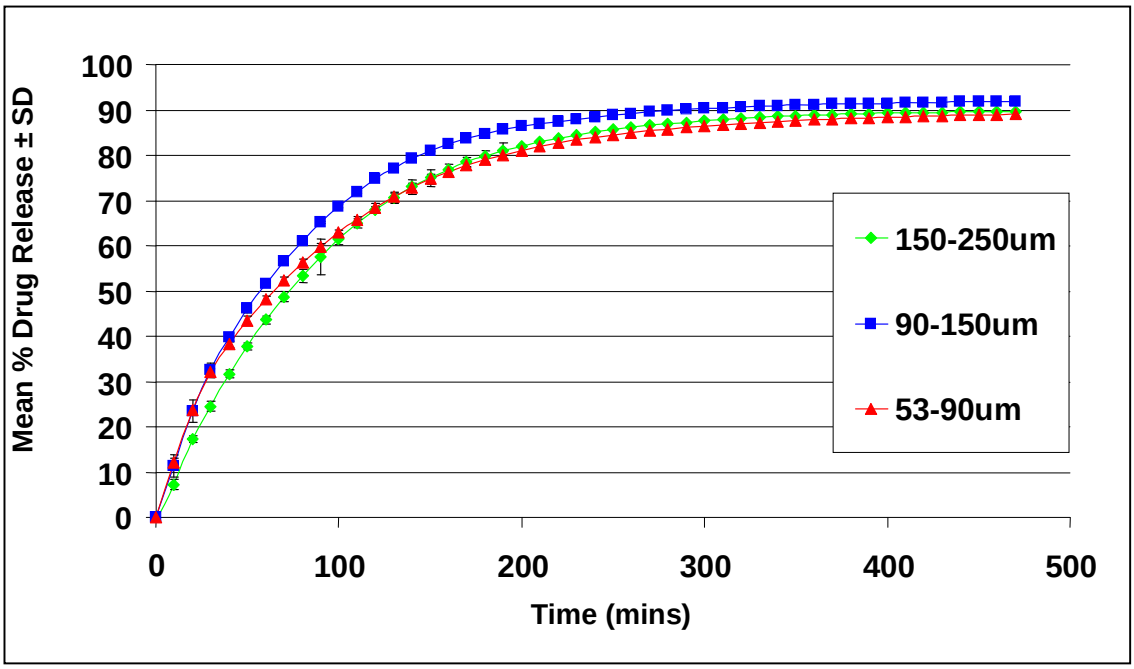


Fig. 5.24 Mean Release Profiles of sprayed 10:90%w/w ibuprofen-GMS sprayed mixtures with varying ibuprofen particle size fractions (n=6)

No significant difference (f2 value > 50) was observed between the dissolution release profiles for the three granule formulations manufactured incorporating ibuprofen of different particle sizes into a GMS mixture (Figure. 5.24). This suggests that the initial ibuprofen particle size and rate of ibuprofen crystallisation does not influence the drug release rate for the sprayed mixtures.

Conclusions

Granules of uniform size and shape can be successfully obtained from GMS solid dispersions and solid solutions utilising the agitated hot-melt spray system. The initial particle size of both the hydrophobic and hydrophilic drugs incorporated into the GMS sprayed granules did not significantly effect the PSD of the resultant sprayed granules.

The drug release profiles obtained for 10:90 %w/w GMS-ibuprofen sprayed mixtures do not exhibit immediate release or sustained release properties but are characteristic of modified release (refer to section 1.4).

The use of screening techniques such as DSC, HSM, XRPD and SEM were successfully employed to assess the thermal properties of the ibuprofen and paracetamol GMS sprayed mixtures. They enabled the identification of GMS polymorphic activity and the presence or absence of drug crystallisation within each of the sprayed mixtures.

Both α- and β-polymorphic forms of GMS appear to be present in all the Ibuprofen-GMS sprayed materials. The results appeared to correlate with the findings in Chapter 4 where GMS polymorphic forms were also present in the sprayed GMS granules in the absence of drug. This indicates the presence of these polymorphic transitions is independent of initial drug particle size and drug loading.

During the investigation of the paractamol-GMS sprayed material, the incorporation of ball-milled paracetamol powder less than 90µm in a sprayed solid dispersion of GMS-

paracetamol, impacted on the dissolution performance of the GMS granules. A decrease in the rate of drug release was observed due to the formation of a more effective GMS diffusional barrier. The rate-limiting step for drug release from the GMS matrix appears to be under control of diffusion in this instance. This was further confirmed by the compatibility of the Higuchian release model to the dissolution data. The thermal stability of paracetamol was not affected when the particle size distribution was reduced utilising a ball-milling technique, or during the atomisation process for hot-melt spraying.

For sprayed ibuprofen-GMS solutions, the drug loading of the drug proved to be important parameters for process development of the hot-melt spray system. For the ibuprofen-GMS sprayed material, the initial drug particle size appeared to directly influence the formation of a solid solution, despite molecular dispersion of ibuprofen further investigation is required. The formation of a complete solid solution or partial solid solution was shown to influence the rate of ibuprofen crystallisation post manufacture. This did not appear to have a detrimental effect on the T_0 release characteristics of the product. The ongoing stability of the mixture would need to be investigated to determine any long term effects.

For higher drug loadings than 10%w/w ibuprofen, manufacturing parameters including duration of stirring time and pressure would need to be optimised to allowing sufficient time for a solution or saturated solution to be achieved. The formation of a partial solid solution and solid dispersion co-existing would also result in ibuprofen crystallisation from the GMS during storage.

6. Investigation of Excipients in Hot-Melt Sprayed Hydrophobic Systems

6.1 Introduction

Aims and Objectives

Chapter 5 enabled the characterisation of the sprayed binary mixtures incorporating different APIs. To further investigate the hot-melt spray technique and resulting sprayed material, the effects of additional excipients were investigated. Commercial formulations rarely comprise of two components and as a result various excipients maybe incorporated into the solid solutions and dispersions to impart different properties. The effects of these excipients on physicochemical properties were investigated in this chapter.

Micronised paracetamol was utilised to ensure the particle size was reduced below 1000µm, to enable the drug to pass through the nozzle of the hot-melt spray system during formulation manufacture.

6.2 Methods

6.2.1 Investigation of Inorganic Salts addition and incorporation with ibuprofen and paracetamol sprayed GMS granules

Three types of inorganic salts were incorporated into ibuprofen and paracetamol sprayed GMS granules. The inorganic salts included aluminium hydroxide, aluminium monostearate and magnesium stearate.

Paracetamol and ibuprofen formulations with the compositions defined in Table 6.1 were manufactured using a hot-melt spray system at a temperature of 80^{o}C.

Table 6.1 Composition of the sprayed GMS granules.

Formulation	**API composition (%w/w)**	**GMS Composition (%w/w)**	**IMS Composition (%w/w)**
1	Paracetamol (10)	GMS (82.5)	Al monostearate (7.5)
2	Paracetamol (10)	GMS (82.5)	Al hydroxide (7.5)
3	Paracetamol (10)	GMS (82.5)	Mg stearate (7.5)
4	Ibuprofen (10)	GMS (82.5)	Al monostearate (7.5)
5	Ibuprofen (10)	GMS (82.5)	Al hydroxide (7.5)
6	Ibuprofen (10)	GMS (82.5)	Mg stearate (7.5)

These formulations were evaluated by PSD (section 2.4.2.1) and DSC (section 2.4.5). The dissolution of both paracetamol and ibuprofen from matrix systems were established using the methodology previously described (section 2.4.8).

6.2.2 Investigation of aluminium monostearate

6.2.2.1 Effect of processing temperature on GMS sprayed material

GMS formulations with the compositions and temperatures defined in Table 6.2 were manufactured using a hot-melt spray system.

Table 6.2 Composition and temperature of the sprayed GMS granules.

Formulation	**Processing temperature (ºC)**	**Composition (%w/w)**
1	80	GMS (97.5): Al monostearate (2.5)
2	80	GMS (95): Al monostearate (5)
3	80	GMS (92.5): Al monostearate (7.5)
4	80	GMS (90): Al monostearate (10)
5	125	GMS (97.5): Al monostearate (2.5)
6	125	GMS (95): Al monostearate (5)
7	125	GMS (92.5): Al monostearate (7.5)
8	125	GMS (90): Al monostearate (10)

These formulations were analysed by PSD (section 2.4.2.1) and DSC (section 2.4.5).

6.2.2.2 Effect of composition on GMS hot-melt material produced via wax fusion

GMS formulations with the compositions defined in Table 6.3 were manufactured using wax fusion at a temperature of 80^{o}C.

Table 6.3 Composition of the hot-melt GMS material.

Formulation	**Composition (%w/w)**
1	GMS (97.5): Al monostearate (2.5)
2	GMS (95): Al monostearate (5)
3	GMS (92.5): Al monostearate (7.5)
4	GMS (90): Al monostearate (10)

These formulations were evaluated by DSC (section 2.4.5).

6.2.2.3 Effect of composition on release rate of ibuprofen from sprayed GMS granules

Ibuprofen formulations with the compositions defined in Table 6.4 were manufactured using a hot-melt spray system at a temperature of 80^{o}C.

Table 6.4 Composition of the ibuprofen sprayed GMS granules.

Formulation	**Composition (%w/w)**
1	GMS (87.5):Ibuprofen (10): Al monostearate (2.5)
2	GMS (85):Ibuprofen (10): Al monostearate (5)
3	GMS (80):Ibuprofen (10): Al monostearate (10)

These formulations were evaluated by PSD (section 2.4.2.1) and DSC (section 2.4.5). The dissolution of ibuprofen from the matrix was established using the methodology previously described (section 2.4.8).

6.2.2.4 Effect of aluminium monostearate concentration on release rate of paracetamol from sprayed GMS granules

Paracetamol formulations with the compositions defined in Table 6.5 were manufactured using a hot-melt spray system at a temperature of 80^{o}C.

Table 6.5 Composition of the paracetamol sprayed GMS granules.

Formulation	**Composition (%w/w)**
1	GMS (87.5):Paracetamol (10): Al monostearate (2.5)
2	GMS (85):Paracetamol (10): Al monostearate (5)
3	GMS (82.5):Paracetamol (10): Al monostearate (7.5)
4	GMS (80):Paracetamol (10): Al monostearate (10)

These formulations were evaluated by DSC (section 2.4.5). The dissolution of paracetamol from the matrix was established using the methodology previously described (section 2.4.8).

6.2.3 Characterisation of Glyceryl Dibehenate (Compritol® 888 ATO) in sprayed GMS material

10% w/w of ibuprofen was incorporated into varying compositions of GMS:GDB sprayed formulations. The compositions of GMS:GDB are defined in Table 6.6 and were manufactured using a hot-melt spray system at a temperature of 80^{o}C.

Table 6.6 Composition of the sprayed GMS:GDB granules.

Formulation	GMS:GDB Composition (%w/w)
1	GMS (90):GDB (10)
2	GMS (80):GDB (20)
3	GMS (70):GDB (30)
4	GMS (60):GDB (40)

These formulations were evaluated by PSD (section 2.4.2.1) and DSC (section 2.4.5). The dissolution of ibuprofen from the matrix was established using the methodology previously described (section 2.4.8).

6.3 Results and Discussion

6.3.1 Investigation of Inorganic Multivalent Salts (IMS) incorporation with ibuprofen and paracetamol sprayed GMS granules.

6.3.1.1 Ibuprofen sprayed granules

The PSD of sprayed granules are shown in Figure 6.1.

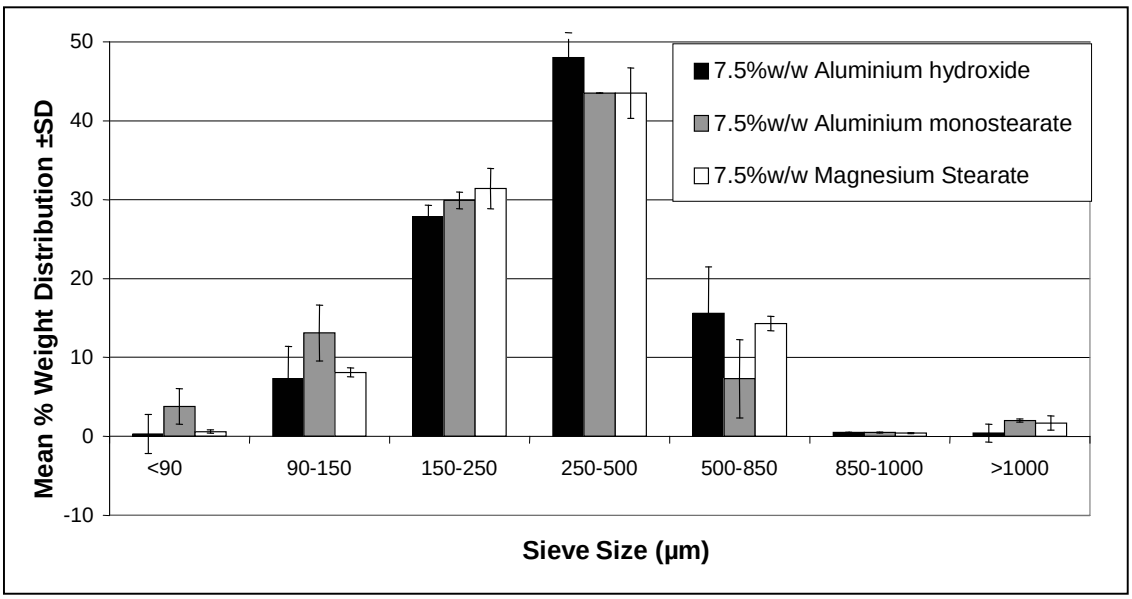


Figure 6.1 Particle size distribution of sprayed ibuprofen-GMS material incorporating inorganic multivalent salts (n=3)

Statistical comparison of the PSD (Figure 6.1) indicated there was no significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed granules is independent of the metal adjuvant incorporated into the GMS matrix.

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the sprayed granules with varying metal adjuvant compositions. The DSC profiles of sprayed materials monitored are shown in Figure 6.2.

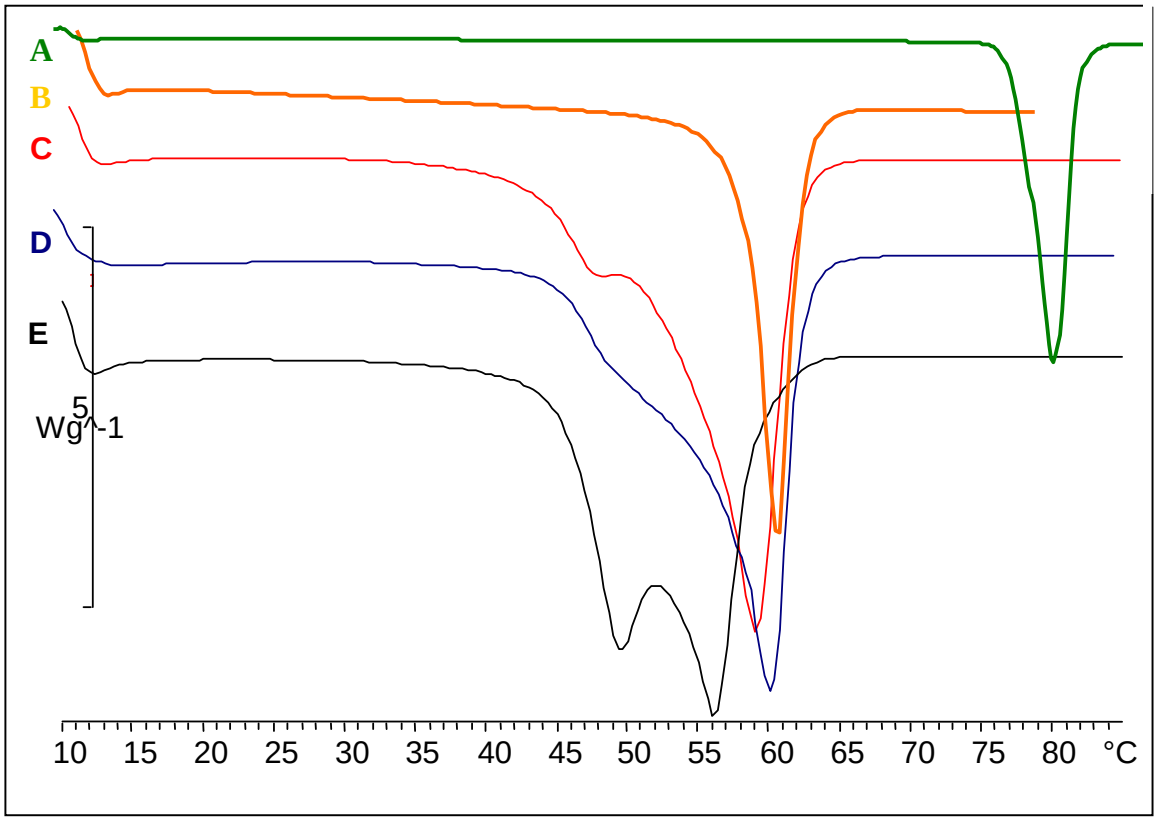


Figure 6.2 DSC profiles of sprayed ibuprofen-GMS material with varying metal adjuvant composition at Day 1 A) Ibuprofen only, (B) GMS only, (C) Magnesium stearate, (D) Aluminium monostearate and (E) Aluminium hydroxide (scale bar = heat flow of 5 watts per gram).

From Figure 6.2, all sprayed granules have an absent drug peak at ~70˚C indicating the ibuprofen may dissolve in the molten wax during processing. The endotherms for aluminium monostearate, aluminium hydroxide and magnesium stearate are not visible

on the thermogram as the melting point of these materials are 125^{o}C, 300^{o}C and 88^{o}C respectively (Lower, 1982; Parojcic & Corrigan, 2008). These temperatures were beyond the temperature range (10-85^{o}C) of this DSC method.

DSC analysis of the ibuprofen-GMS sprayed material containing aluminium hydroxide illustrated primary and secondary endotherms at ~49˚C and 56˚C. These results appear to correspond to the endotherms obtained for ibuprofen-GMS binary sprayed mixtures in Section 5.3.2, indicating the presence of aluminium hydroxide in the sprayed formulation (figure 6.2) does not interact with ibuprofen or GMS and formation of the ibuprofen-GMS solid solution is achieved. Kararli et al (1989) also did not detect any interactions between the aluminium hydroxide and ibuprofen when stored at 55^{o}C for 15 months and was attributed to the chemicals lower basicity in solid form. The DSC method utilised for Kararli et al (1989) was run beyond 160^{o}C and no further endotherms were identified at the higher temperatures.

Hamdani et al (2003) indicated for lipophilic glycerides a non-significant endothermic shift of ±2˚C may represent polymorphic transitions when compared to XRPD results. As a result, polymorphic changes of GMS may be present in this sample that cannot be detected utilising DSC alone, the results must be interpreted cautiously in the absence of XRPD and an assumption these results correlate to figure 5.13 cannot be made. Further consideration is also required when interpreting the results from figure 6.2, as weak acid ibuprofen has been demonstrated to react in a solid state with various basic oxides, hydroxides and salts (Kararli et al., 1989). Mg^{2+} and Al^{3+} salts have been demonstrated to

interact with ibuprofen via the same mechanism to form eutectic solutions with magnesium stearate, calcium stearate, stearic acid and stearyl alcohol all with melting points below 59^{o}C (Bharate et al., 2010; Khan et al., 1995).

Sprayed formulations comprising of aluminium monostearate and magnesium stearate both exhibit primary peaks at 60˚C and 59^{o}C, respectively and correlate to the melting point of either β-form GMS or stearic acid. The melting point of stearic acid, a component of both aluminium and magnesium stearate, is characterised at 60^{o}C (British Pharmacopoeia, 2012), however it is improbable dissociation of metal stearates can take place in a non-aqueous environment. Further characterisation of this endotherm needs to be undertaken via XRPD or FT-IR.

The presence of both metal stearate additives in sprayed ibuprofen-GMS mixtures appear to promote the presence of the GMS primary endotherm and was also exhibited for sprayed GMS material. The presence of free β-form GMS would suggest the GMS matrix is not fully saturated by the presence of both ibuprofen and metal stearates. It would be of interest to determine the maximum drug loading capabilities of this delivery system, to determine whether the presence of the metal stearates impact the saturation capability of the matrix when compared to ibuprofen-GMS binary materials only (Section 5.3.2).

A decrease in the secondary peak (~48^{o}C) intensity is observed for the formulation comprising of aluminium monostearate when compared to aluminium hydroxide and previous binary ibuprofen GMS mixtures (section 5.3.2). This indicates the presence of

the metal stearates may be increasing the transition rate of GMS to the more stable β-form meaning ibuprofen may be forming solid solutions with both the β-form and the α-form of GMS (Section 5.3.2). However, it is difficult to interpret whether there is an endotherm present at ~55^{o}C due to the broad primary endotherm but the DSC method could be adapted and run at a higher rate to enable further peak separation on the thermogram. Further analysis should be undertaken utilising XRPD, to identify the polymorphic GMS forms and solid solutions that may be present. Also a stability study could be undertaken such as Lerdkanchanaporn et al (2001) to determine if further transition may occur from any eutectic solutions formed in the presence of multivalent stearates.

The dissolution profile of the sprayed ibuprofen-GMS granules with varying multivalent organic salts are shown in Figure 6.3.

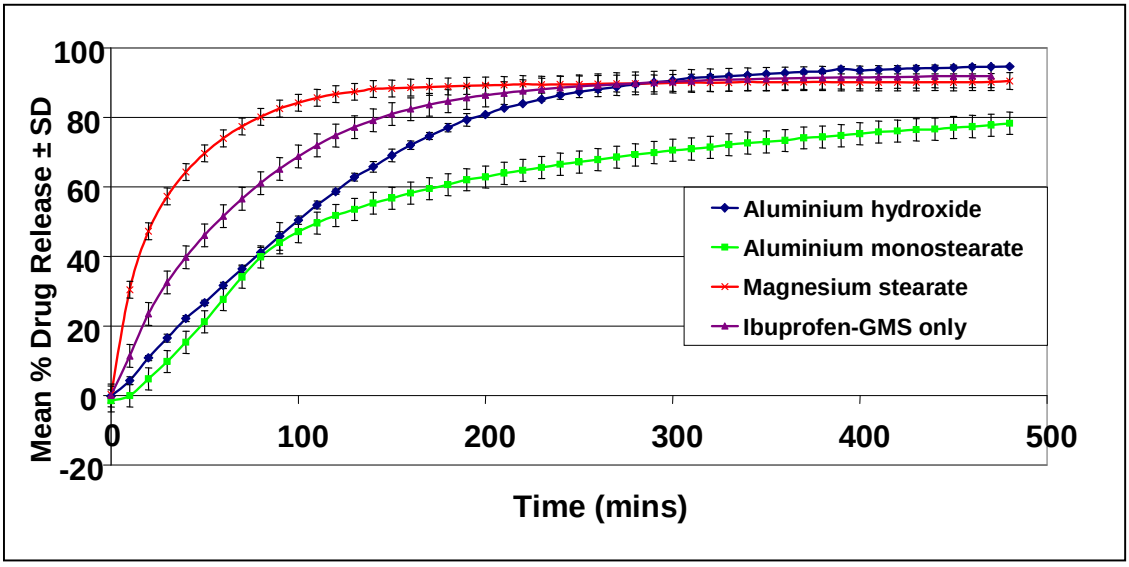


Figure 6.3 Mean Release Profiles of sprayed ibuprofen-GMS material with varying metal additive inclusion (n=6).

Mean drug release profiles for ibuprofen sprayed granules (Figure 6.3) indicate that the type of metal additive incorporated into the granules has a significant impact on the drug dissolution performance of the resultant product. Both aluminium hydroxide and aluminium monostearate significantly decrease the ibuprofen dissolution rate from resultant granules (f_2 value < 50). It appears the presence of the aluminium salt has a more pronounced effect on the dissolution rate than the wax polymorphic state of the delivery system. This is anticipated as the salt form of a drug can have a profound impact on the physicochemical properties of an organic molecule more than any other single means (Qiu et al., 2009).

The sprayed material incorporating the magnesium stearate is classified as modified release and not immediate release, as less than 75% of the drug had been released by 45 minutes (British Pharmacopoeia, 2012). The drug release rate for magnesium stearate sprayed material is faster than the binary GMS-ibuprofen only sprayed mixture, indicating the presence of the magnesium stearate in the GMS mixture significantly enhances the drug release rate (Parojcic & Corrigan, 2008). Similar effects were observed with magnesium hydroxide and magnesium oxides leading to enhanced ibuprofen solubility, dissolution and bioavailability, with formulation and process variables being the rate limiting step (Kararli et al., 1989; Neuvonen, 1991; Ogawa & Echizen, 2011).

These observations may be attributed to a pH effect due to the alkaline nature of magnesium stearate. The increase in local (surface) solution pH would promote the

ibuprofen salt to be formed which has a higher solubility than the unionised form (Aulton, 2002; Shaw et al., 2005).

The drug release from the sprayed material incorporating the aluminium hydroxide was prolonged significantly longer than for the magnesium stearate sprayed material and the binary GMS-ibuprofen sprayed mixtures (Figure 5. 24). However, the sprayed material incorporating the aluminium hydroxide is also classified as modified release rather than sustained release as 30% of the initial drug release was prior to 60 minutes (Section 1.4). The mechanism of the prolonged release is inconclusive but may be due to the presence of the multivalent salt Al^{3+} forming an insoluble complex with the ibuprofen salt at the point of surface dissolution (Ogawa & Echizen, 2011; Parojcic & Corrigan, 2008).

The sprayed material incorporating the aluminium monostearate is classified as sustained release as only 27.6% ± SD of the drug was release by 60 minutes, 50% ± SD drug release was achieved by 120 minutes and 80% ± SD of the drug release took over 340 minutes to achieve (British Pharmacopoeia, 2012). The maximum drug release achieved in 8hrs for the aluminium monostearate granules was approximately 80%. Ethanolic extraction was undertaken to confirm if the anticipated quantity of ibuprofen was present in the granules. The mean amount of ibuprofen extracted from the sprayed granules was 102.2% ± 4.1, confirming the expected drug loading was achieved during manufacture but incomplete drug dissolution was achieved over the test period.

The presence of the multivalent salt Al^{3+} appears to significantly retard the drug release rate and correlates to an observation by Parojcic & Corrigan (2008) indicating in the presence of aluminium hydroxide an insoluble ibuprofen salt is formed with Al^{3+}. From figure 6.3, release profiles obtained for aluminium monostearate and aluminium hydroxide follow this observed trend until 100 minutes. Post 100 minutes, even though the drug release rates remain more retarded for the formulations containing Al^{3+}, the ibuprofen is released more rapidly from the aluminium hydroxide formulation than the aluminium monostearate formulation, indicating the mechanism of drug release changes. The observed changes between aluminium formulations may be due to their different interaction with the aqueous environment.

It is possible that once the aluminium hydroxide formulation has commenced dissolution, the aqueous environment provides an opportunity for the Al^{3+} and ibuprofen to interact. It is possible in the presence of the aqueous phase the basic compound aluminium hydroxide increases the pH of the aqueous phase after 100 minutes, promoting ibuprofen to become ionised and increasing the drug solubility. Equal consideration is required for aluminium monostearate in an aqueous environment where potential interactions may contribute to the decrease in drug release rate observed. In the presence of aluminium stearate in a pH neutral aqueous solution promotes partial dissociation of aluminium stearate (US Environmental Protection Agency, 2003), this dissociation during dissolution may lead to a reduction in the pH of the aqueous solution significant enough to decrease the ibuprofen solubility (Parojcic & Corrigan, 2008). Both suggested

explanations could be confirmed by testing the pH of the dissolution vessels throughout the dissolution run to detect any pH alteration.

It is of significant importance to determine whether the difference between aluminium monostearate and aluminium hydroxide is due to pH differences during dissolution or whether there is also physicochemical interactions taking place. As literature indicates the presence of an aluminium salt of stearic acid may also contribute to the hydrophobicity of the GMS matrix system, reducing the surface wetting ability of the dissolution media thereby further decreasing the drug release (Attwood & Florence, 2008; Hamdani et al., 2003). Investigation into the possible presence of stearic acid in the molten mixture is a consideration on the product performance due to its various polymorphic forms and documented interactions with the S-enantiomer of ibuprofen (Corvis et al., 2011; Lerdkanchanaporn et al., 2001).

Consideration of the aluminium manufacturing vessel and ibuprofen adsorption due to aluminium complex formation was eliminated due to the 100% drug recovery from the ethanolic extraction method. Developing inert equipment is an important attribute for pharmaceutical application in a manufacturing environment where multiple products are manufactured utilising the same equipment. Successful removal of active materials from manufacturing equipment surfaces prevents cross-contamination between different products and eliminates potential formulation problems due to API adsorption that may reduce the effective concentration (Qiu et al., 2009).

Visual examination of GMS-ibuprofen sprayed granules are shown in figure 6.4.

Figure 6.4 Macroscopic appearance of ibuprofen-GMS sprayed granules produced at 80^{o}C with varying multivalent organic salts at 7.5%w/w.

Sprayed material comprising of magnesium stearate or aluminium hydroxide did not visually appear any different to sprayed material composed of ibuprofen-GMS binary mixtures (Section 5.3.2.2). This indicates the liquid properties of the molten ibuprofen-GMS mixtures were not significantly affected by the addition of either magnesium stearate or aluminium hydroxide. Visual examination of the ibuprofen-GMS sprayed granules (Figure 6.4) indicated granules containing aluminium monostearate to be 'fluffy' and light in texture at 7.5%w/w content. Any changes in viscosity could not be visually confirmed prior to spraying when each formulation was molten at 80^{o}C but changes in

viscosity would be anticipated to influence the size range of the sprayed material. Changes in the size range have been shown to impact the spray angle and speed in which the sprayed material is atomised, impacting on the solidification time during descent in the spray chamber (Maschke et al., 2007; Nuyttens et al., 2007).

Further characterisation of the sprayed GMS material with aluminium monostearate is required to evaluating any thickening effect on the molten solution prior to spraying that may explain the effects observed (Section 6.3.3).

6.3.1.2 Micronised paracetamol sprayed granules

The PSD of sprayed granules are shown in Figure 6.5.

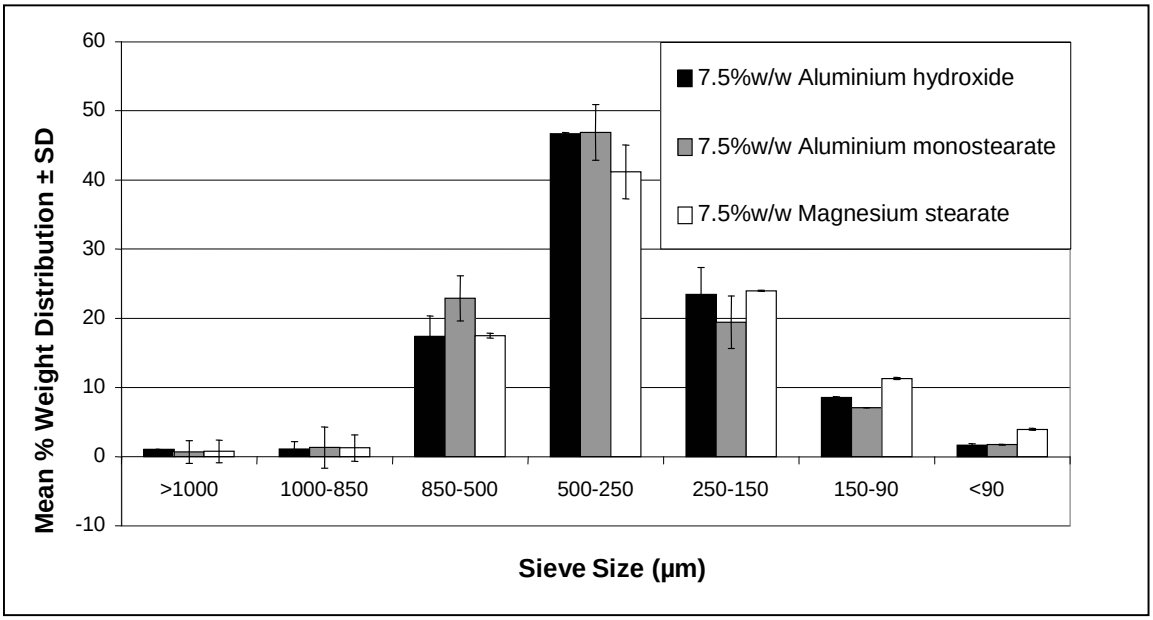


Figure 6.5 Particle size distribution of sprayed paracetamol-GMS material (n=3).

Statistical comparison of the PSD (Figure 6.5) indicated there was no significant difference in the distributions obtained for the sprayed paracetamol-GMS material

containing different multivalent inorganic salts (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed paracetamol-GMS material is independent of the type of multivalent inorganic salt incorporated into the GMS matrix.

In addition, there is no significant difference between sprayed paracetamol-GMS material (figure 6.5) and paracetamol-GMS sprayed binary material (figure 5.5), indicating the presence of a multivalent inorganic salt does not effect the PSD of sprayed material produced.

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the sprayed paracetamol-GMS material with varying inorganic multivalent salt compositions (figure 6.6).

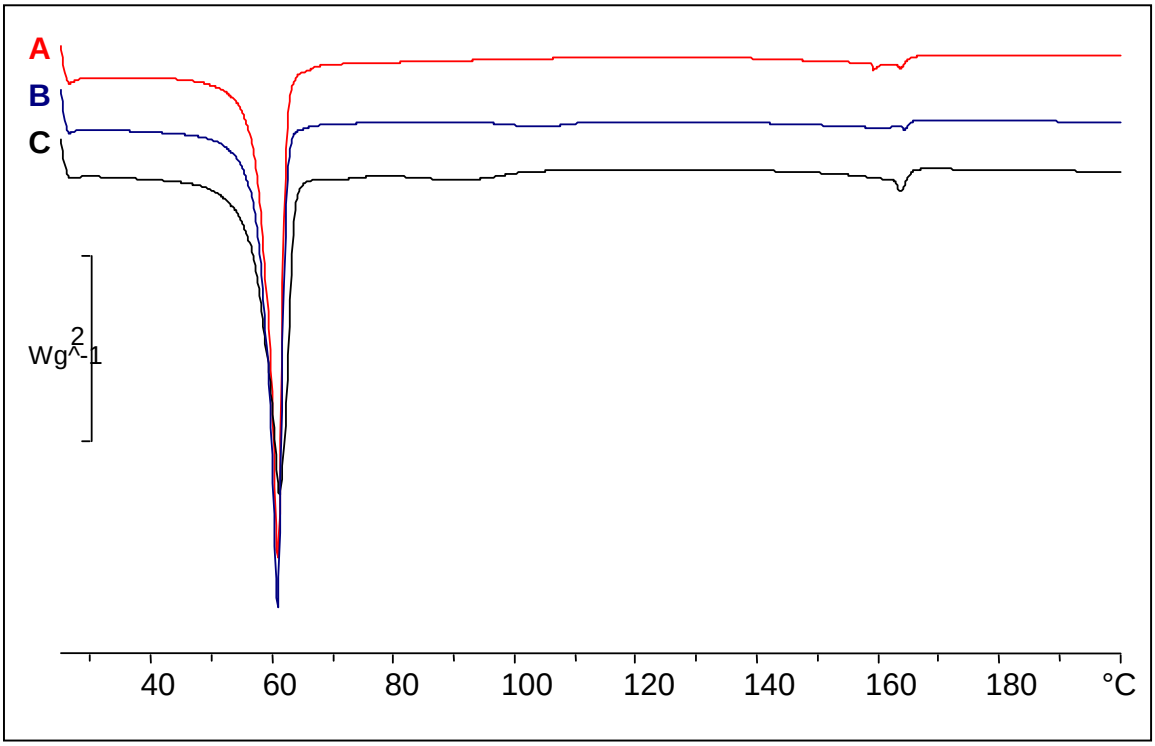


Figure 6.6 DSC profiles of sprayed paracetamol-GMS material with varying metal adjuvant composition at Day 1 (A) Aluminium hydroxide, (B) Aluminium monostearate and (C) Magnesium Stearate (scale bar = heat flow of 2 watts per gram).

From Figure 6.6, all sprayed paracetamol-GMS granules have a primary peak at ~60^{o}C and a secondary peak at ~163^{o}C. Slight endotherms are exhibited also at 88^{o}C and 105^{o}C correlating to the metal stearates. The melting point for aluminium hydroxide would be anticipated at 300^{o}C and would not be visible in figure 6.6 as the DSC method was run between 20-200^{o}C.

Aluminium monostearate is anticipated at 125^{o}C suggesting a possible interaction has occurred with the GMS or paracetamol, binary mixtures of GMS and aluminium monostearate are investigated in figure 6.15. The primary peak exhibited at 60^{o}C is

representative of the GMS in the sprayed solid dispersion. The secondary primary peak at 163^{o}C cannot be characterised without further confirmatory analysis via FT-IR or XRPD.

Milled paracetamol was characterised with a melting point of 171^{o}C (figure 5.3), no endotherm corresponding to paracetamol was observed in figure 6.6. This indicates either the paracetamol is not present in the same crystalline form when in the presence of the inorganic multivalent salts or the proportion present is below the sensitivity of the detection method. The secondary endothermic peak at 163^{o}C, present in all paracetamol-GMS formulations, does not correlate to the paracetamol anticipated melting point polymorphic forms. However, the presence of the GMS lipid may dissolve a portion of the paracetamol and reducing the melting endotherm but would require confirmation via XRPD. The melting point of polymorph form I would be anticipated at 167^{o}C and the metastable polymorph from II at 159^{o}C (Giordano et al., 2002). The slight endotherm exhibited at 159^{o}C in the sprayed granules containing aluminium hydroxide will need confirmatory analysis for the presence of paracetamol form II, as this may contribute to the release rate of the formulation. In figure 6.6, the paracetamol formulations do not indicate formation of eutectic mixtures as no endotherms were expressed below the melting points of the formulation components.

A number of divalent and trivalent cations have been shown to interact with paracetamol, including Al^{3+}, Fe^{3+}, Mg^{2+}, Ca^{2+} (Albin et al., 1985; Bharate et al., 2010; Iwuagwu & Aloko, 1992; Ogawa et al., 2011; Wen & Park, 2010). Further investigation involving

HSM and XRPD is required to define the paracetamol crystalline state in the sprayed granules (Martino et al., 1996; Moynihan & Hare, 2002).

Complex thermal behaviour of surfactants and stearates must be considered when interpretating the thermogram in figure 6.6, as some surfactants and stearates are able to form mesomorphic phases between the solid and liquid crystal phases (Hattianghi et al., 1949; Rosevear, 1968). In a study undertaken by Roblegg et al. (2011), to evaluate calcium stearate pellets produced via hot-melt extrusion, structural rearrangement of calcium stearate was observed into a mesomorphic state. Thermal analysis observed an endotherm at 163^{o}C correlating to the transition from the smectic to the nematic mesomophic state. Further understanding of the crystalline behaviour between the solid and liquid crystalline state is required to define the design space for these formulations.

The results of the sprayed paracetamol granules with varying metal adjuvant compositions are shown in Figure 6.7.

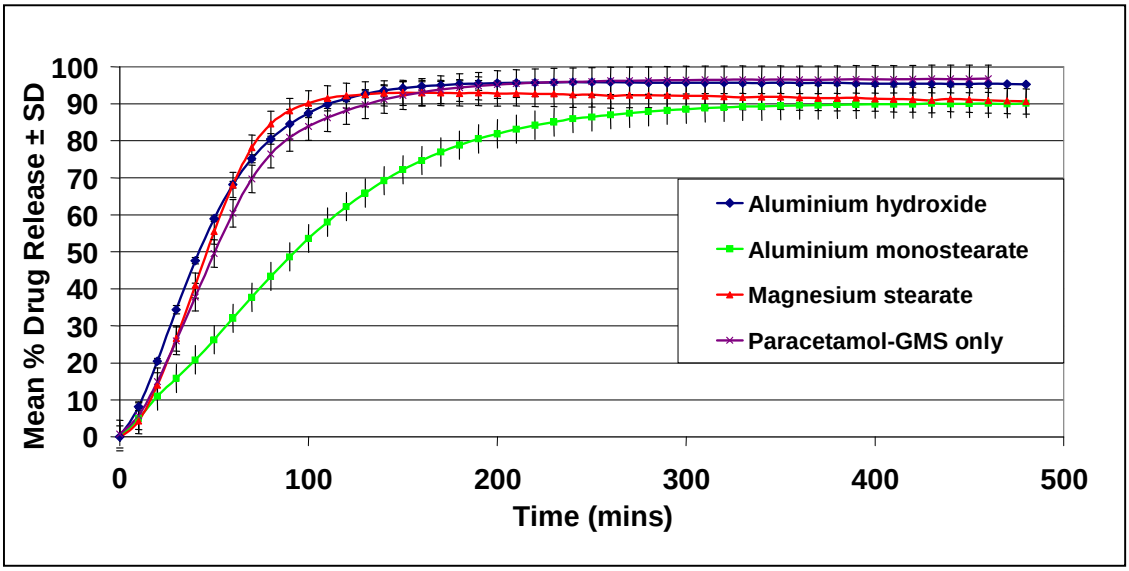


Figure 6.7 Mean release profiles of sprayed paracetamol granules with varying metal additives composition (n=6).

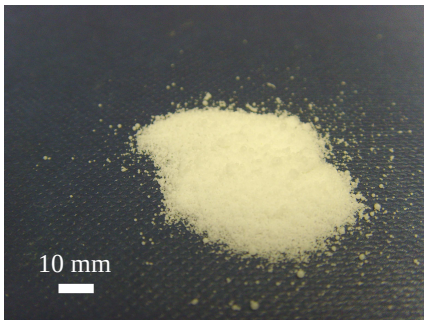
Mean drug release profiles for paracetamol-GMS sprayed granules (Figure 6.7) indicate that the type of metal additive incorporated into the granules has a significant impact on the dissolution performance of the resultant product.

Incorporation of the aluminium monostearate significantly decreases the drug release rate, enabling a sustained-release pattern to be achieved for the paracetamol-GMS sprayed material, unlike the release rates obtained for sprayed material containing paracetamol-GMS only (f_2 value < 50). Total drug release was achieved during the dissolution test period (Ogawa & Echizen, 2011). Further investigation into the relationship between the aluminium monostearate concentration and the drug release is required.

The drug release for paracetamol-GMS sprayed material incorporating the aluminium hydroxide was classified as modified release but was not as significantly prolonged as the drug release rate observed for the ibuprofen equivalent formulation (f_2 value < 50). This indicates the mechanism of drug release is dependent on the drug incorporated for formulations comprising of aluminium hydroxide. Also, the mechanism of drug release is different for aluminium hydroxide and aluminium monostearate formulations incorporating paracetamol, as the presence of aluminium does not appear to contribute to the release effects observed in figure 6.7. Further characterisation of the thermal properties is required to determine whether the differences between the drug release rates of the two aluminium based formulations is attributed to the differences observed in the thermograms (figure 6.6).

Sprayed material incorporating magnesium stearate appears to have a prolonged drug release rate in paracetamol-GMS sprayed material than observed in the ibuprofen equivalent sprayed material. During dissolution in aqueous phase, it appears the release rate of the paracetamol based formulation is not enhanced as observed in the ibuprofen equivalent formulation (Aulton, 2002; Shaw et al., 2005).

Visual examination of paracetamol sprayed granules are shown in figure 6.8.



Magnesium stearate

Aluminium hydroxide

Aluminium monostearate

Figure 6.8 Digital photographs of paracetamol-GMS sprayed granules produced at 80^{o}C with varying multivalent salts at 7.5%w/w.

Visual examination of the paracetamol sprayed granules (Figure 6.8) indicated the different multivalent salts had no significant effect on the appearance of the resultant material. The appearance of the paracetamol-GMS sprayed material is granular, not fluffy and light in texture. This physical morphology of the aluminium monostearate formulation incorporating ibuprofen was significantly different in appearance (figure 6.4).

6.3.2 Investigation of aluminium monostearate

6.3.2.1 Effect of concentration and spray temperature on hot-melt GMS:aluminium monostearate binary mixtures

The PSD of sprayed GMS granules with varying aluminium monostearate concentrations at two different processing temperatures are shown in Figure 6.9 and 6.10. No API was included in this study.

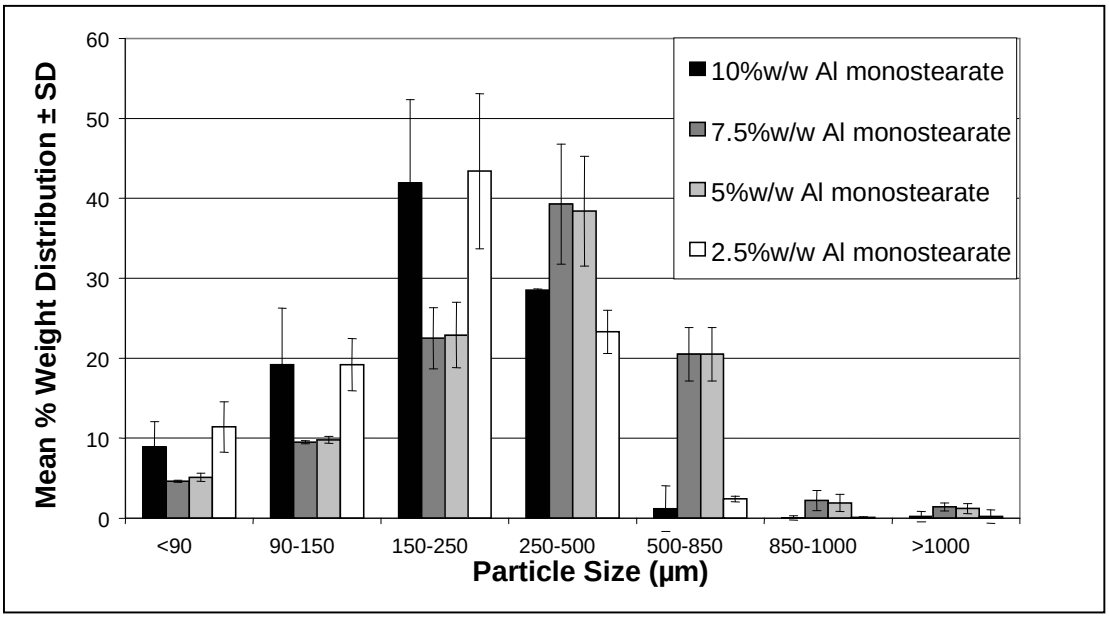


Figure 6.9 Particle size distribution of sprayed GMS material with varying aluminium monostearate concentrations at 80˚C (n=3).

Statistical comparison of the PSD (Figure 6.9) indicated there was a significant difference in the PSD (Two-way ANOVA; $p<0.05$) when different concentrations of aluminium monostearate were incorporated into the molten GMS at 80˚C.

Sprayed GMS (figure 4.1) had a prevalent size range of 250-500µm and less than 5% of the weight distribution was greater than 850µm. As observed from figure 6.9, an aluminimum monostearate concentration between 5-7.5%w/w yields a larger proportion of particles in the 500-850µm size range, however, the majority of the particles remain between 250-500µm.

The PSD profiles obtained for the spray material incorporating both 2.5%w/w and 10%w/w aluminium monostearate are similar. Both exhibit a significant downward shift in the PSD with the most prevalent size range being 150-250µm for the sprayed binary material. To further understand this observation the thermal properties of the mixtures must be evaluated (Section 6.3.2.1). The molten solution at 80^{o}C had a low viscosity and the aluminium monostearate added remained undissolved in the molten mixture.

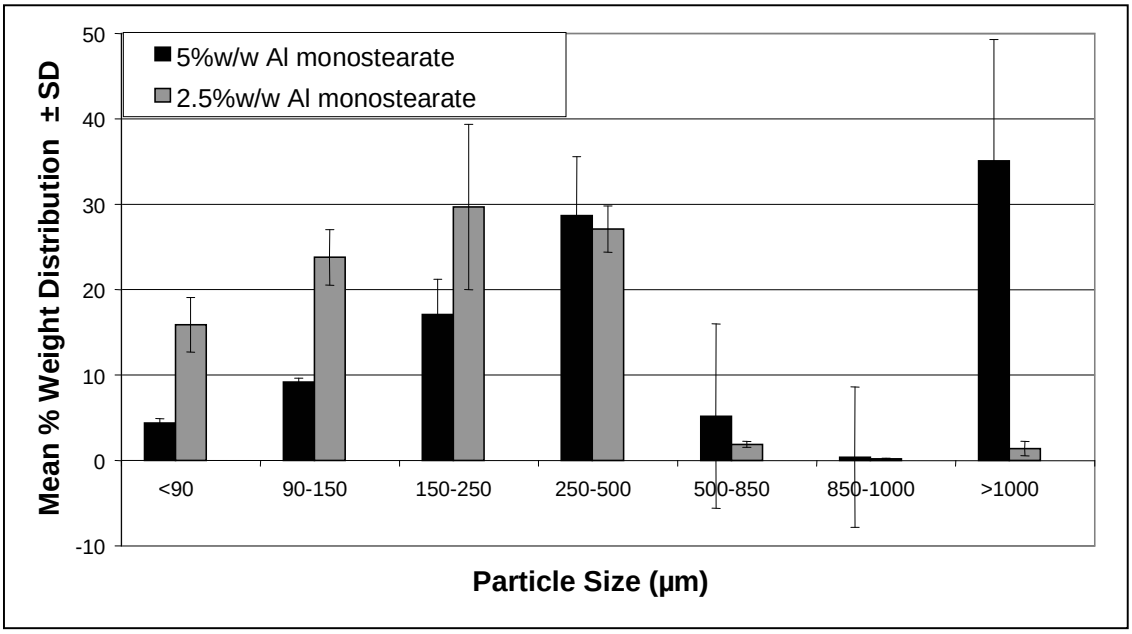


Figure 6.10 Particle size distribution of sprayed GMS material with varying aluminium monostearate concentrations at 125˚C (n=3).

Statistical comparison of the PSD (Figure 6.10) indicated there was a significant difference in the PSD of the sprayed material with 2.5 and 5%w/w aluminium monostearate (Two-way ANOVA; $p<0.05$) when different concentration of aluminium monostearate were incorporated into the molten GMS at 125^{o}C.

When 2.5%w/w aluminium monostearate is utilised at the elevated temperature the majority of the particles are between 150-250µm (30%), this correlates to the PSD obtained in figure 6.9, when 2.5%w/w aluminium monostearate was incorporated into sprayed granules at 80^{o}C. This indicates that the increase in the processing temperature had no significant effect on the resultant sprayed granules.

When 5%w/w aluminium monostearate is utilised at the elevated temperature the majority of the particles are greater than 1000µm (36%), the PSD were not normally distributed with 36% greater than 1000µm. The remaining particles were below 500µm. Sprayed material containing more than 5%w/w could not be sieved as the material texture had altered and was too fluffy/fibrous in texture (figure 6.11).

Sprayed GMS (figure 4.1) and ibuprofen-GMS binary mixtures (figure 5.11) had a prevalent size range of 250-500µm and less than 5% of the weight distribution was greater than 850µm. As observed from figure 6.10, the PSD for sprayed mixtures at 125^{o}C containing an aluminium monostearate concentration between 2.5-5%w/w do not correspond to the sprayed GMS material (figure 4.1) or ibuprofen-GMS sprayed binary mixtures (figure 5.11).

The increase in the PSD when 5%w/w aluminium monostearate is utilised, and the change in the nature of the sprayed material greater than 5%w/w can be related to the melting point of the aluminium monostearate (125^{o}C). Aluminium monostearate dissolves to a gel when heated to its melting point and is known to form permanent, transparent and viscous solutions or gels (Lower, 1982).

Digital photographs of the resultant sprayed GMS material processed at 80^{o}C are illustrated in figure 6.11. Prior to spraying the molten GMS had a low viscosity and the molten solution was white due to the presence of undissolved aluminium monostearate. No API was included in this study.

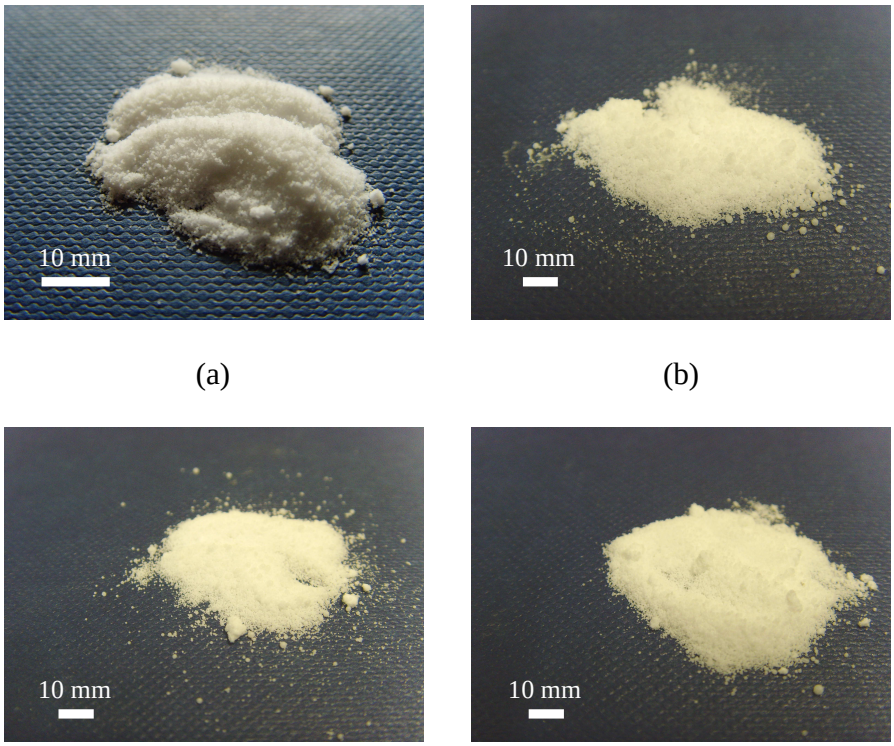


Figure 6.11 Macroscopic characteristics of GMS sprayed granules containing varying aluminium monostearate concentrations (a) 2.5%w/w, (b) 5%w/w, (c) 7.5%w/w, (d) 10%w/w at a processing temperature of 80˚C.

Visual examination of the sprayed GMS material (Figure 6.11) indicated that for the sprayed material manufactured at 80˚C the amount of aluminium monostearate incorporated into the sprayed GMS had no significant effect on the appearance of the resultant sprayed material.

Digital photographs of the resultant sprayed GMS material processed at 125^{o}C are illustrated in figure 6.12. Prior to spraying, the molten GMS containing the aluminium

monostearate appeared to have a higher viscosity than the molten material at 80°C. As the concentration of the aluminium monostearate increased the viscosity of the molten mixture increased. In all instances clear gels were formed during agitation at 125°C and the aluminium monostearate was no longer visible in the molten GMS. Thermal analysis would need to be conducted to confirm whether the aluminium monostearate has dissolved in the molten wax or simply melted at 125°C as anticipated (Section 6.3.2.1).

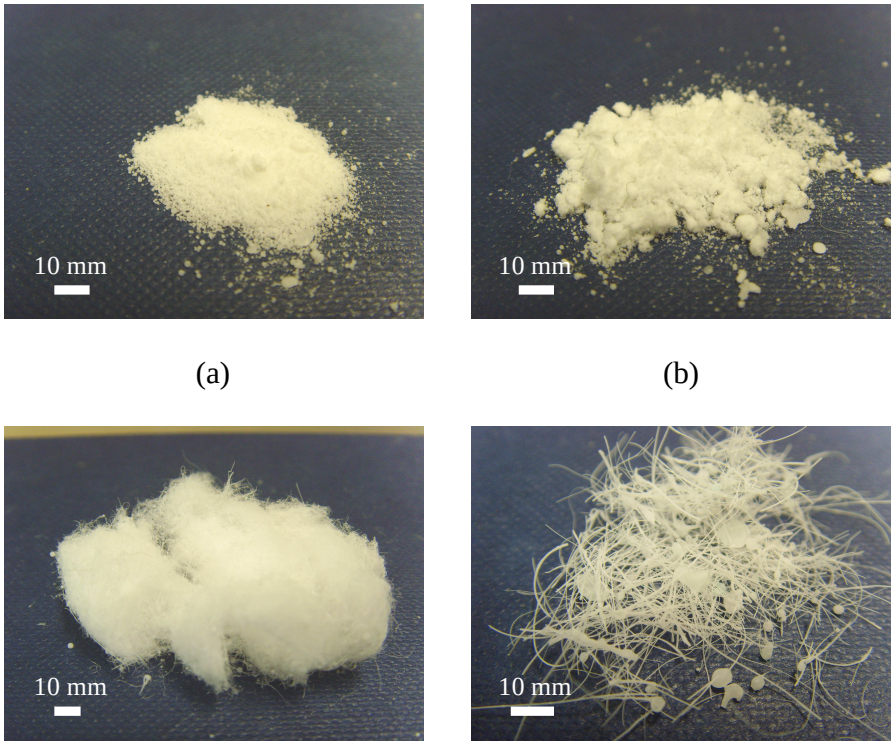


Figure 6.12 Macroscopic characteristics of GMS sprayed granules produced with varying aluminium monostearate concentrations (a) 2.5%w/w, (b) 5%w/w, (c) 7.5%w/w, (d) 10%w/w at a processing temperature of 125˚C.

Visual examination of the sprayed GMS material (Figure 6.12) indicated that for the material manufactured at 125˚C the amount of aluminium monostearate had a significant effect on the appearance of the resultant material.

As the aluminium monostearate concentration increases the sprayed GMS material transformed into a light, fluffy material, becoming long and 'cotton wool-like' properties and ligaments. With 10%w/w aluminium monostearate the sprayed GMS is string-like and becomes more brittle and less fluffy.

At 2.5%w/w aluminium monostearate, the molten solution produced at 125^{o}C can still be atomised to form droplets. At a greater concentration of aluminium monostearate, the viscosity increases sufficiently, such that the ability of the molten GMS solution to be atomised was compromised. By 7.5%w/w aluminium monostearate, the viscosity of the molten GMS solution has increased to a point where the solution could no longer be atomised into droplets, but remained as ligaments forming cotton-wool like properties and then progressing to a brittle 'string-like' format at 10% w/w aluminium monostearate.

It appears the aluminium monostearate is having a thickening effect on the molten wax when at an elevated temperature of 125^{o}C, indicating the processing temperature has a significant impact on the appearance of the resultant sprayed material. High viscosity liquids have been demonstrated to produce a narrower spray angle when compared to water or lower viscosity liquids (Maschke et al., 2007; Nuyttens et al., 2007). This may

impact the particle size distribution of the resultant material and/or hydrophobicity of the matrix system. Incorporation of API would be required to assess the impact of this critical parameter on the overall performance of this matrix system (Section 6.3.2.3).

The increase in viscosity of the molten wax, prior to spraying at 125^{o}C, correlates to the melting temperature of the aluminum monostearate. Thermal analysis was undertaken to further characterise the relationship between GMS and aluminium monostearate from the resultant material produced (Section 6.3.2.1).

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the sprayed material with varying aluminium monostearate concentration at processing temperatures of 80^{o}C and 125^{o}C. The DSC profiles of sprayed granules monitored are shown in Figure 6.13.

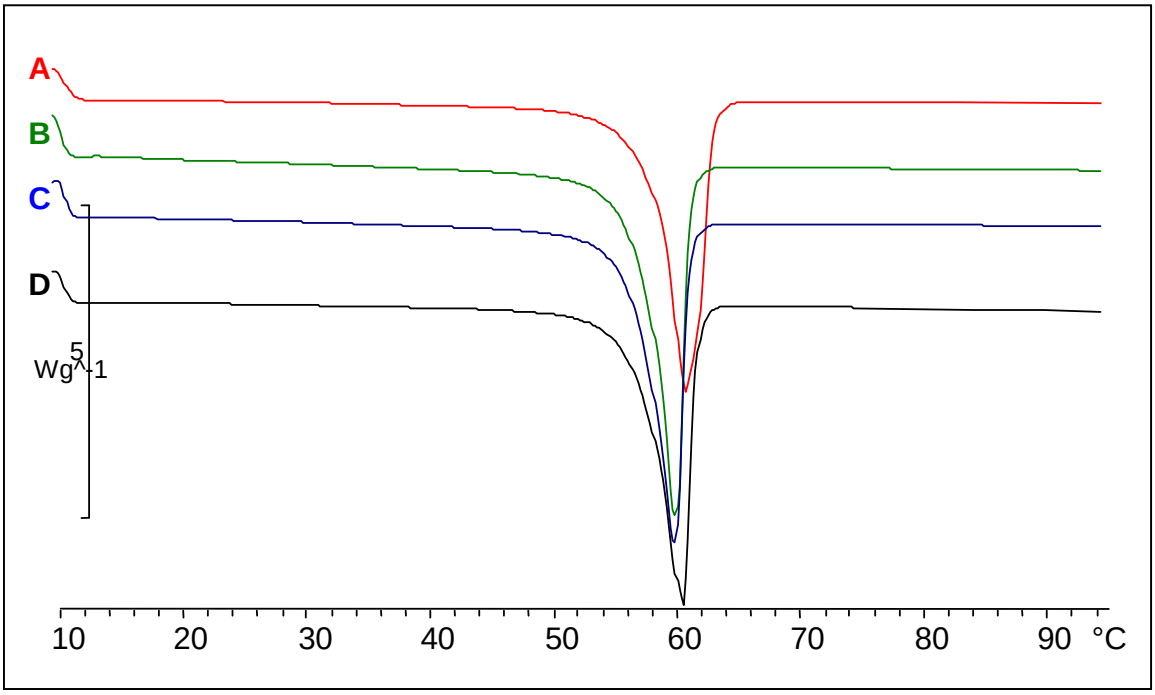


Figure 6.13 DSC profiles of sprayed GMS with varying aluminium monostearate composition at 80˚C (A) 2.5% w/w, (B) 5%w/w, (C) 7.5%w/w and (D) 10%w/w (scale bar = heat flow of 5 watts per gram).

From Figure 6.13, one endotherm is exhibited at between 60-61˚C for each of the sprayed GMS mixtures. No significant difference was exhibited between the endotherms obtained for the sprayed GMS material with varying aluminium monostearate concentration. The slight downward trend in the GMS endotherm melting point on increased aluminium monostearate concentration require XRPD analysis to eliminate polymorphic transitional activity (Hamdani et al., 2003).

The aluminium monostearate endotherm would be anticipated at 125^{o}C but the DSC method was only run between 10-95^{o}C.

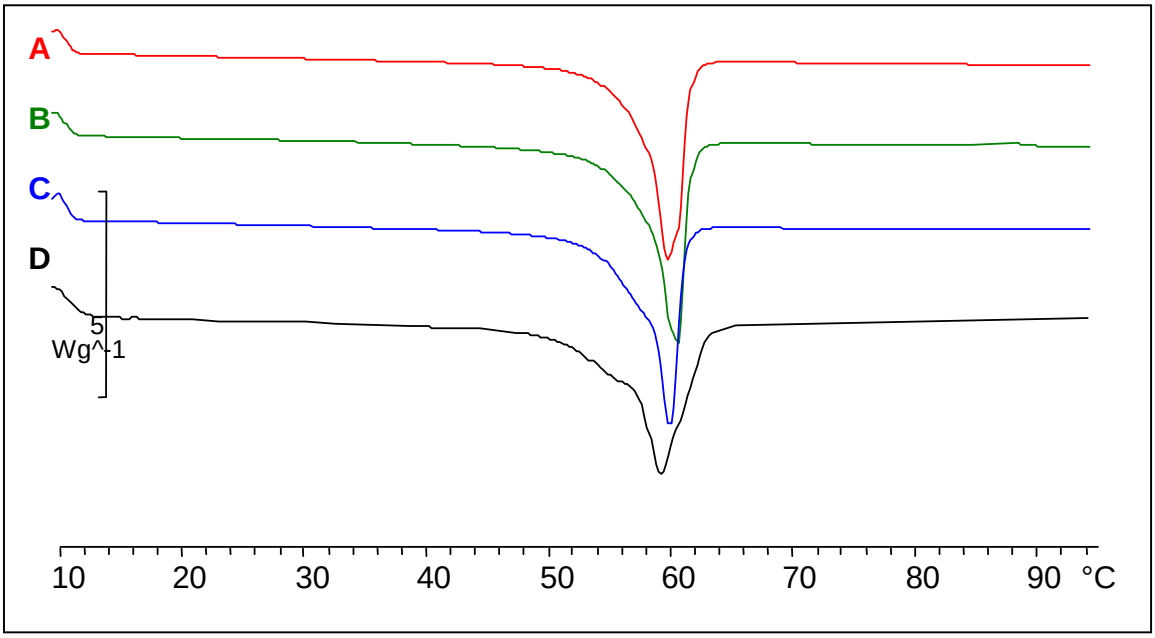


Figure 6.14 DSC profiles of sprayed GMS with varying aluminium monostearate composition at 125˚C (A) 2.5% w/w, (B) 5%w/w, (C) 7.5%w/w and (D) 10%w/w (scale bar = heat flow of 5 watts per gram).

From Figure 6.14, there is a primary endotherm exhibited between 59-60˚C for each of the sprayed GMS mixtures, as observed in Figure 6.13. However, at 125^{o}C the slight downward trend in the primary endotherm melting point is also accompanied by a shoulder (~55^{o}C) that becomes more pronounced with the increasing aluminium monostearate concentration. The observed shoulder at ~55^{o}C suggests an interaction may be occurring between the GMS and aluminium monostearate when processed at 125^{o}C, as it is not observed in the samples produced at 80^{o}C. The increased prevalence of the secondary peak also corresponds to the observed changes in the physical morphology of the sprayed GMS material (Figure 6.10) and the increased viscosity observed in the molten GMS once the aluminium monostearate melts into a gel at 125^{o}C.

The gelling effect observed in the molten GMS on addition of aluminium monostearate at 125^{o}C is an unusual phenomenon. However, it appears at a higher temperature and increased aluminium monostearate concentration the binary mixture exhibits a phase transition. Possible identification of the phase transition was not possible utilising DSC alone and further investigation would be required. Due to the unknown and potentially complex chemistry that has been documented for lipophilic glycerides and metal salts it would be recommended to characterise both the chemical structure and the crystalline nature of the binary mixtures utilising XRPD, HSM, NMR and/or FT-IR (Dag et al., 2004; Hamdani et al., 2003).

Thermal analysis was also undertaken on samples manufactured at 80^{o}C via wax fusion and not sprayed (Section 6.3.2.2).

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the GMS mixtures with varying aluminium monostearate compositions utilising wax fusion at a processing temperature of 80^{o}C. The DSC profiles of the hot-melt mixtures are shown in Figure 6.15. These formulations were not sprayed and do not contain API.

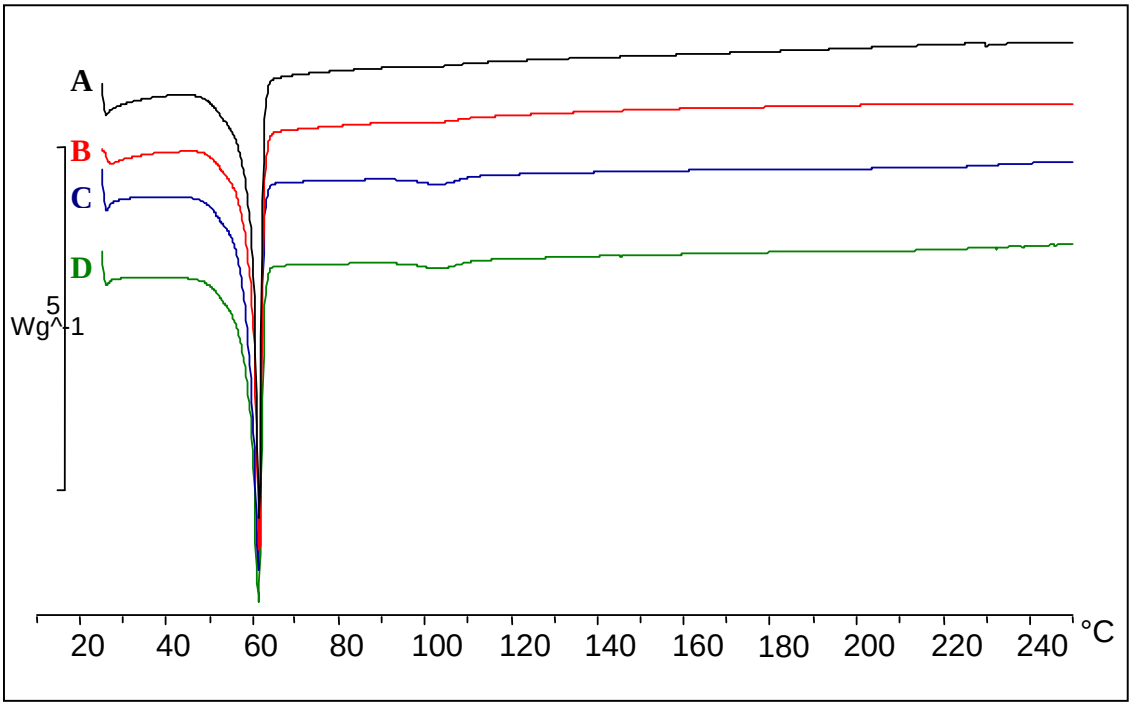


Figure 6.15 DSC profiles of hot-melt GMS mixture (unsprayed) with varying aluminium monostearate composition at 80˚C (A) 2.5% w/w, (B) 5%w/w, (C) 7.5%w/w and (D) 10%w/w (scale bar = heat flow of 5 watts per gram).

DSC analysis (Figure 6.15) indicated no significant shifts in the endotherms for the hot-melt GMS containing different concentrations of aluminium monostearate. A primary endotherm is similarly exhibited at approximately 60˚C for each of the sprayed GMS mixtures, corresponding to the β-form of GMS.

The DSC method had a greater range (10-250^{o}C) than the method used in Figure 6.13 and 6.14 (10-95^{o}C). As a result, a secondary endotherm can be identified at approximately (100-105^{o}C) for hot melt material incorporating greater than 5%w/w aluminium monostearate. The absence of a peak at 125^{o}C indicates the aluminium monostearate has

dissolved in the GMS molten mixture. In addition, it is noted the thermogram correlates to the sprayed GMS material processed at 80^{o}C (figure 6.13) and not the sprayed material at 125^{o}C (figure 6.14).

The appearance of an endotherm at ~100-105^{o}C as the concentration of aluminium monostearate is increased above 5% w/w suggests as the GMS matrix becomes more saturated a transition may be taking place. The mechanism of reactions between stearates and metal stearates is not widely understood but the chemistry is complex and polymorphic metal stearates have also been identified (Gilbert et al., 2001). Further investigation into the identification of this endotherm may consider the presence of aluminium tristearate (melting point of 103^{o}C) or H_2O loss.

6.3.2.3 Effect of aluminium monostearate concentration on release rate of sprayed ibuprofen-GMS granules

The PSD of sprayed ibuprofen material are shown in Figure 6.16.

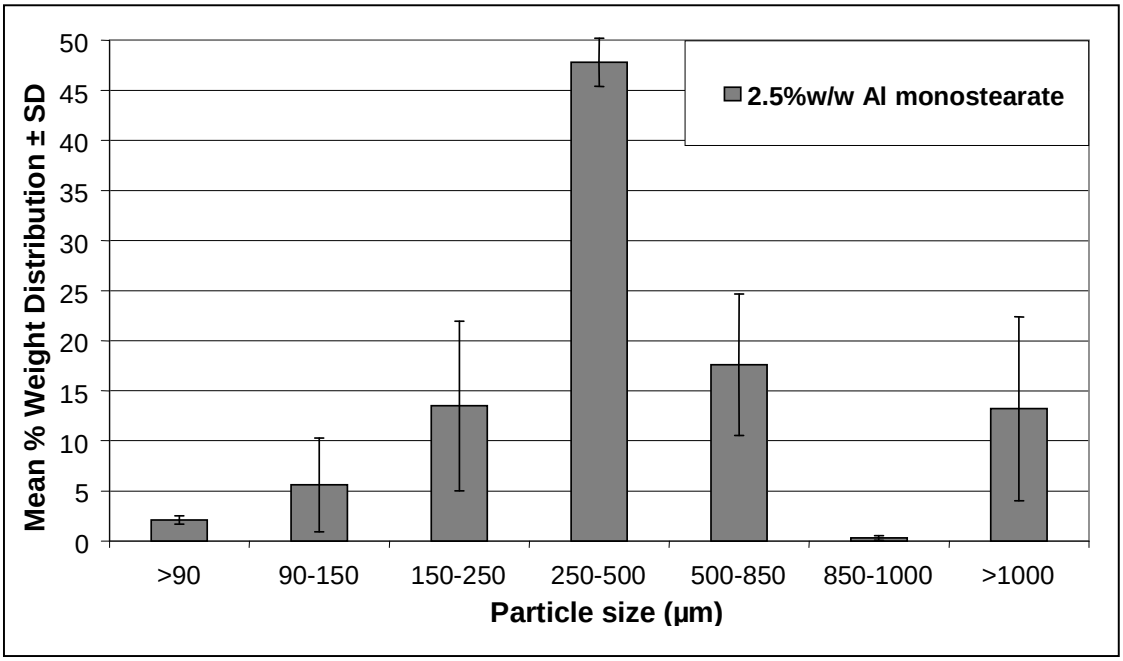
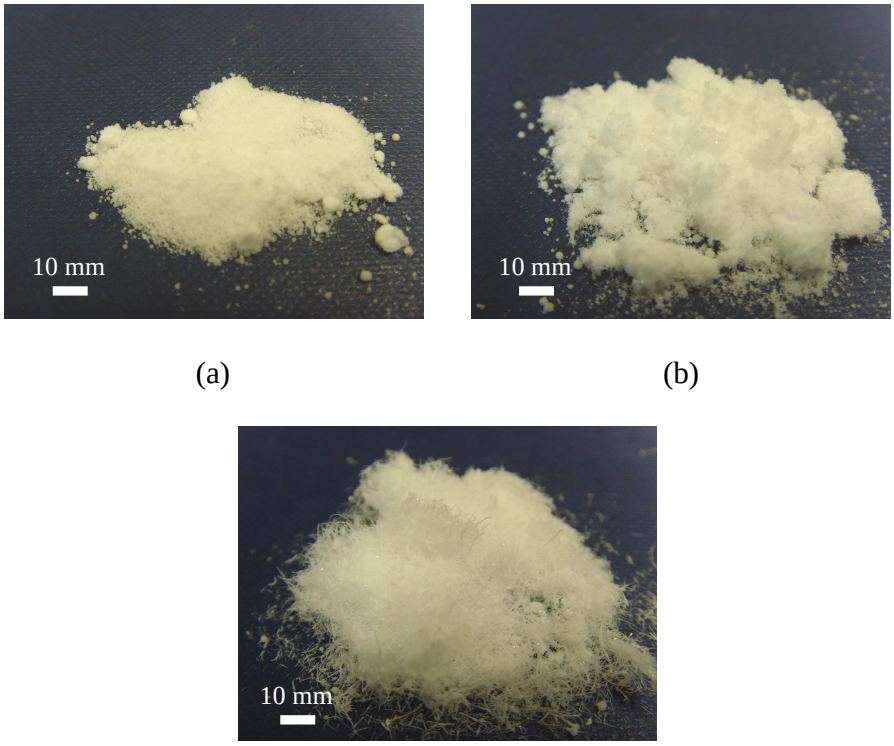


Figure 6.16 Particle size distribution of sprayed ibuprofen:GMS material with a 2.5%w/w aluminium monostearate concentration at 80˚C (n=3).

Statistical comparison of the PSD (Figure 6.16) was not possible for sprayed ibuprofen formulations containing more than 2.5%w/w aluminium monostearate as the material texture altered and sieve analysis could not be performed (Section 6.3.2.3.2). When 2.5%w/w aluminium monostearate is incorporated into ibuprofen-GMS sprayed granules the majority of the particles are between 250-500µm (>45%).

The incorporation of ibuprofen into sprayed material has a significant effect on the particle size distribution that was not observed in GMS-aluminium monostearate binary mixtures processed at 80^{o}C and 125^{o}C (figures 6.9 and 6.10). Inclusion of ibuprofen yielded sprayed granules with a larger mean particle size of 250-500µm than was observed for sprayed material containing no API (150-250µm).

Digital photographs of the resultant sprayed ibuprofen GMS material processed at 80^{o}C are illustrated in figure 6.17. Prior to spraying, the ibuprofen dissolved into the GMS mixture, on addition of the aluminium monostearate the molten ibuprofen-GMS solution appeared white due to the presence of the aluminium monostearate and did not appear to dissolve at 80^{o}C. As the concentration of the aluminium monostearate increased the mixture viscosity did not appear to thicken as was observed with the molten GMS at 125^{o}C (Figure 6.12).



(a) (b)

(c)

Figure 6.17 Macroscopic characteristics of ibuprofen-GMS sprayed granules produced with varying aluminium monostearate concentrations (a) 2.5%w/w, (b) 7.5%w/w, (c) 10%w/w at a processing temperature of 80˚C.

From Figure 6.17, the amount of aluminium monostearate had a significant effect on the appearance of the resultant Ibuprofen-GMS material. As the aluminium monostearate concentration increases the sprayed ibuprofen-GMS material appears fluffy and light in texture becoming long ligaments that are 'cotton wool-like'.

In figure 6.12, formation of 'cotton wool-like' material was thought to be associated with an increased viscosity on addition of the aluminium monostearate at 125^{o}C. However, in the presence of ibuprofen, the material observed is promoted via a different mechanism, as no significant difference in viscosity was observed.

The dissolution results of the bulk sprayed ibuprofen-GMS granules with varying aluminium monostearate concentrations are shown in Figure 6.18.

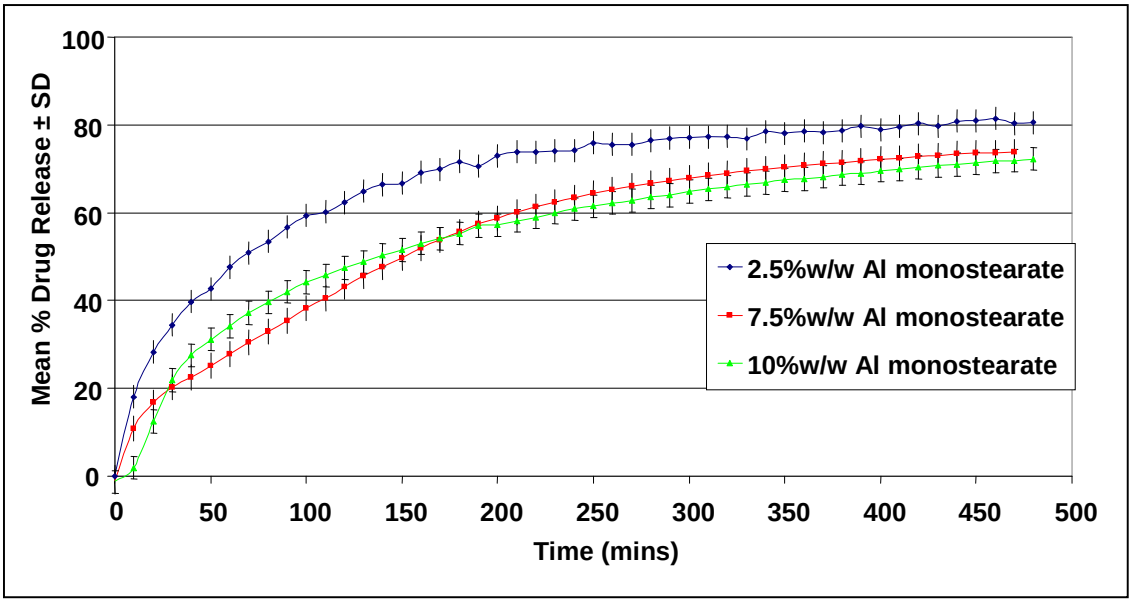


Figure 6.18 Mean release profiles of sprayed ibuprofen-GMS granules with varying aluminium monostearate concentrations (n=6)

From figure 6.18, as the aluminium monostearate concentration increases the drug release rate significantly decreases (f_2 value < 50) and correlates to the morphological changes observed in figure 6.17.

Sprayed material incorporating at least 7.5%w/w aluminium monostearate achieved sustained release, 27.6% (n=6) of the drug was release by 60 minutes, 50% (n=6) drug release was achieved by 120 minutes and 80% (n=6) of the drug release took over 340 minutes to achieve (British Pharmacopoeia, 2012). The sprayed material incorporating 2.5%w/w aluminium monostearate exhibited modified drug release properties.

As aluminium monostearate concentration increases the total drug release achieved in an 8 hour test period also significantly decreases. Ethanolic extraction was undertaken to determine the amount of ibuprofen present. The mean amount of ibuprofen extracted from the sprayed granules was 102.2% ± 4.1. Indicating the expected drug loading was achieved during manufacture but incomplete drug dissolution was achieved over the test period.

This does not confirm whether an insoluble complex is being formed between aluminium and ibuprofen (Kararli et al., 1989; Neuvonen, 1991; Ogawa & Echizen, 2011). The dissolution test period would need to be extended to determine whether 100% drug release is achieved with increased time.

6.3.2.4 Effect of aluminium monostearate concentration on release rate of paracetamol-GMS sprayed granules

The PSD of sprayed paracetamol-GMS material are shown in Figure 6.19.

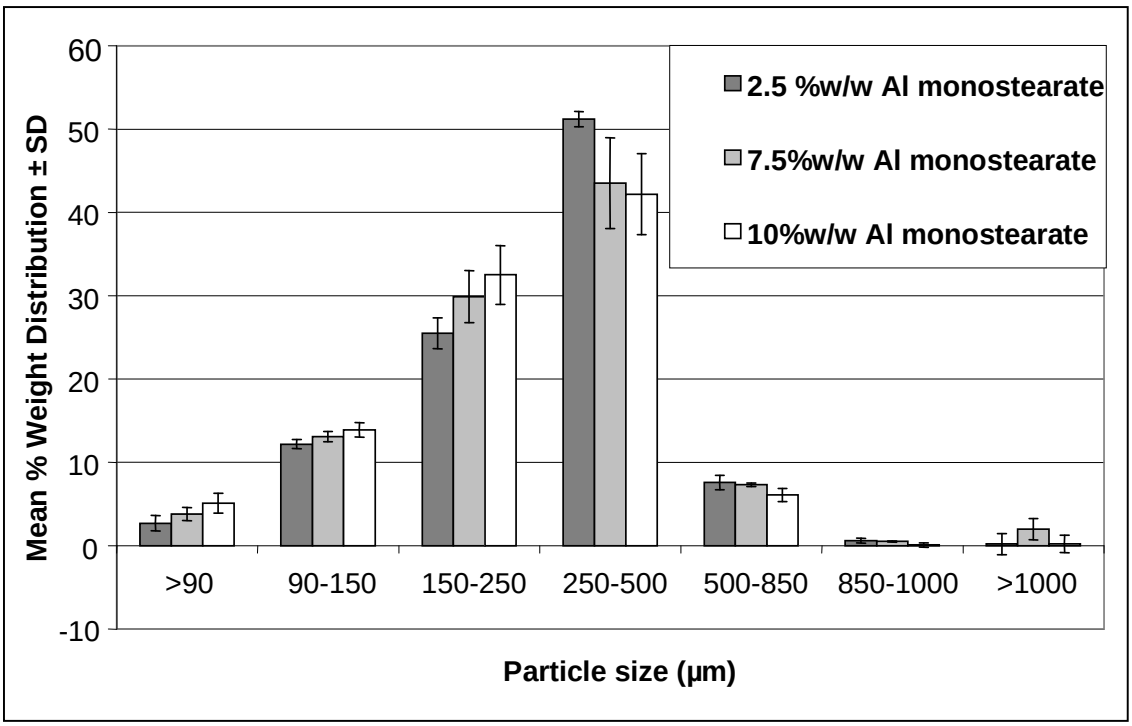


Figure 6.19 Particle size distribution of sprayed paracetamol-GMS material with varying aluminium monostearate concentrations at 80˚C (n=3).

Statistical comparison of the paracetamol formulations (Figure 6.19) indicated there was no significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the paracetamol sprayed granules is independent of the aluminium monostearate concentration incorporated into the GMS matrix.

The results of the sprayed paracetamol-GMS granules with varying aluminium monostearate concentration are shown in Figure 6.20.

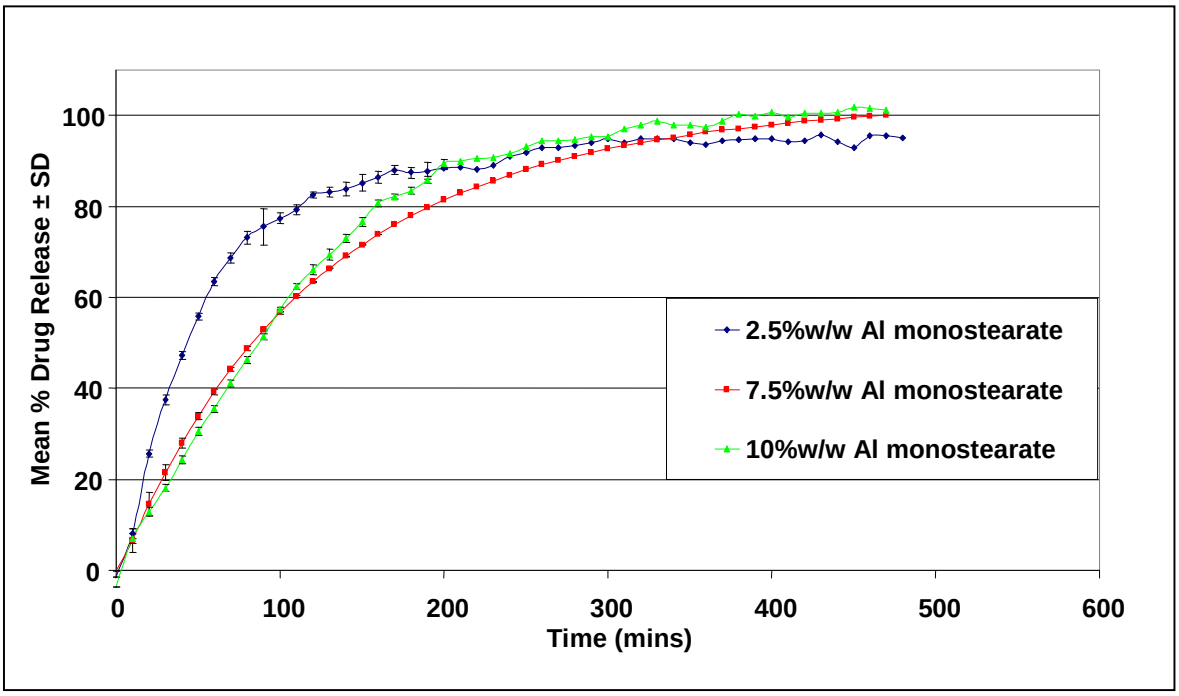


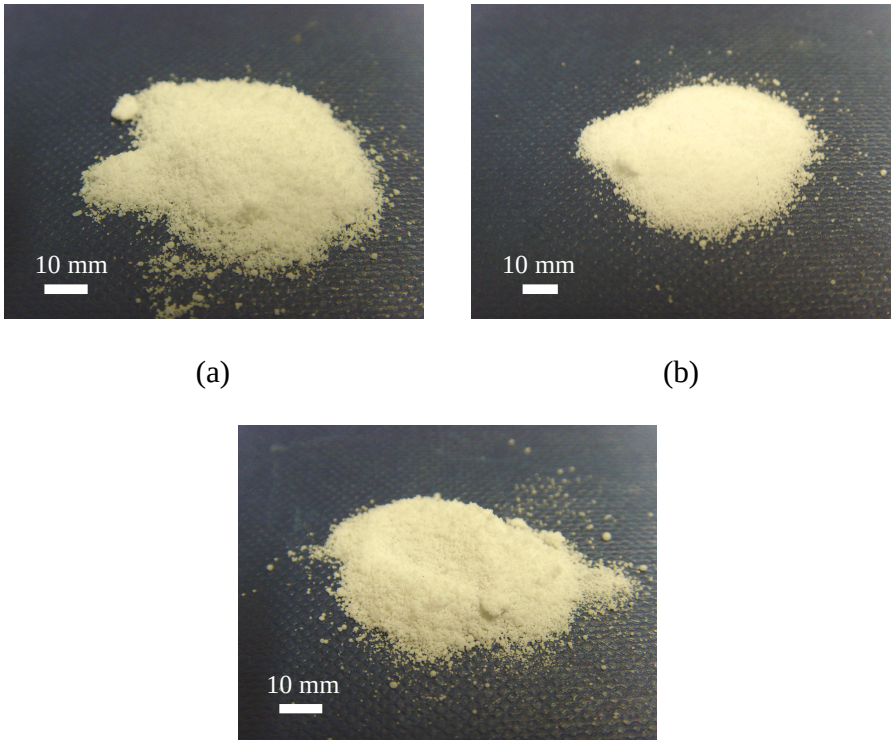
Figure 6.20 Mean Release Profiles of sprayed paracetamol-GMS granules with varying aluminium monostearate concentration (n=6).

From figure 6.20, the drug release rate appears to be modulated by the concentration of aluminium monostearate incorporated into the paracetamol-GMS sprayed material. A significant decrease in the release is achieved when at least 7.5%w/w aluminium monostearate is incorporated into the formulation (f_2 value < 50).

To achieve sustained release classification 7.5%w/w aluminium monostearate must be incorporated into the paracetamol sprayed granules. Modified release is achieved on incorporation of 2.5%w/w aluminium monostearate (British Pharmacopoeia, 2012).

Increasing the aluminium monostearate concentration from 7.5%w/w to 10%w/w did not prolong the drug release further. This suggests the mechanism by which sustained release is being achieved has been maximised for the current formulation. Total release of the paracetamol was achieved during the run time which was not achieved in the ibuprofen equivalent formulation. The mechanism of sustained release and identification of paracetamol-aluminium complexes would need to be confirmed via further analysis.

Digital photographs of the resultant sprayed paracetamol-GMS material processed at $80^{o}C$ are illustrated in figure 6.21. Prior to spraying the paracetamol did not appear to dissolve in the molten GMS, forming a solid dispersion upon spraying. On addition of the aluminium monostearate the molten solution had a low viscosity and was white due to the presence of both the paracetamol and aluminium monostearate that had not dissolved.



(a) (b)

(c)

Figure 6.21 Digital photographs of paracetamol sprayed granules produced with varying aluminium monostearate concentration (a) 2.5%w/w, (b) 7.5%w/w, (c) 10%w/w at a processing temperature of 80˚C.

Visual examination of the paracetamol sprayed material (Figure 6.21) appears granular in nature with the increasing aluminium monostearate concentration having no significant effect on the appearance of the resultant sprayed material. It appears the sustained release properties exhibited by these formulations are not related to the physical morphology of the resultant granules.

6.3.3 Characterisation of Glyceryl Di-Behenate (Compritol® 888 ATO) in sprayed GMS formulation

The PSD of sprayed GMS:GDB material is shown in Figure 6.22.

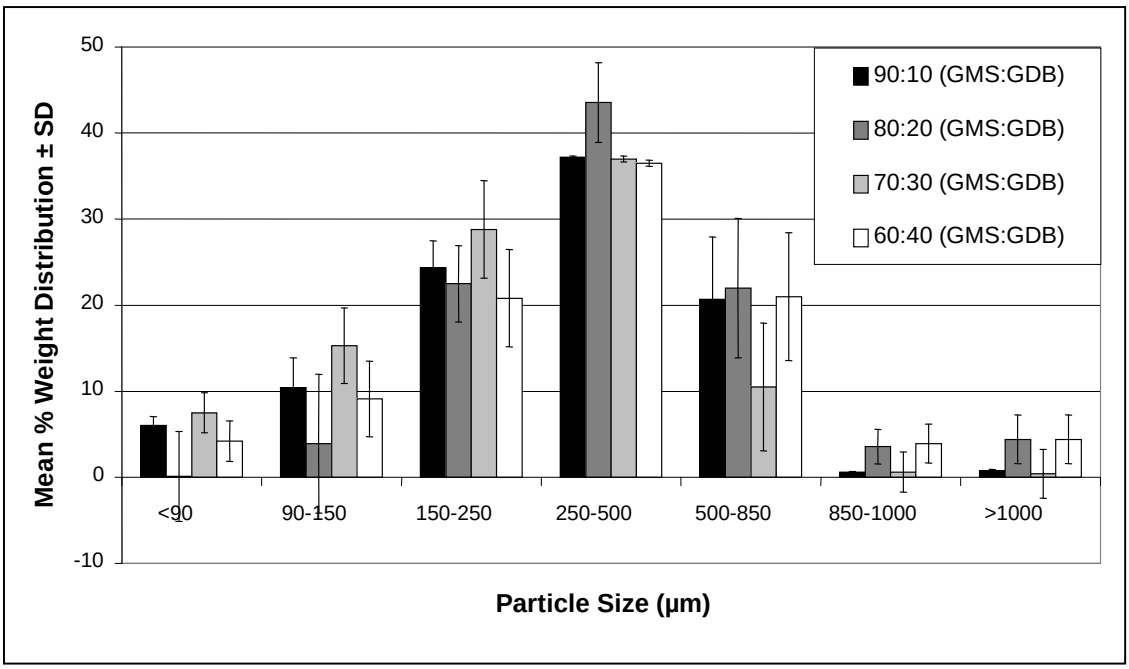


Figure 6.22 Particle size distribution of sprayed material with varying GMS:GDB compositions (n=3).

The particle size distribution of the sprayed granules (Figure 6.22) was Gaussian in nature with the prevalent particle size being within the 250-500µm size range. Statistical comparison of the PSD obtained for the four ibuprofen granule batches indicated there was no significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed granules is independent of the GDB composition incorporated.

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the sprayed GMS:GDB material. The DSC profiles of sprayed material monitored are shown in Figures 6.23-6.24.

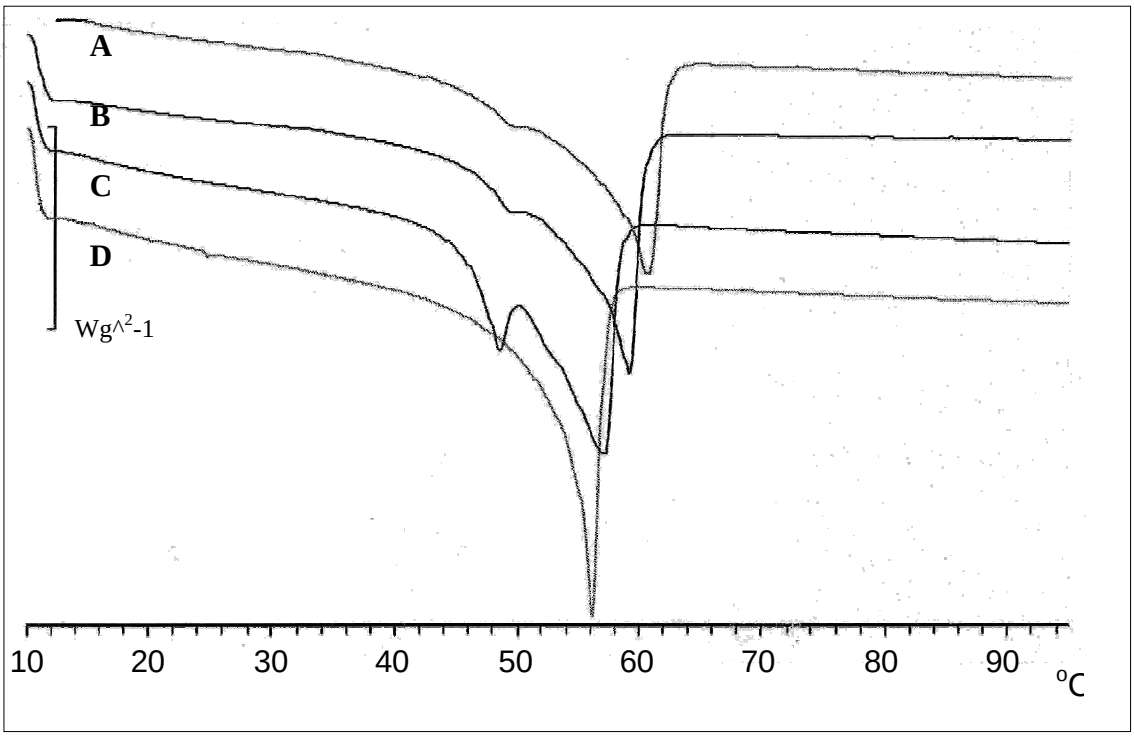


Figure 6.23 DSC profiles of sprayed ibuprofen granules with varying GMS:GDB concentrations at Day 1, (A) 60:40, (B) 70:30, (C) 80:20 and (D) 90:10 (scale bar = heat flow of 2 watts per gram).

DSC profiles of the raw wax materials indicated GDB has a melting peak of ~72˚C and GMS has a melting peak of ~60˚C (Long et al., 2006). From figure 6.23, there are two trends that can be observed when the concentration of the GMS:GDB is altered within the sprayed ibuprofen granules. As the GMS ratio of the wax mixture is increased and the GDB decreased, the secondary peak at ~50˚C becomes more pronounced. In addition, there is a slight downward shift in the primary endotherm (56˚C -60˚C).

In figure 6.23, when the GMS decreases below 90%w/w there is evidence of a eutectic solution being formed, as an endotherm appears below the melting point of all formulation components. As the concentration of the GMS increases the endotherms correspond to the ibuprofen:GMS binary mixtures (Figure 5.13), corresponding the same eutectic mixtures formed between ibuprofen and GMS α- and β-forms. By increasing the GDB concentration there is a significant upward shift in the endotherms and a decrease in the peak intensity, indicating less eutectic mixture is being formed between ibuprofen and GMS.

In figure 6.23, when the GMS is present at its highest concentration (90%w/w) the ibuprofen–GMS α-form eutectic mixture is prevalent. The presence of GDB in the sprayed granules significantly effects the proportion of eutectic mixtures formed with ibuprofen. When the proportion of GDB is increased above 20%w/w the ibuprofen:GMS α-form eutectic mixture is also formed. It would appear on increasing the GDB concentration the formation of the α-form of GMS becomes more prevalent and is the more unstable form of GMS.

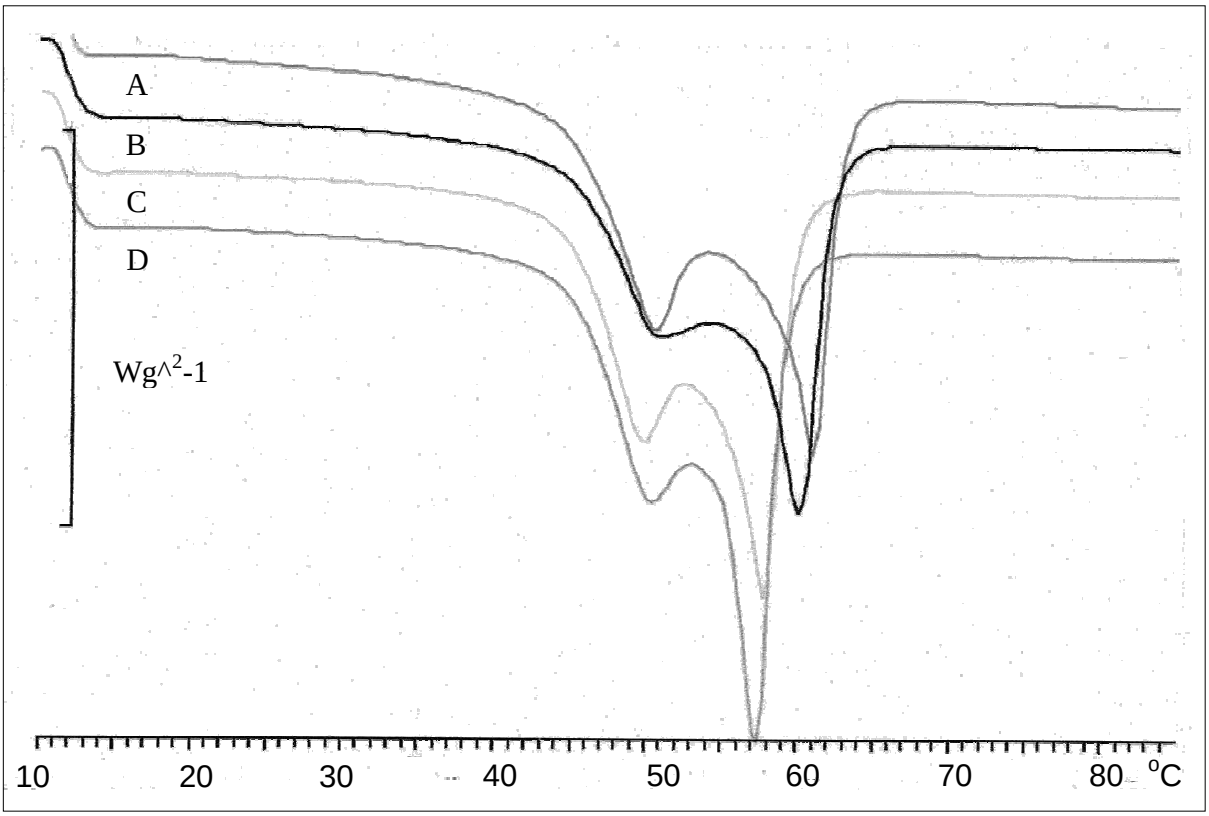


Figure 6.24 DSC profiles of sprayed ibuprofen granules with varying GMS:GDB concentrations at Day 4 (A) 60:40, (B) 70:30, (C) 80:20 and (D) 90:10 (scale bar = heat flow of 2 watts per gram).

Post 4 days manufacture (figure 6.24) both ibuprofen-GMS eutectic mixtures appear to be present in all formulations. This indicates the formulations exhibiting eutectic mixtures with the GMS α-form are undergoing a transition to the more stable β-form of GMS with time. Those with the higher concentration of GDB appear to be transitioning to the β-form at a faster rate than those with higher concentration of GMS. Whether this transition rate will be maintained would have to be monitored in a stability study.

The dissolution profiles of the sprayed ibuprofen granules with varying GMS:GDB concentrations are shown in Figure 6.25.

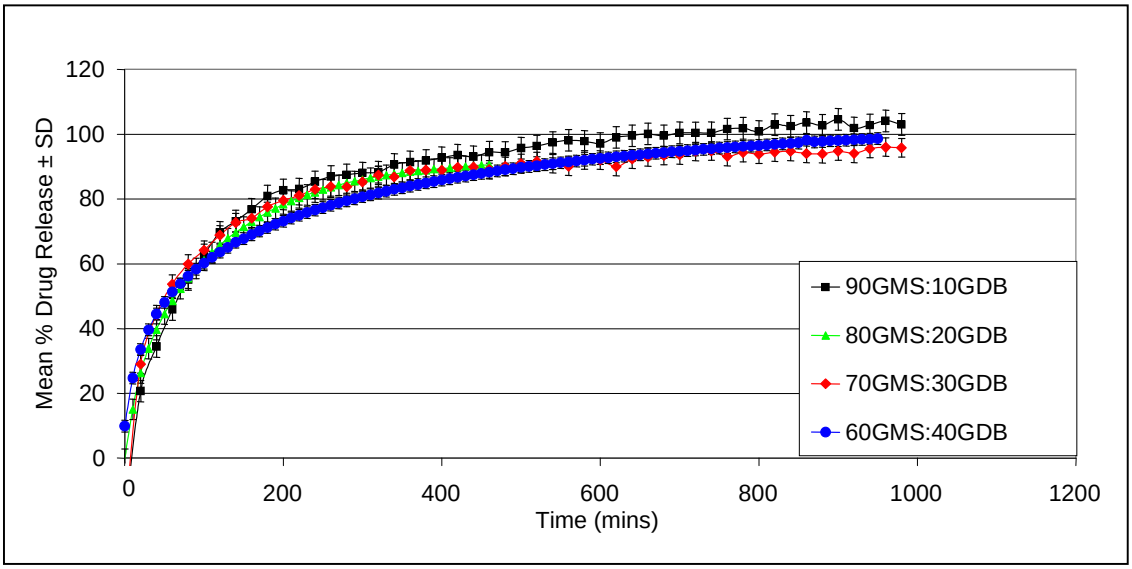


Figure 6.25 Mean Drug Release from sprayed ibuprofen granules with varying GMS:GDB concentrations (n=6).

No significant difference (f_2 value > 50) was observed between the dissolution release profiles for the four sprayed ibuprofen formulations comprising of various GMS:GDB concentrations.

The drug release profiles obtained for the sprayed ibuprofen:GMS:GDB mixtures do not exhibit immediate release or sustained release properties but are characteristic of modified release (refer to section 1.4). The addition of GDB into the GMS:ibuprofen solution does not appear to contribute to the hydrophobicity of the matrix despite its composition of longer fatty acids (C_{22}), no significant sustained release was observed between the formulations containing GBD and GMS/ibuprofen binary sprayed granules.

As the dissolution study was performed post 4 days, no comparison could be established between the varying eutectic mixtures. A dissolution study should be performed to determine whether the prevalence of β- or α-form eutectic mixtures impacts on the release profiles.

6.4 Conclusions

The presence of divalent/trivalent organic salts within both paracetamol and ibuprofen sprayed GMS formulations had a significant influence on the release characteristics of the resultant sprayed material. Physical appearance (ibuprofen only), thermal properties and dissolution of the sprayed material were significantly affected by the presence of multivalent salts. A further study of aluminium monostearate with GMS revealed the manufacturing temperature was also critical in the morphology and thermal properties of the resultant sprayed material.

Thermal analysis via DSC was performed on all formulations. The technique was useful as a preliminary assessment of the thermal properties. However, formulations comprising of GMS and/or metal stearates should be interpreted with caution in the absence of XRPD. For lipophilic glycerides, a non-significant endothermic shift of ±2˚C may represent polymorphic transitions when compared to XRPD results (Hamdani et al., 2003). In addition, the mechanism of reactions between stearates and metal stearates is not widely understood but the chemistry is complex, polymorphic metal stearates have also been identified (Gilbert et al., 2001). Consideration to the limit of detection of this analytical technique is required, as during the analysis of paracetamol formulations the

paracetamol endotherm was absent, confirmation of the presence of paracetamol is required to determine whether the limit of detection had been exceeded for this analytical technique.

The presence of aluminium hydroxide in the ibuprofen-GMS formulation exhibited no significant changes in the physical morphology of the sprayed granules. No additional interaction between the excipients and ibuprofen was observed (Kararli et al., 1989) only the presence of an ibuprofen-GMS eutectic solution, previously identified in binary ibuprofen-GMS mixtures (Chapter 5). Aluminium hydroxide was found to have a significant impact on the product performance resulting in a modified release formulation being achieved. The mechanism for this is not fully understood but may be due to an insoluble complex formation between ibuprofen and aluminium, during the presence of an aqueous phase (Albin et al., 1985). Further investigation to characterise potential pH effects during dissolution is also required.

The presence of aluminium hydroxide in the paracetamol-GMS formulation exhibited no significant changes in the physical morphology of the sprayed granules. For the sprayed solid dispersions, differences were observed in the release rates and thermograms for both aluminium-based additives. Further characterisation of the thermal properties are required to establish whether aluminium hydroxide is present at 300^{o}C and identify the crystalline forms of the paracetamol in all formulations. This will assist in determining the mechanism of drug release and identify potential stability issues. XRPD or FT-IR could

be undertaken to determine the presence of polymorphs and identify interactions (Giordano et al., 2002).

Sprayed granules incorporating metal stearates appeared to have similar thermal properties, all formulations exhibit a primary endotherm that may correlate to β-form GMS from previous investigation (Chapter 5). In ibuprofen based formulations, the presence of metal stearates appears to reduce the ibuprofen-GMS eutectic solution being formed (Chapter 5). The mechanism of how this is achieved is not fully understood but may be due to complex formation between ibuprofen and Mg^{2+} or Al^{3+} salts (Bharate et al., 2010; Khan et al., 1995), reducing ibuprofen available to form a eutectic solution with GMS.

Unexplained physical morphology exhibited by ibuprofen and GMS sprayed granules correlates to the thermal analysis of formulations comprising at least 7.5%w/w aluminium monostearate. Further investigation is required to characterise and correlate both the physical and chemical properties of these mixtures, as this may contribute to matrix hydrophobicity and/or the physical morphology observed for some sprayed granules (Attwood & Florence, 2008; Hamdani et al., 2003; Moniruzzaman & Sundararajan, 2004).

In both paracetamol and ibuprofen formulations, there was no evidence of an interaction on addition of magnesium stearate and no significant effect observed on the release rates

from paracetamol formulations. Confirmation of complex formation or pH effects during dissolution should be established for these formulations.

Sustained release was successfully achieved when a minimum of 7.5%w/w aluminium monostearate was incorporated into both ibuprofen and paracetamol sprayed GMS granules. This also correlated to the change in PSD and physical morphology that led to the 'cotton-wool' like appearance of the sprayed formulation. In ibuprofen and paracetamol formulations, 100% of the expected drug loading was verified. The mechanism by which sustained release is achieved for the hot-melt spraying of a solid dispersion or solid solution is currently unknown. A rheological study should be undertaken to characterise the molten solution prior to spraying. High viscosity liquids can have a narrower spray angle when compared to water or lower viscosity liquids (Maschke et al., 2007; Nuyttens et al., 2007) this may impact matrix hydrophobicity contributing to the sustained release exhibited in the ibuprofen formulations (Hamdani et al., 2003).

During the investigation of a tertiary system of the ibuprofen-GMS sprayed material with glyceryl dibehenate, the incorporation of glyceryl dibehenate in the sprayed solid solution of GMS-ibuprofen, impacted on the thermal properties but had no significant impact on the dissolution performance or the particle size distribution of the sprayed granules. Sustained release could not be achieved by incorporating GBD into the formulation.

From the results in this chapter, the presence of tertiary components significantly impacts the solid dispersions and solid solution based formulations. The formation of drug-excipient complexes can both assist and hinder the ability to achieve sustained release properties. A greater understanding to the relationship of lipophilic glycerides and metal stearates via dissociation of the metal stearates or polymorphism is required, as this has been identified as a critical parameter impacting product performance.

7. Characterisation and Compatibility of Minocycline HCl Incorporated into Sprayed Material

7.1 Introduction

Chapters 4, 5 and 6, involved characterisation of the hot-melt spray system and the production of reproducible granules from a variety of drug and excipient mixtures. However, this research had been developed from an investigation into the minocycline product, Sebomin, and the production of granules/pellets from a less invasive manufacturing process.

The main objective of the final chapter is to undertake a direct comparison of minocycline granules produced from the hot-melt spray system and the extrusion/spheronisation process. Incorporation of minocycline HCl (log *P* value 1.48) into the sprayed material will enable investigation of the drug in the GMS matrix system, characterising its behaviour during atomization and the effect on in vitro drug release from the final sprayed products.

7.2 Methods

A size reduction technique was not required for minocycline powder as fractionation of the powder particles enabled sufficient minocycline particles within the desired range of 50-250 microns to be collected (Section 2.4.2.1).

Preliminary experiments (Chapter 3) showed minocycline (log P value 1.48) had minimal solubility in the molten GMS. Taking this into consideration, a two phase liquid

suspension is produced between the GMS and minocycline HCl incorporating agitation to maintain a homogenous solution during mixing and spraying.

Binary mixtures of GMS and minocycline HCl were sprayed at different ratios to establish the highest drug loading with GMS that could be successfully sprayed using the hot-melt spray system. Granules were achieved from a maximum of 60% w/w drug loading.

7.2.1 Effect of initial minocycline HCl particle size

In previous studies (Chapter 5), 10%w/w of API had been utilised successfully to characterise binary mixtures with GMS and was utilised in this study instead of the maximum drug loading of minocycline HCl 60% w/w.

GMS sprayed material with 90% w/w GMS and 10% w/w minocycline HCl were produced at 80ºC (Section 2.3.4). The minocycline was sieved into varying particle size fractions and incorporated into different sprayed formulations (Table 7.1).

Table 7.1 GMS sprayed granule formulations containing various size fractions of minocycline HCl.

Formulation	**Minocycline HCl Particle Size (microns)**
A	150-250
B	90-150
C	75-90
D	53-75

The resultant material was analysed utilising the following analytical techniques (Table 7.2).

Table 7.2 Analytical techniques utilised in the characterisation of GMS sprayed material comprising of minocycline HCl.

Analytical Technique	**Method Information**
PSD	Section 2.4.2.1
Dissolution	Section 2.4.7.2
FT-IR	Section 2.4.4

7.2.2 Production of hot-melt and sprayed minocycline-GMS binary granules

Binary mixtures of the minocycline-GMS granules were produced via two different hot-melt methods. One batch of the hot-melt mixture was allowed to cool to room temperature and hand milled (Wax fusion), to produce granules. The second batch of hot-melt mixture was directly sprayed utilising the hot-melt spray system to produce sprayed granules (Section 2.3.4).

Due to limited supply of API, binary mixtures comprising of 5% w/w minocycline HCl and 95% w/w GMS were produced at 80ºC for analysis. This would be sufficient to characterise thermal and release properties of both sprayed and non-sprayed granules. The resultant material was analysed utilising the following analytical techniques (Table 7.3).

Table 7.3 Analytical techniques utilised in the characterisation of milled and sprayed granules.

Analytical Technique	**Method Information**
DSC	Section 2.4.5.2
Dissolution	Section 2.4.7.2

7.2.3 Development of a minocycline formulation produced by two different manufacturing techniques.

Two batches of Sebomin were to be produced using two different manufacturing techniques; extrusion/spheronisation and the hot-melt spray system. However, the formulation outlined in table 7.4 failed to atomise despite a maximum drug load of 60%w/w being achieved for sprayed minocycline-GMS binary mixtures (See section 7.2).

Successful atomisation could not be achieved due to the lack of moisture in the formulation, the molten GMS and granulation fluid were insufficient due to the large proportion of minocycline HCl and Avicel® (microcrystalline cellulose).

Table 7.4 Sebomin® Formulation

Formulation Components	**Quantity Required (%w/w)**
Minocycline Hydrochloride	60.7
Imwitor 900K	10.5
Povidone K-30	4.7
Microcrystalline Cellulose (Avicel® PH101)	24.1
Ethanol/H_2O solution	56%v/v

To overcome these issues and to achieve atomisation, the Sebomin formulation was modified (table 7.5). Two batches of the modified Sebomin formulation were produced using the two different manufacturing techniques; extrusion/spheronisation and the hot-

melt spray system. The modified formulation is outlined in Table 7.5 and a batch size of approximately 65g was produced:

Table 7.5 Modified Sebomin Formulation

Formulation Components	**Quantity Required (%w/w)**
Minocycline Hydrochloride	4.8
Imwitor 900K	83.1
Povidone K-30	3.8
Microcrystalline Cellulose (Avicel® PH101)	8.3
Ethanol/H_2O solution (56%v/v)	12ml

The resultant material was analysed utilising the following analytical techniques (Table 7.6).

Table 7.6 Analytical techniques used to characterise the minocycline HCl pellets and sprayed granules.

Analytical Technique	**Method Information**
PSD	Section 2.4.2.1
DSC	Section 2.4.5
Dissolution	Section 2.4.7.2
HSM	Section 2.4.7.3

7.3 Results and Discussion

7.3.1 Effect of initial minocycline HCl particle size

The results of the particle size distribution for the minocycline HCl-GMS (10:90%w/w) sprayed mixture incorporating various drug particle size fractions are in Figure 7.1.

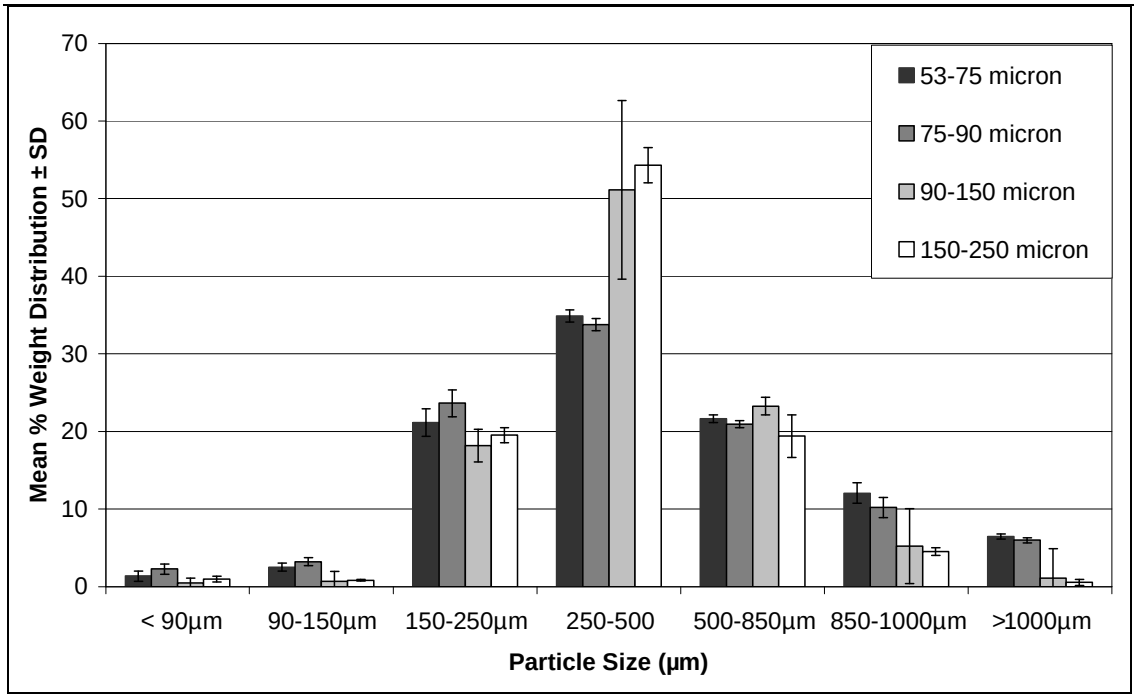


Figure. 7.1 Particle size distribution of sprayed GMS material with varying minocycline HCl particle size fractions (n=3).

For all four batches of sprayed minocycline-GMS material the majority of the resultant particles were within the 250-500µm size range (Figure 7.1). Statistical comparison of the PSD obtained for the minocycline-GMS batches indicated there was no significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed minocycline-GMS material is independent of initial drug particle size. These findings are consistent with the PSD results obtained with paracetamol and ibuprofen

binary sprayed mixtures (Chapter 5) and were also independent of the initial drug particle size.

The effect of initial distribution of minocycline particle size on the resultant drug dissolution rate from sprayed GMS material is shown in Figure 7.2.

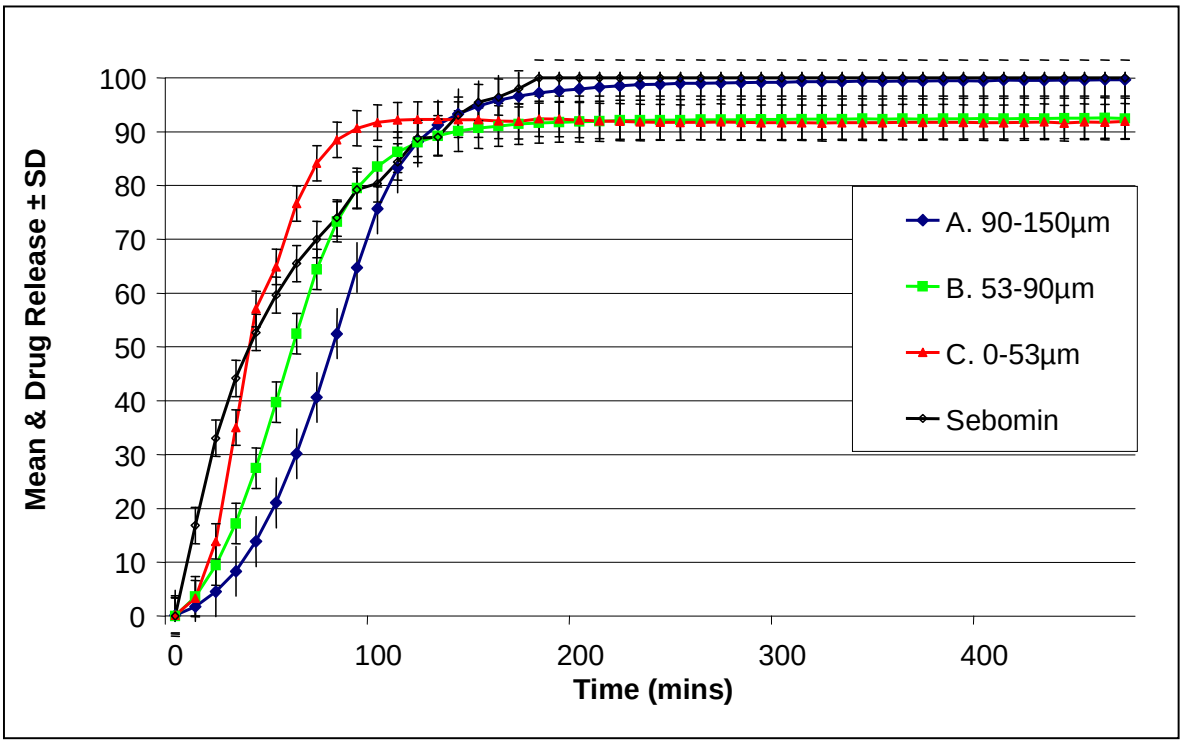


Figure 7.2 Mean Release Profiles of sprayed 10:90%w/w minocycline-GMS sprayed mixtures with varying minocycline particle size fractions (n=6).

Mean drug release profiles for minocycline sprayed binary mixtures (Figure 7.2) indicate that as the particle size of the active ingredient within the GMS increases above 90 microns the rate of drug release significantly decreases (f_2 value < 50). Binary sprayed mixtures of minocycline-GMS have a significantly faster dissolution rate if the initial

drug particle size is below 90 microns. To further confirm thermal properties have no influence on the dissolution results thermal analysis is required (Section 7.3.2).

All minocycline-GMS binary mixtures are classified as modified drug release (Section 1.4). The binary mixture incorporating 90-150µm of minocycline HCl almost achieved sustained release with only 30.1% of the drug being released in 1 hour. If an initial drug particle size range of greater than 150µm were to be utilised it is anticipated that sustained release would be achievable from the sprayed binary GMS material.

The minocycline-GMS mixtures incorporating initial drug particles greater than 50µm had a significantly prolonged release rate than the release rate from the commercial Sebomin pellets (f_2 value<50). Initial drug particle sizes less than 50µm had no significant difference to the Sebomin pellets (f_2 value>50). From these results, the hot-melt spray system is potentially capable of producing material with a greater sustained release capability than pellets produced via extrusion spheronisation.

The FT-IR spectra of micronised minocycline HCl is shown in Figure 7.3.

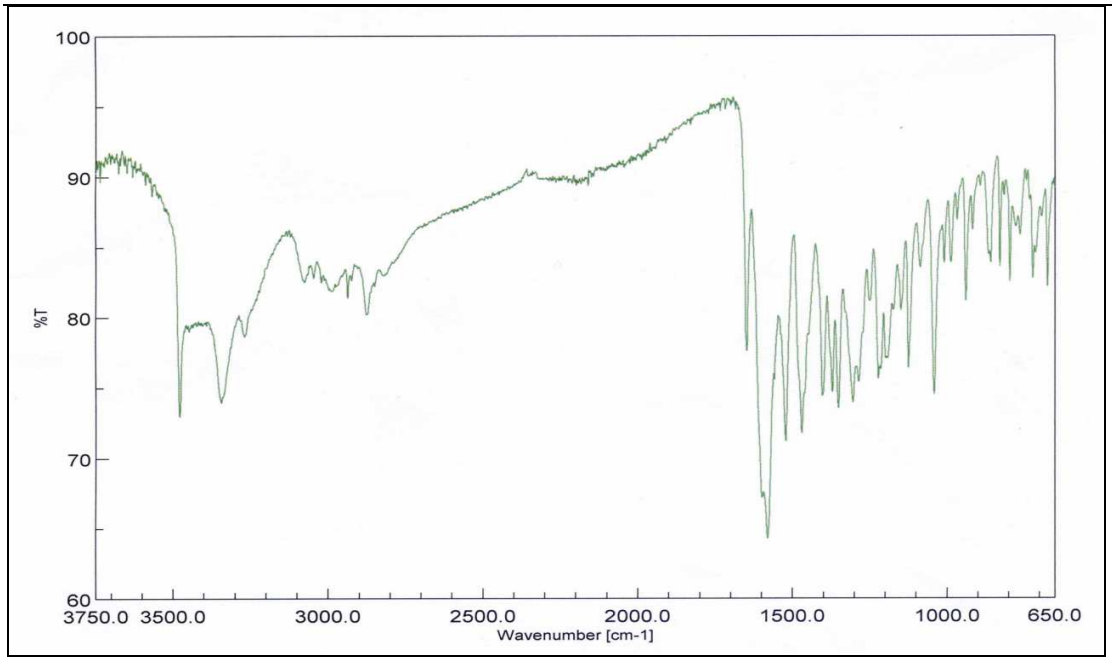


Figure 7.3 FT-IR spectra of minocycline HCl powder

In the FT-IR spectrum depicted in figure 7.3, confirms the minocycline HCl to be crystalline (Mendes et al., 2010). Peaks between 3250-3400cm^{-1} indicate the N-H stretch, the presence of two bands at 3269 and 3478cm^{-1} indicate the primary amine group and is further confirmed by the presence of the N-H bend at 1580 and 1648cm^{-1}. The additional peak in the 3200-3500cm^{-1} region indicates the presence of the O-H stretch. Aromatic hydrocarbons and alkyl hydrocarbons are confirmed both above and below 3000cm^{-1}. The presence of 2351 cm^{-1} indicates possible carbon dioxide present during sample preparation.

The FT-IR spectra of minocycline:GMS mixtures (10:90 %w/w) are shown in Figures 7.4 and 7.5.

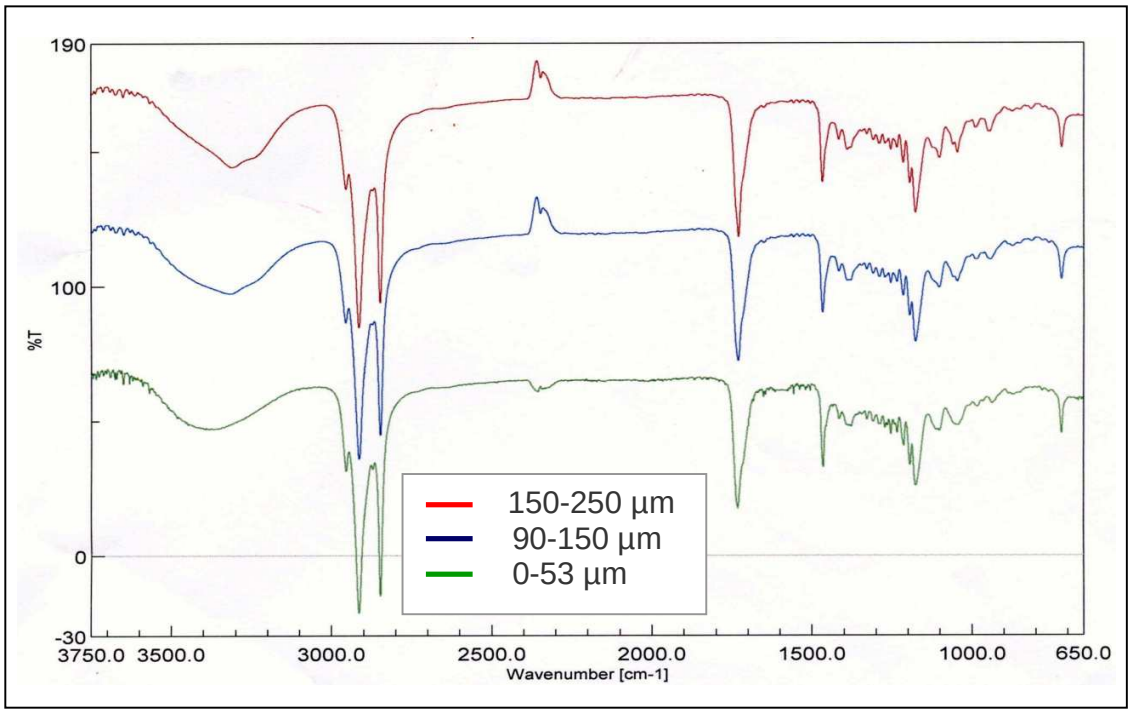


Figure 7.4 FT-IR spectra of sprayed minocycline:GMS binary mixtures (10:90% w/w) with varying initial drug particle sizes at Day 1.

From the minocycline-GMS mixtures (figure 7.4), the presence of peaks between 2848-2956cm^{-1} and at 1734 cm^{-1} indicate alkyl hydrocarbons and C=O stretching, respectively. The C=O stretching is saturated and aliphatic in nature and can be confirmed as an aldehyde due to the slight peak present at 2720cm^{-1}.

The FT-IR spectra (Figure 7.4) for the minocycline-GMS mixture with the initial drug particle size 0-53 micron varies to the spectra for 90-150 micron and 150-250 micron minocycline mixtures. A doublet is present at the 2360cm^{-1} region for the 0-53 micron mixture and indicates the presence of carbon dioxide as does the sharp peak at 667 cm^{-1}

(Hsu, 1997). However, the FT-IR spectra for the minocycline-GMS batch at day 5 did not exhibit a doublet in the 2360cm^{-1} region (Figure 7.5).

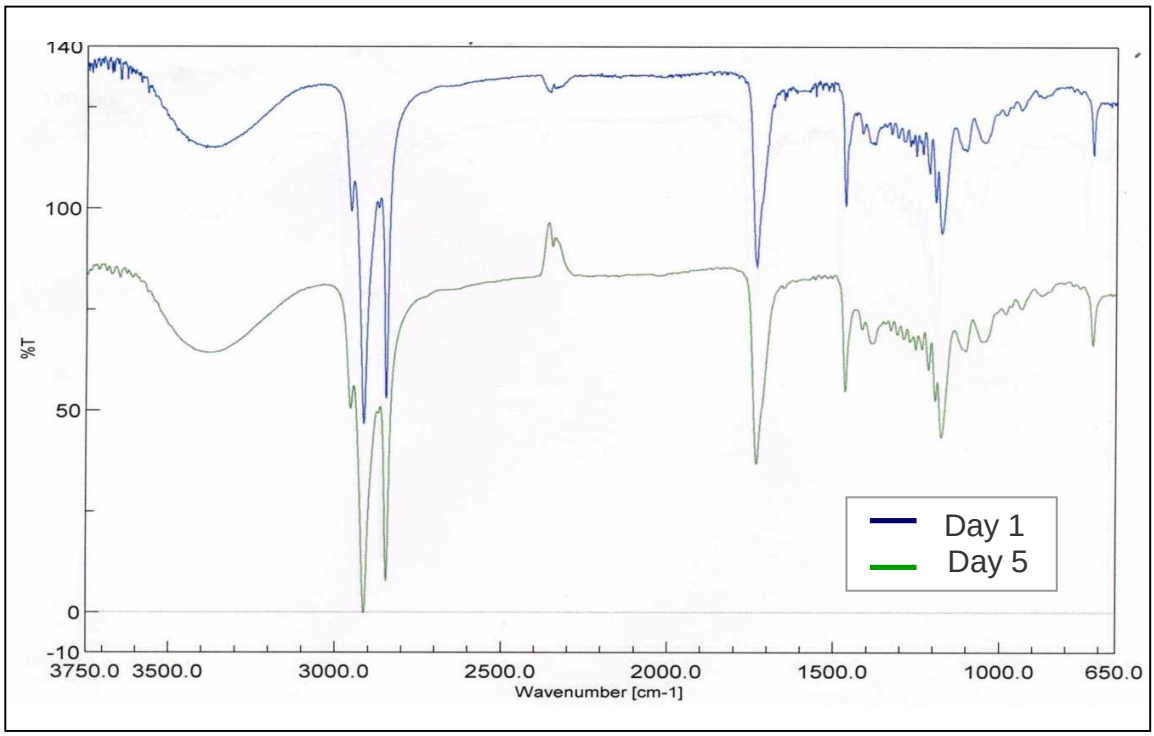


Figure 7.5 FT-IR spectra of a sprayed minocycline:GMS binary mixture (10:90% w/w), incorporating minocycline HCl with a particle size of 0-53µm.

Figure 7.5, suggests the sample at day 5 had a smaller amount of carbon dioxide present in it than the sample exhibiting the carbon dioxide doublet at 2360 cm^{-1} (day 1). This could be attributed to variable conditions during sample preparation or atmospheric conditions during the time of the run.

7.3.2 Production of hot-melt and sprayed minocycline-GMS binary mixtures (5:95%w/w)

To determine if there is a significant difference in the characteristics of the granules produced via milling or hot-melt spraying (both subjected to the same temperatures).

DSC was used to characterise the melting point, crystallisation and polymorphic transformation of the milled and sprayed granules. The DSC profiles of both granular materials are shown in Figure 7.6.

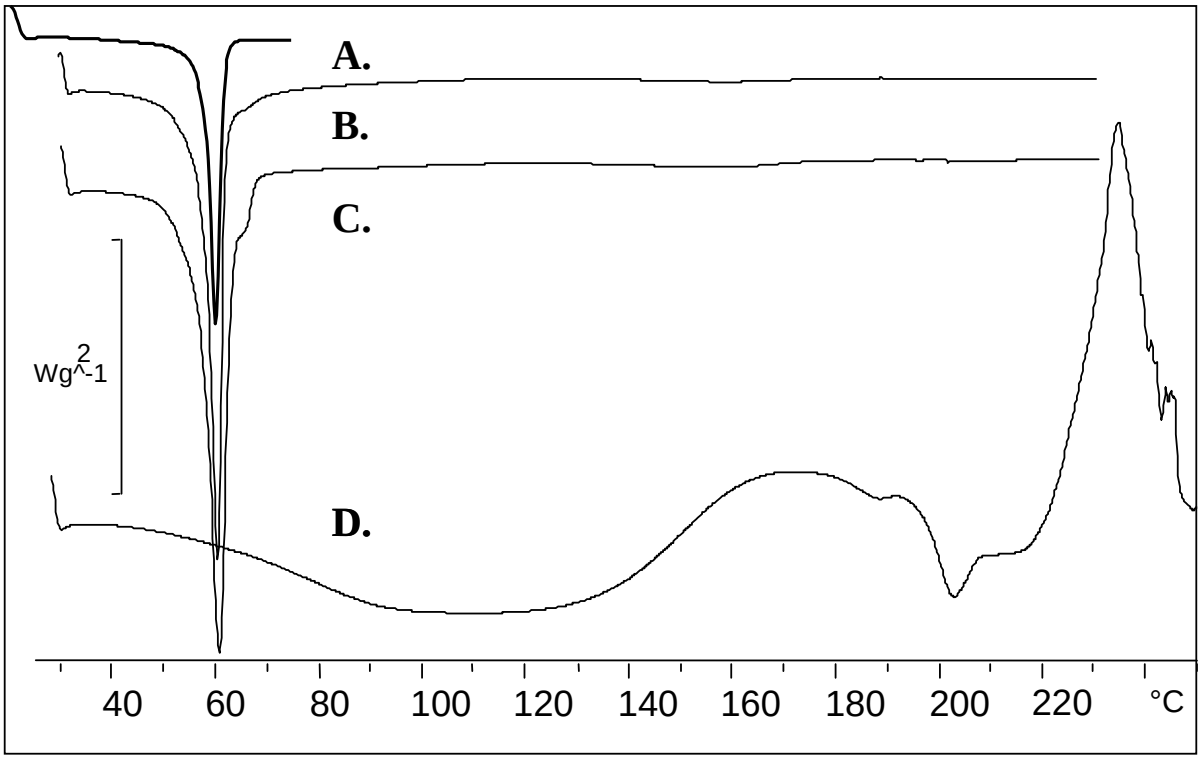


Figure 7.6 DSC profiles of 5:95%w/w minocycline HCl-GMS binary mixtures. (A) GMS powder, (B) sprayed granules, (C) milled granules and (D) minocycline HCl (scale bar = heat flow of 2 watts per gram).

From figure 7.6, the GMS powder exhibits an endotherm at 60^{o}C and correlates to the GMS melting point. Minocycline HCl exhibits a broad endotherm with an extrapolated peak at 110^{o}C, followed by two further endotherms, one at ~187^{o}C and the other endotherm at ~202^{o}C. These endotherms correlate to the three polymorphic crystalline forms of minocycline, form I, II and III (Mendes et al., 2010). The exothermic peak post 220^{o}C is representative of the decomposition of the minocycline HCl. Due to the broad peak exhibited at 110^{o}C should be reviewed for the presence of free water via TGA.

DSC analysis of both minocycline-GMS binary mixtures (Figure 7.6) revealed sharp primary endotherms for GMS, exhibited between 59-61˚C. There were no endotherms corresponding to the minocycline forms identified in (D), indicating the drug maybe in an amorphous form as minocycline is hydrophilic in nature and will not dissolve in the GMS (Mendes et al., 2010; Cardoso et al., 2008). The endothermic shoulder present at approximately 63^{o}C on both mixtures does not correlate to the GMS but may represent some small, dispersed crystallisation nuclei (Cardoso et al., 2008).

Thermal analysis indicates the formation of amorphous minocycline and the possible presence of crystallisation nuclei for both hot-melt methods of production. The shoulder at approximately 63^{o}C is more pronounced for the milled granules than for the batch manufactured utilising the spray system, this may indicate an increased rate of crystallisation when hand milling. However, to further confirm this XRPD would need to be utilised and further batches manufactured.

Visual examination of milled granules and sprayed granules are shown in figure 7.7.

(1) (2)

Figure 7.7 Digital photographs of (1) Minocycline HCl milled granules and (2) Minocycline HCl sprayed granules.

Visual examination of the minocycline HCl milled granules and Minocycline HCl sprayed granules (Figure 7.7) indicated the milled granules to be significantly larger and more irregular in shape than the sprayed granules. Confirmation of this observation could be achieved by sieving the material to obtain the PSD for each batch.

The results of the dissolution studies for both milled minocycline-GMS granules and sprayed minocycline-GMS granules are shown in Figure 7.8.

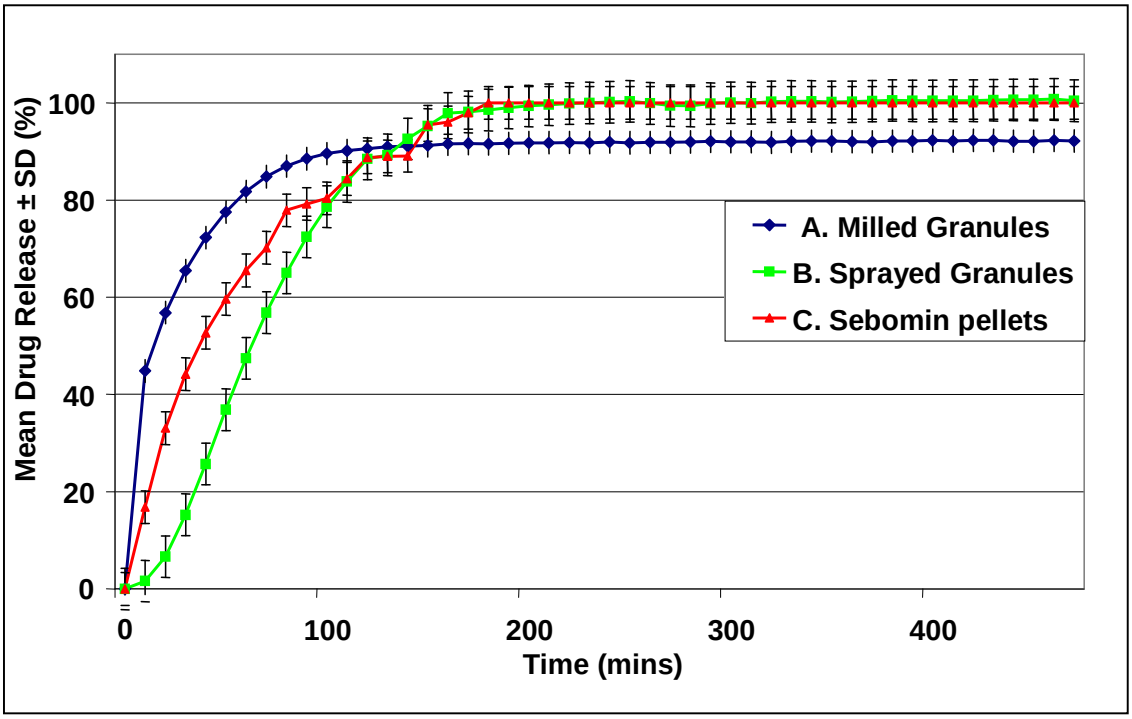


Figure 7.8 Mean Release Profiles of 5:95%w/w milled and sprayed minocycline-GMS mixtures (n=6).

The minocycline-GMS granules have significantly different (f_2 value < 50) drug release profiles (Figure 7.8), indicating the method of granule preparation has a significant effect on the overall release of the drug. The bulk granules prepared via holt-melt and milled have an immediate release profile as 75% drug was released within 45 minutes. Whereas the bulk granules prepared via the holt-melt spray system were classified as modified drug release as approximately 50% drug release was achieved prior to 60 minutes (Section 1.4).

The dissolution results suggest the sprayed granules may be more compact/densified than the hand-milled granules. Aerodynamic forces exhibited during atomisation may

contribute to the formation of more compact spherical droplets (Lefebvre, 1989). Increased densification reduces diffusional pathways within the wax matrix, delaying the ability for the dissolution media to penetrate the sprayed granules and drug dissolution. The same principle was observed when the spheronisation time was increased during pellet production in chapter 3.3.1.2.

Milled granules exhibit a significantly increased drug release rate than both the sprayed granules and the Sebomin® formulation. There may be a combination of factors contributing to the increased dissolution rate observed in figure 7.8. Milling will expose the drug crystals suspended in the GMS matrix to the surface of the granule. This will enable direct contact between the drug and dissolution media increasing the dissolution rate.

Thermal analysis of the milled granules (figure 7.7) may indicate a larger proportion of minocycline crystallisation nuclei. This may correlate to drug exposure on the granule surface promoting a faster rate of crystallisation of amorphous minocycline. There is evidence to suggest the minocycline solubility increases at crystallisation nuclei (Cardoso et al., 2008), although further investigation of this mechanism is required.

The difference in the appearance of the milled granules (section 7.3.2) may contribute surface area effects and influence the dissolution properties. However, the irregular shape and increased size observed for the milled granules would promote a slower drug release rate and not correlate to the observations in figure 7.8. In this instance it would be

anticipated for milled granules and sprayed granules of a given size to exhibit a more pronounced difference in their dissolution rates than observed in figure 7.8. To confirm these findings PSD of milled and sprayed granules requires investigating.

Milled granules investigated in section 3.3.4.2 exhibited a faster drug release rate than the milled granules exhibited in figure 7.8 but this increased drug release rate would be attributed to the higher drug loading in the GMS (minocycline 10%w/w).

7.3.3 Development of a minocycline formulation produced by two different manufacturing techniques.

The results of the particle size distribution for the minocycline HCl pellets and minocycline HCl sprayed granules are in Figure 7.9.

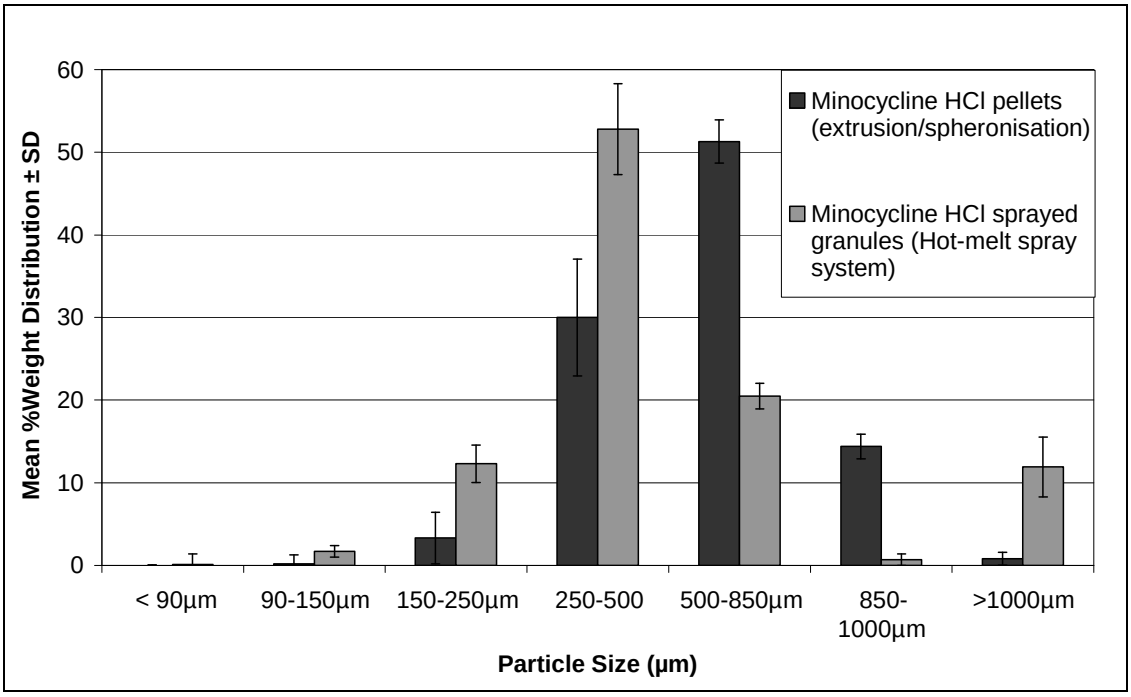


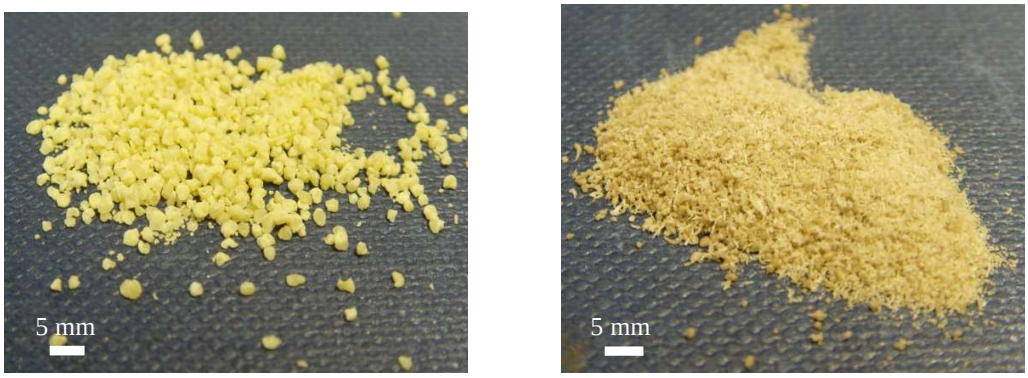
Figure 7.9 Particle size distribution of Minocycline HCl pellets and sprayed granules produced via extrusion/spheronisation and hot-melt spray system, respectively.

The majority of the resultant particles, for the minocycline pellets produced by extrusion/spheronisation, were within the 500-850µm size range (Figure 7.9). Whereas, the majority of the resultant particles, for the minocycline sprayed granules, were within the 250-500µm size range (Figure 7.9). Statistical comparison of the PSD obtained for the two minocycline batches indicated there was a significant difference in the PSD (Two-way ANOVA; $p>0.05$). Therefore, the overall PSD of the sprayed material is dependent on the manufacturing technique used to produce the minocycline drug product.

For the minocycline pellets, 53% of the particles were greater than 500µm compared to only 35% of the minocycline sprayed material. The pellets may exhibit a larger PSD due

to the method of PVP addition during granulation. On PVP addition, the granule surface becomes adhesive and promotes agglomeration. During spraying, the PVP and MCC are added to an agitated system whilst the carrier is molten, this will not promote agglomeration of the particles.

Visual examination of minocycline HCl pellets and sprayed granules are shown in figure 7.10.



(1) (2)

Figure 7.10 Digital photographs of (1) Minocycline HCl pellets and (2) Minocycline HCl sprayed granules.

Visual examination of the minocycline HCl pellets and sprayed granules (Figure 7.10) indicated the appearance of the batches were significantly different. The pellets appeared spheroid and larger than the sprayed granules, which is consistent with the PSD results (figure 7.9). The sprayed granules appeared darker in colour, smaller in size and irregular in shape. To determine whether the impact is only cosmetic the sprayed granules release and thermal characteristics were also investigated (Section 7.3.3).

Sprayed granules in figure 7.10 appear different to the sprayed minocycline-GMS granules in figure 7.7. In figure 7.10, the colour of the sprayed material is a darker shade of yellow and the particles appear coarser in texture and irregular. This implies the addition of PVP and MCC and the method of addition has an impact on the appearance of the product (Law & Deasy, 1997). MCC is known to assist in the formation of spherical shaped pellets during spherionisation (Rajesh, 2010).

The viscosity of the molten solution may also have to be considered as this could have altered due to the incorporation of the additional excipients. This could also impact on the particle shape/spray pattern of the resultant sprayed material.

The DSC profiles of the minocycline HCl pellets and sprayed granules produced via extrusion/spheronisation and hot-melt spray system are shown in Figure 7.11.

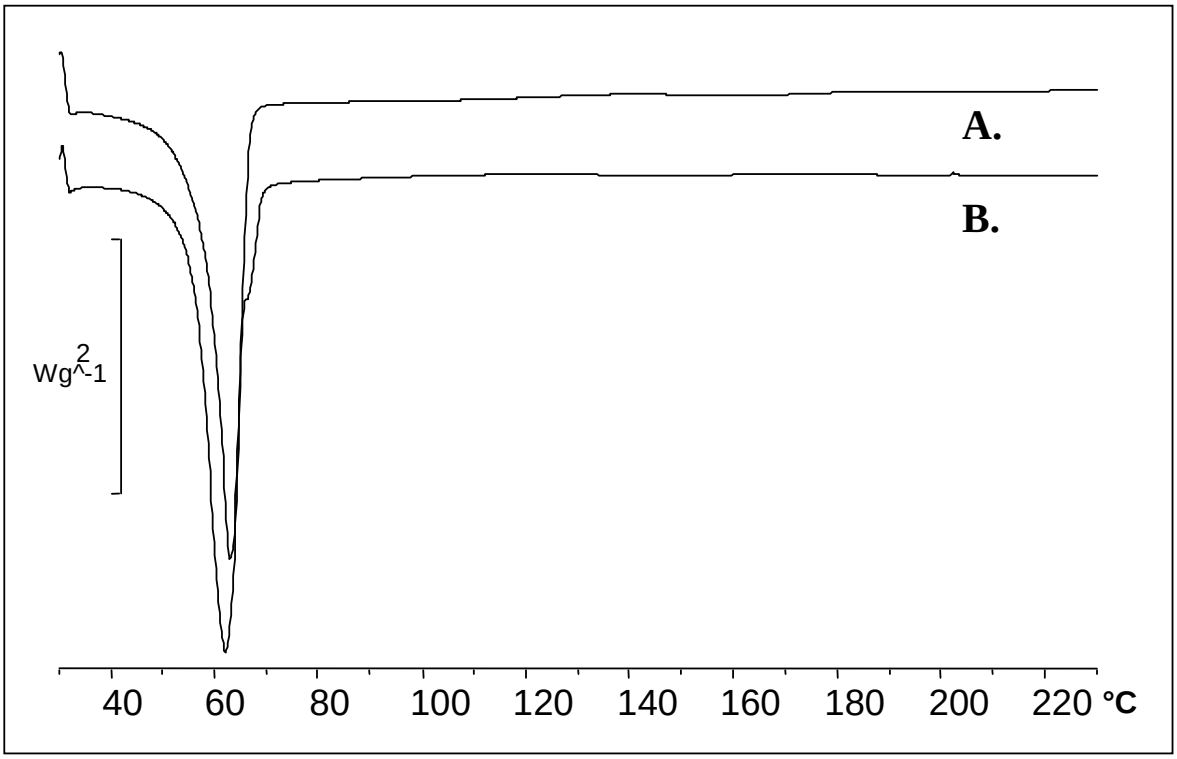


Figure 7.11 Effect of manufacturing technique on the DSC profiles of (A) minocycline HCl pellets produced by extrusion/spheronisation, (B) minocycline HCl sprayed granules produced by a hot-melt spray system (scale bar = heat flow of 2 watts per gram).

DSC analysis (Figure 7.11) of the pellets and sprayed granules exhibited sharp primary endotherms at 62-63^{o}C correlating to GMS. In figure 7.11, there is a slight upward shift in the GMS endotherms than observed for GMS in figure 7.6 and can be attributed to the dilution of GMS present in the formulations. A small endotherms can be observed at 202^{o}C corresponding to the minocycline form III (identified in figure 7.6), suggesting some drug is present in a crystalline form (Mendes et al., 2010; Cardoso et al., 2008).

The sprayed granules in figure 7.11 exhibit an endothermic shoulder at approximately 65^{o}C and may be representative of some small, dispersed crystallisation nuclei (Cardoso et al., 2008). This was also observed in figure 7.6 at 63^{o}C, the slight upward trend observed must be due to the dilution factor of the GMS.

From figure 7.11, the shoulder at 65^{o}C was not observed for the minocycline pellets. It may indicate crystallisation nuclei have not formed in the pellets. However, in the milled granules (figure 7.6) prior to processing into pellets, the shoulder at 65^{o}C was observed. This indicates the addition of intragranular material, such as PVP and MCC, during wet granulation may contribute to the inhibition of the secondary peak.

From figure 7.11, MCC would be anticipated at 260-270^{o}C, this exceeds the 20-240^{o}C range of the DSC method and is not characterised in the thermogram. In addition, no endotherm corresponding to PVP was observed for either batch, Tg at 164^{o}C (ISP technologies Inc, 2011; Kaewnopparat et al., 2009). PVP is water soluble and will dissolve in the water/ethanol mixture added to both batches of granules during processing. PVP has also been reported to retard crystallisation, stabilise amorphous forms of drug in a matrices and can form complexes with some drugs (Kaewnopparat et al., 2009; Ranade & Cannon, 2011).

From the sprayed material, inclusion of PVP in the molten matrix does not appear to retard crystallisation. This suggests the method of binder addition yields different thermal properties and may be an important formulation parameter (Iveson et al., 2001).

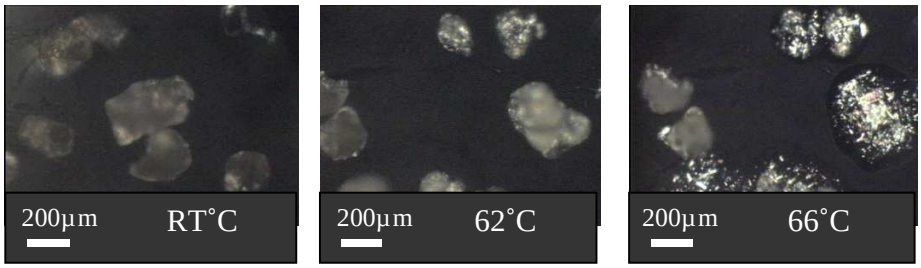
Investigation of these effects on the dissolution properties were undertaken in section 7.3.3.

A stability study of both milled granules and pellets would be required to determine if crystallisation occurs on ageing of the formulation. PVP concentration could also be modulated further to correlate any crystallisation effects.

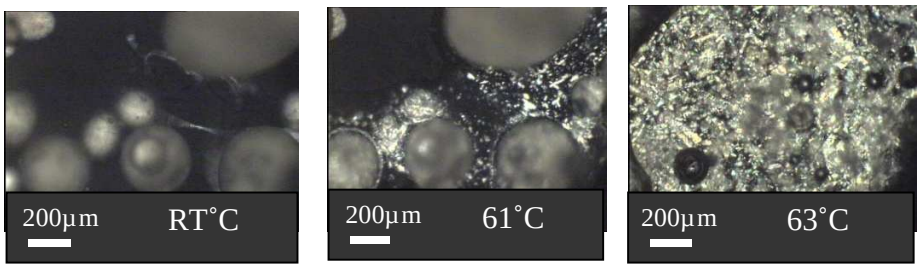
The incorporation of water/ethanol during granulation has no effect on the thermal analysis. The water/ethanol solution is evaporated during the drying phase and is no longer present in the drug delivery system.

During manufacture of the sprayed granules there is no drying phase, the molten solution incorporating the excipients is sprayed at 80^{o}C and forms granules during descent under gravity. During agitation of the molten solution, some drug may dissolve into the water/ethanol phase present in the molten solution and form a two phase system. For the water/ethanol phase consideration of the ethanol boiling point (78.5^{o}C), temperature and duration prior to and during spraying would become important factors and impact on the release characteristics of the sprayed granules (section 7.3.3).

The hot-stage microscopy images of the minocycline HCl pellets and sprayed granules are in Figure 7.12.



Minocycline HCl pellets



Minocycline HCl sprayed granules

Figure 7.12 Hot-Stage Microscopy of minocycline HCl formulations produced with different manufacturing methods at a x10 magnification.

From figure 7.12, the microscopic images indicate the GMS has a lower melting temperature (63^{o}C) when produced via the hot-melt spray method than the minocycline HCl pellets produced via extrusion/spheronisation (66^{o}C). At room temperature crystalline minocycline HCl can be observed within the sprayed granules, on melting of the wax matrix the crystalline API can be observed. However, at room temperature no API crystals can be observed within the pellets. On melting of the pellets there is evidence of some crystalline API being present but it is significantly less than for the sprayed granules. As both of these batches contain the same quantity of minocycline HCl,

the reduced visual appearance of crystalline API in the pellets does not suggest the API is not present but merely in an amorphous form. This observation would correspond to the thermal analysis data in figure 7.11.

The release profiles of the minocycline HCl pellets and sprayed granules produced via extrusion/spheronisation and hot-melt spray system are shown in Figure 7.13.

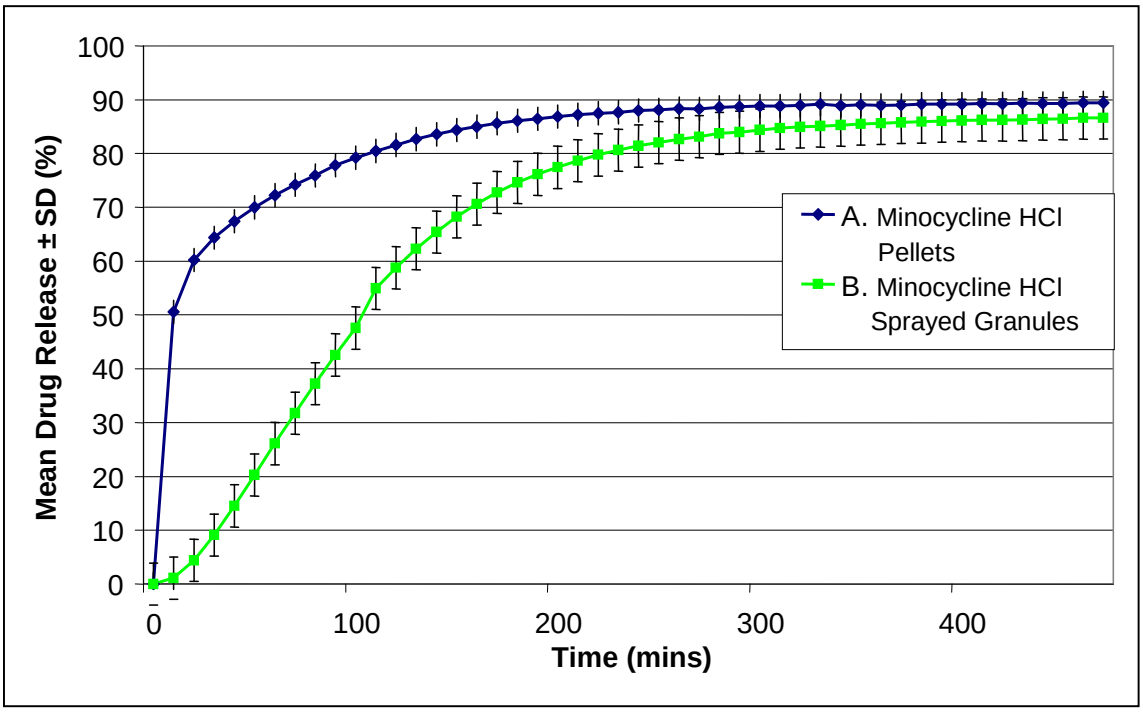


Figure 7.13 Mean Release Profiles of (A) minocycline HCl pellets produced by enxtrusion/spheronisation, (B) minocycline HCl sprayed granules produced by a hot-melt spray system (n=6). Both batches incorporate 5% w/w minocycline HCl and 83% w/w GMS.

The minocycline pellets and sprayed granules have significantly different (f_2 value < 50) drug release profiles (Figure 7.13), indicating the method of granule preparation has a significant effect on the overall release of the drug.

Pellets prepared by extrusion/spheronisation have a faster rate of drug release compared to granules prepared by a holt-melt spray system. The pellets were classified as modified release and not immediate release as less than 75% of the drug was released by 45 minutes (section 1.4).

The sprayed minocycline material was classified as sustained release as only 26.1% (n=6) of the drug was release by 60 minutes, 50% (n=6) drug release was achieved by 100 minutes and 80% (n=6) of the drug release was achieved in 230 minutes (Section 1.4). The maximum drug release achieved in 8hrs for the sprayed minocycline granules was approximately 87%.

From the PSD results (figure 7.9), it would be anticipated for the sprayed granules to have a faster dissolution rate due to the majority of particles having a smaller particle size. However, as indicated by the binary mixture of minocycline HCl and GMS (Section 7.3.2), the hot-melt spray system significantly sustains the drug release rate of the drug product. This prolonged release implies the sprayed granules may have a greater level of densification which is achieved utilising aerodynamic forces during atomisation. The same level of densification could not be achieved utilising rotational and centrifugal forces during extrusion/spheronisation.

The additional excipients in the sprayed granules and the pellets both have a significant effect on the drug release rate. However, the release of the sprayed granules appears to be prolonged by their addition, whereas the pellets appear to have a faster drug release rate (figure 7.13).

The pellets in figure 7.13 had a significantly faster drug release profile than the commercial Sebomin MR pellets. The quantity of PVP was reduced to 3.8% w/w to enable successful spraying of Sebomin to be achieved. However, product manufactured via wet granulation had significantly less binder (PVP) present in the mixture. The reduction of the binder decreases the intragranular bonding between the particles during granulation (Colorcon, 2005). The number, size and viscosity of the liquid bridges formed between particles can directly impact the PSD of the granules. Less binder present in granulation fluid produces less viscose liquid bridges during agglomeration. Liquid bridges with low viscosity in the nucleation zone can only support small particles that will be weaker and more porous (Iveson et al., 2001; Qiu et al., 2009). This mechanism may explain why the pellets with the faster drug dissolution in figure 7.12 have a significantly smaller PSD (figure 7.9) than the commercial Sebomin pellets (figure 3.3).

MCC assists as a disintegrant during dissolution, provides plasticity during extrusion and cohesion during wet massing. A 34% reduction in MCC quantity was undertaken (table 7.5) to enable successful spraying. This decrease in MCC quantity may have resulted in

less cohesion during granulation and brittle pellets being formed. Previous investigations have described such findings, as well as pellets less spherical in nature and a faster drug release (Sadeghi et al., 2011).

The water/ethanol concentration was not modulated for the pellet formulations (table 7.4 and 7.5). However, in the pellets, the volume of liquid versus binder would have been higher but less water would have been taken up with MCC and PVP. As a result, a greater amount of water/ethanol would have been available for the drug to dissolve in. When the water/ethanol solution is evaporated during the pellet drying phase drug crystals may form on the pellet surface as the water evaporates. This may account for the initial burst release exhibited in figure 7.13 (Rajesh, 2010).

Unlike the pellets, incorporation of PVP, MCC and ethanol/water into the sprayed material significantly sustains the drug release rate (figure 7.12). This retardation in drug release is also significantly prolonged in comparison to the sprayed minocycline-GMS binary mixture (figure 7.8). This suggests the binder addition method and distribution may impart on the release characteristics of the resultant granules.

Atomisation with agitation has been demonstrated to be the best binder distribution method with narrow size distributions achieved (Iveson et al., 2001). PVP and MCC would be homogenously distributed throughout the molten mixture and assist with coating the minocycline drug particles with the excipients during agitation, prior to spraying. This would enable a droplet to be formed around the minocycline particles

increasing the adhesive and cohesion intragranular forces that would form on cooling of the sprayed material.

The rate of crystallisation for the sprayed material (figure 7.11) at 63^{o}C is greater than the binary sprayed material (figure 7.6). Suggesting PVP addition does not appear to retard crystallisation in a molten matrix. The water/ethanol solution present in the molten GMS also promotes crystallisation of the drug at 202^{o}C in the sprayed granules, corresponding to minocycline form III. The presence of two types of crystals in the sprayed material is due to the inclusion of both GMS and water/ethanol in the sprayed mixture, promoting a two phase system to form.

This would indicate the minocycline has dissolved in the water/ethanol phase, whilst the remaining minocycline is suspended in the GMS. Evaluation of the ethanol evaporation rate at 80^{o}C would need to be investigated to determine the proportion of ethanol present in these sprayed formulations. The water/ethanol present in the mixture would not be anticipated to further evaporate during a drying phase, the minocycline may remain in two phases. Drug crystallisation may occur at different rates for each of these phases promoting different forms of minocycline to be formed. Different forms of minocycline have been demonstrated to have difference release characteristics (Cardoso et al., 2008).

If a two phase system does exit in the sprayed granules, the proportion of API in each phase would be unknown. XRPD would need to be undertaken to quantify the API forms. The greater appearance of crystalline API in the HSM may account for the API present in

the water phase (figure 7.12), as the sprayed system was molten on the addition of the water/ethanol the dispersion of API into the water may have been greater than for the pellets. This may indicate the rate of dispersion of the water/ethanol on manufacturing may have a significant impact on the proportion of API present in the formulation in an amorphous or crystalline state. For a spray system, elimination of the water/ethanol from the sprayed formulation would be preferable to prevent a two phase system, enabling reproducibility of the drug stability and release profiles. Further investigation into the systems stability and quantification of the crystalline and amorphous API entities is desirable.

7.4 Conclusions

The effect of the initial minocycline HCl particle size does not have a significant effect on the PSD or the structural molecules and their orientation. However, the initial particle size of the drug does have a significant effect on the dissolution of the binary mixture.

Binary mixtures of minocycline and GMS processed into granules utilising different methods of preparation had significantly different release profiles. The bulk granules prepared via holt-melt and milled exhibited an immediate release profile, whereas the bulk granules prepared via the holt-melt spray system were characterised as having a modified drug release.

Despite a greater proportion of the milled granules being larger in size than sprayed granules this did not appear to be a contributing factor in the primary drug release

mechanism. Further investigation into the porosity and mechanical strength of the batches would be required to determine the possibility of sprayed granules being more compact/densified. If this is the case the compaction/densification effect achieved via atomisation (aerodynamic forces) would be significantly greater than the rotational and centrifugal forces achieved by extrusion/spheronisation.

A sustained release minocycline formulation could be achieved utilising the hot-melt spray system. Sustained release could not be achieved utilising extrusion/spheronisation technology even when the pellets has a significantly larger particle size than the sprayed granules. The difference in the release rates may be due to the densification of the granules during the atomisation process. Thermal properties of the batches were similar, except for the presence of a secondary shoulder when the material was sprayed and was attributed to crystallisation nuclei present in the granules. The API appeared to be amorphous in both batches.

The modification of the Sebomin formulation to enable spraying was favourable to the granules produced via the hot-melt spray system. A disadvantage of utilising this system was the inability to achieve sprayed granules with a high drug loading ability due to the hydrophilic nature of the drug. As required with Sebomin, a drug loading of 60.7% w/w would be impossible to achieve utilising a hot-melt spray gun. The solution would be a semi wet-plastic mass which is not suitable for atomisation.

However, high drug loadings could be achieve utilising a hot-melt spray system for a hydrophobic matrix delivery system with a hydrophobic drug. Due to the drug's potential ability to dissolve in the carrier, the only rate-limiting steps would be the compatibility and saturation of the carrier. However, inclusion of excipients such as PVP may generate supersaturated solutions, leading to a higher drug loading being achieved. This may have both formulation and processing implications and would need to be investigated in a similar manner as demonstrated for excipients in chapters 5 and 6.

Binary mixtures of minocycline and GMS processed into granules utilising different methods of preparation had significantly different release profiles. The bulk granules prepared via holt-melt and milled exhibited an immediate release profile, whereas the bulk granules prepared via the holt-melt spray system were characterised as having a modified drug release.

The sprayed granules were further enhanced to achieve sustained release via the addition of PVP and MCC into the minocycline-GMS molten solution. This modulated formulation did not enhance the release characteristics of pellets but produced an immediate release product. The method of addition, distribution and quantity of PVP, MCC and water/ethanol solution have a significantly different effect on the two manufacturing processes. It was also demonstrated to potentially modulate the crystalline or amorphous forms of the minocycline. Amorphous minocycline HCl was demonstrated to have faster dissolution properties, whereas sprayed granules containing crystalline minocycline had a slower drug release rate.

From the results of the study and various supporting literature, the drug release characteristics for both drug delivery systems can be further modulated. By utilising quality by design concepts, formulation optimisation could be achieved for reproducible sustained release oral dosage forms utilising extrusion/spheronisation and hot-melt spray systems.

8. Conclusions and Future Work

8.1 General Conclusions

During the investigation of the hydrophobic matrix pellets via extrusion/spheronisation, process limitations were identified which led to the development of a hot-melt spray system. In parallel, the use of GMS in a solid dispersion and solid solution were characterised, with interactions between GMS, API and excipients documented.

Hydrophobic matrix pellets were produced via wax fusion and extrusion/spheronisation. Incorporation of either minocycline HCl or paracetamol yielded immediate or modified release matrix pellets. Product performance could be modulated by both process and formulation variables. Process critical parameters included milling and spheronisation time whilst formulation critical parameters included wax content, granulation fluid composition and pellet particle size.

Quality by design enabled successful identification of critical parameters impacting upon the performance of the product. In Chapter 3, the design space of Sebomin MR and a paracetamol equivalent could be defined in accordance with the manufacturing process (extrusion/spheronisation). Modulation of both process and formulation parameters did not yield sustained release matrix pellets. In pursuit of a sustained release hydrophobic matrix pellet delivery system a hot-melt spray system was developed.

Development of a hot-melt sprayed system was successfully implemented with reproducible, spherical, hydrophobic sprayed material being produced. Design of experiments was an extremely useful analytical tool in generating sufficient data for determining critical process and formulation parameters in comparison to the OFAT approach. Critical processing parameters impacting upon the particle size distribution included voltage and nozzle diameter, with interactions being observed between factors including the wax type-voltage and wax type-nozzle diameter.

During this thesis, a direct comparison of manual sieve analysis techniques versus laser diffraction was undertaken and although the determinations were correct and in accordance with the procedures, limitations of each method were identified resulting in different particle size distributions being obtained for the sprayed material. Confirmatory size analysis techniques, such as image analysis and microscopic techniques are available but are extremely time-consuming and require dispersion. This highlights the need for improved dispersion techniques to be developed, to enable laser diffraction to fulfill its potential as a simple and rapid size analysis technique.

Preliminary batches manufactured via the hot-melt spray system incorporated GMS only. A stability study of this material revealed a polymorphic transformation occurs in sprayed GMS granules over time. Both sprayed and hot-melt GMS formulations appeared to be a mixture of the α- and β-form of GMS polymorphs with the α-form still the most predominant polymorph present in the mixture 30 hours post-manufacture. During storage a transition from the unstable α-form to the stable β-form was observed, the rate

of transformation was enhanced by a faster annealing rate and accelerated storage conditions. However, even at accelerated temperatures complete transformation of GMS to the β-form was not achieved post 108 days storage. The GMS polymorphic transition was inhibited when the sprayed granules were stored at $4^{o}C$ but would not be a convenient storage solution for sprayed GMS based products.

When incorporating active ingredients into the GMS sprayed granules, GMS polymorphic transitions were still observed and appeared to be independent of initial drug particle size and drug loading. However, the initial drug particle size, drug loading and crystalline state of the drug appeared to have a more pronounced effect on the dissolution rate than the wax polymorphic state of the delivery system. For ibuprofen-GMS sprayed material, the initial drug particle size has no significant effect on a single phase solid solution but once the carrier becomes saturated a two phase molten solution was observed and the rate of ibuprofen recrystallisation influenced. No significant effect to the T_0 release performance was observed for the ibuprofen-GMS sprayed granules. However, the initial particle size of a drug forming a solid dispersion in the GMS sprayed material significantly impacts upon the subsequent drug release rate, as observed in paracetamol and minocycline sprayed granules but was independent of thermal or PSD changes. The primary drug release mechanism from the sprayed granules is via diffusion, but no sustained release was achieved in the binary mixtures.

Modulation of a minocycline formulation enabled sustained release to be achieved via the hot-melt spray system. However this was not reproduced by an equivalent formulation

manufactured by extrusion/spheronisation technology. The difference in the release rates did not appear to correlate to any differences in thermal properties or particle size observed. Further investigation into the porosity and mechanical strength of the batches would be required to understand the mechanism of sustained release achieved via the atomisation process.

A disadvantage of the hot-melt spray system was its inability to achieve high drug loading when spraying GMS solid dispersions but fformulating granules from GMS solid solutions omitted drug loading limitations. Incorporation of some excipients and processing parameters may achieve supersaturation in these systems but the impact on the resultant material would need to be explored. Despite this limitation, the hot-melt spray system developed in this thesis has indicated the potential to produce sustained release hydrophobic drug products, contributing to the pharmaceutical industrial requirement for simple, reproducible manufacturing techniques capable of yielding reproducible sustained release granules.

Further potential of the sprayed hydrophobic matrix was identified on incorporation of a variety of inorganic/organic multivalent salts. Modified and sustained release capabilities were observed in these drug delivery systems, with product performance being dependent on the type of multivalent salt and the drug incorporated into the GMS matrix. The presence of metal stearates also promoted a change in the physicochemical properties of GMS, ibuprofen and paracetamol, although further definition of the crystal chemistry was not possible utilising DSC alone and additional investigation is recommended utilising

DSC in combination with XRPD or FT-IR. Other important parameters requiring further investigation include the possible presence of drug-metal ion complexes, pH effects and a stability study of formulations comprising of lipophilic glycerides and metal stearates.

In a further study of aluminum monostearate and GMS, processing temperature was identified as a critical parameter in the physical morphology of the resultant sprayed granules. Increases of the concentration above 7.5%w/w yielded 'cotton-wool like' material in both GMS material processed at 125^{o}C and ibuprofen-GMS mixtures manufactured at 80^{o}C. The mechanism by which these morphological changes take place is not fully understood. Additional investigation into the formation of mesomorphic phases should be investigated and consideration of both aluminium di- and tri- stearates and their possible contribution to increased matrix hydrophobicity should be determined. Sustained release was also achieved in paracetamol-GMS formulations but was independent of the thermal and physical characteristics described for the ibuprofen equivalent formulations. This indicates the primary mechanism for sustained release in the paracetamol formulations is not related to the physical morphology of the sprayed paracetamol granules.

This thesis illustrates the limited knowledge of lipophilic glycerides which are often associated with instabilities and irreproducible product performance via processing and storage. Further understanding and characterisation of the potential interactions of lipophilic glycerides for use as solid dispersions and solid solutions is critical in development of hot-melt technologies. As demonstrated in this thesis, using a quality by

design strategy can assist in optimising manufacturing and processing parameters and enable definition of the product design space.

8.2 Future Work

- Development of an improved dispersion method for improved particle size measurements.
- Further hot-melt spray system development:
    - Investigate different methods to prepare hot-melt solid dispersions. Evaluate the use of various air coolants during hot-melt spraying, such as cooled air flow, gases, liquid nitrogen and refridgerants to assess the effect of annealing on the polymorphic transformation rate of GMS.
    - Assess the effect of different wax compositions on the hot-melt spray system.
    - Development of a re-dispersible dry emulsion utilising a spray system. . Spray drying of an O/W formulation to yield a dry emulsion for reconstitution could be evaluated, utilising water soluble polymer as a solid carrier.
    - Evaluate the potential for sprayed granules to be utilised in downstream processing such as compression into tablets and pelletisation.
        - Prior to downstream processing, the spray system could be assessed for its ability to improve the granule flow properties.

        - Downstream processing, properties such as tensile strength and friability could be characterised to assess the potential of utilising sprayed granules in additional manufacturing processes.
    - Considerations for scale up of the hot-melt spraying process.
- Further characterisation of solid solution and solid dispersion delivery systems:
    - Incorporation of additional hydrophobic drugs and their influence on the sprayed granule performance.
    - Investigate the porosity and mechanical strength of sprayed granules.
    - Consideration of a hot-melt spray process to achieve high drug loading in solid dispersions.
    - Undertake XRPD on paracetamol and minocycline binary mixtures to define the crystalline nature of API and excipients.
- Further characterisation of the GMS sprayed granules incorporating multivalent salts:
    - Rheological study to evaluate if incorporation of these excipients impacts the viscosity during the molten state and may contribute to the physical changes observed in this thesis.
    - Stability study in accordance with the ICH Harmonised Tripartite Guideline (2009).
    - Confirmatory analysis of thermal properties via XRPD, to define the crystalline nature of API and excipients.

- Identify any chemical or physical reactions taking place between GMS and metal stearates via FT-IR. Determine any drug-metal ion complexes and pH effects.
- Incorporate a study with similar lipophilic glycerides such as glyceryl palmitostearate (GPS) and Gelucires Further characterisation could include waxes, fats and oils to compare all types of glycerides.
- Characterisation of release performance in sprayed GMS-aluminium mono-, di- and tri-stearate granules processed at 125^{o}C.
- Incorporation of an oil phase to determine whether organogel formation can be achieved in the GMS system.
- *In vitro- in vivo* correlation studies

- Further investigation on the sustained release minocycline sprayed formulation
  - Stability study
  - SEM analysis
  - Optimise the formulation via QbD
  - *In vitro- in vivo* correlation studies

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