



From Particle to Tablet: Understanding Long-term Physical Stability of Immediate-release tablets

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Abstract

Understanding how excipient properties evolve under storage conditions and how these changes impact tablet performance is crucial for designing physically stable oral solid dosage forms (OSDFs). However, the relationship between stability rate processes at the particle and tablet scales remains insufficiently understood, limiting predictive capabilities of how early particle-level changes translate to long-term tablet properties such as mechanical integrity, moisture uptake, and disintegration performance. This thesis presents a multi-scale investigation into how excipient-level changes, particularly moisture sorption and swelling, determine the stability of directly compressed immediate-release (IR) tablets over time.

At the particle level, dynamic vapour sorption (DVS) was used to characterise excipient responses to controlled humidity exposure across eight materials. Sorption kinetics and equilibrium moisture contents were quantified under varying temperature and humidity conditions. Particle imaging revealed irreversible swelling for disintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG), and partial reversibility for microcrystalline cellulose (MCC), establishing the mechanistic basis for particle-level storage responses. The study then scaled these insights to the tablet level using MCC and MCC-CCS binary formulations prepared at different porosities by direct compression. By combining DVS data with real-time storage, scaling factors were established that link early DVS data to long-term uptake behaviour, allowing prediction of both equilibrium and kinetic parameters at the tablet level. Structural consequences, including rapid losses

in tensile strength and porosity, most pronounced on the first day of storage, were captured within this framework, demonstrating its ability to connect accelerated particle-level data with tablet-scale stability. Finally, formulation complexity was introduced through the addition of magnesium stearate and lactose. These excipients generated new interactions that markedly altered disintegration behaviour, extending beyond the influence of porosity and mechanical strength. The results demonstrated that liquid absorption and wetting kinetics are more reliable predictors of post-storage disintegration than tensile strength. In parallel, applying the predictive framework for time-scale translation of moisture uptake to these multi-component systems provided a robustness test, confirming its applicability beyond simple binary formulations. These investigations enabled the tracking of the timeline upon which storage-driven physical changes occurred, distinguishing between effects triggered by early moisture exposure and those emerging during prolonged storage. The rate of tensile strength loss was also estimated and shown to correlate with the kinetics of moisture uptake, further reinforcing the predictive basis of the framework.

Together, this work establishes a particle-to-tablet approach for understanding the physical stability of IR tablets. By bridging DVS-derived sorption dynamics with real storage ones, validating this time-scale translation across both simple and complex formulations, and identifying early versus prolonged moisture exposure-driven changes, the thesis provides a practical foundation for rational excipient selection, predictive modelling and accelerated formulation development.

Contents

Abstract	ii
List of Figures	x
List of Tables	xvii
Abbreviations	xix
Nomenclature	xx
Acknowledgement	xxii
Research outputs	xxiii
1. Introduction	1
1.1 Pharmaceutical development	2
1.2 Oral solid dosage forms (OSDFs)	3
1.3 Performance of immediate-release tablets (IR)	4
1.4 Factors affecting the performance of IR tablets	9
1.4.1 The effect of raw material properties	10
1.4.1.1 Particle size	11
1.4.1.2 Polymer crosslinking	12
1.4.1.3 Swelling volume	13
1.4.1.4 Liquid uptake	14
1.4.1.5 Solubility and intrinsic dissolution rate	15
1.4.1.6 Hygroscopicity	16
1.4.2 The effect of formulation factors	18
1.4.3 The effect of manufacturing route and processing parameters	21
1.4.4 The effect of storage conditions	23
1.5 Water in oral solid dosage forms	28
1.5.1 Mechanisms of water-solid interactions	28
1.5.1.1 Adsorption and absorption	29
1.5.1.2 Crystal hydrate formation	31

1.5.1.3	Deliquescence.....	31
1.5.1.4	Capillary condensation.....	32
1.5.2	Moisture sorption isotherms.....	32
1.5.3	Experimental aspects of water vapour sorption analysis.....	34
1.6	Stability of oral solid dosage forms.....	37
1.6.1	Stability testing and regulatory frameworks.....	38
1.6.1.1	Conventional ICH stability studies.....	40
1.6.1.2	Accelerated predictive stability studies.....	42
1.6.2	Prediction and modelling approaches.....	44
1.7	Summary of the knowledge gaps.....	47
2.	Aim and Objectives.....	52
3.	Materials and Methods.....	56
3.1	Materials.....	57
3.1.1	Excipients.....	57
3.1.2	Saturated salt solution.....	58
3.2	Methods.....	59
3.2.1	Raw material characterisation.....	59
3.2.1.1	Moisture sorption and desorption analysis.....	59
3.2.1.2	Moisture sorption and desorption rate constant model.....	62
3.2.1.3	True density.....	65
3.2.1.4	Particle size analysis.....	65
3.2.2	Tablet manufacturing.....	67
3.2.3	Tablet storage.....	68
3.2.4	Tablets Characterisation.....	70
3.2.4.1	Moisture sorption dynamics and capacity.....	70
3.2.4.2	Weight, dimensions, and tensile strength.....	71
3.2.5	Data analysis and visualisation.....	72

4. Particle-based investigation of excipients' stability: the effect of storage conditions on moisture content and swelling	73
4.1 Introduction	74
4.2 Materials and methods.....	78
4.2.1 Materials	78
4.2.2 Moisture sorption and desorption analysis	79
4.2.3 Sorption and desorption kinetic rate constants	79
4.2.4 Storage-induced particle size changes.....	79
4.2.4.1 Excipients dispersion and powder storage	79
4.2.4.2 Powder storage	80
4.2.4.3 Particle size analysis.....	81
4.3 Results and discussion.....	83
4.3.1 Effect of RH level on EMC and kinetic rate constant	83
4.3.2 Effect of temperature on EMC and the kinetic rate constant	89
4.3.3 Particle size analysis.....	94
4.3.3.1 Characterisation of particles before storage	94
4.3.3.2 Effect of storage on particle size/ shape characteristics of swelling excipients.....	95
4.4 Conclusion.....	106
4.5 Future implications.....	106
5. Linking powder to tablet stability: length- and time-scale prediction of moisture sorption.....	108
5.1 Introduction	109
5.2 Materials and methods.....	111
5.2.1 Materials	111
5.2.2 Raw materials characterisation.....	111
5.2.2.1 Moisture sorption analysis.....	111
5.2.2.2 Sorption kinetic rate constant model	111
5.2.2.3 True density	111

5.2.3	Tablet manufacturing.....	111
5.2.4	Sample Storage.....	112
5.2.5	Tablet characterisation.....	113
5.2.5.1	Moisture sorption dynamics and capacity	113
5.2.5.2	Weight, dimensions, and tensile strength	113
5.2.5.3	Porosity of tablets after storage	113
5.2.5.4	Terahertz time-domain spectroscopy (THz-TDS)	116
5.3	Results	117
5.3.1	Raw materials characterisation.....	117
5.3.2	Tablet characterisation.....	119
5.3.2.1	Moisture sorption.....	119
5.3.2.2	Dimensional changes.....	128
5.3.2.3	Porosity.....	130
5.3.2.4	Tensile strength and bonding capacity.....	131
5.3.2.5	Terahertz spectroscopy	134
5.4	Discussion.....	138
5.4.1	Bridging the gap between DVS and real-storage analysis	138
5.4.1.1	Length-scale assessment: establishing a link between powder and tablet sorption in DVS	139
5.4.1.2	Time-scale assessment: establishing a link between DVS data and real storage	140
5.5	Conclusion.....	144
5.6	Future implications.....	145
6.	From simplicity to complexity: how excipients shape stability and disintegration of IR tablets	147
6.1	Introduction	148
6.2	Materials and Methods	151
6.2.1	Materials.....	151
6.2.2	Raw materials characterisation.....	151

6.2.2.1	Moisture sorption analysis.....	151
6.2.2.2	Sorption kinetic rate constant model	151
6.2.2.3	True density	151
6.2.3	Tablet manufacturing.....	151
6.2.4	Tablet storage	152
6.2.5	Tablet characterisation.....	152
6.2.5.1	Moisture sorption and kinetic rate constants	152
6.2.5.2	Weight, dimensions, and tensile strength	153
6.2.5.3	Porosity.....	153
6.2.5.4	Disintegration time	153
6.2.5.5	Sessile drop method.....	154
6.3	Results	156
6.3.1	Effect of excipient on tablet characteristics before storage.....	156
6.3.1.1	Tensile strength.....	156
6.3.1.2	Disintegration time, liquid absorption, and swelling kinetics	158
6.3.2	Effect of excipient on tablet characteristics after storage.....	164
6.3.2.1	Moisture sorption.....	164
6.3.2.2	Tablet volume	168
6.3.2.3	Tensile strength.....	170
6.3.2.4	Disintegration time	174
6.3.2.5	Liquid uptake and swelling kinetics	177
6.4	Discussion.....	181
6.4.1	Bridging DVS and real storage in multi-component formulations to predict long-term moisture uptake	181
6.4.2	Linking moisture uptake with mechanical and functional changes.....	184
6.4.2.1	Early exposure-driven weakening of tensile strength: Kinetic coupling between moisture uptake and tensile strength loss.....	185
6.4.2.2	Prolonged exposure-driven change in disintegration	186

6.4.3	Linking disintegration to liquid absorption rate and mechanical changes	187
6.4.4	The effect of excipients on tablets' physical stability	189
6.5	Conclusion.....	191
6.6	Future implications	193
7.	General conclusion and future work.....	195
7.1	General conclusion	196
7.2	Limitations and outlook of the present work.....	199
7.3	Innovative contributions and methodological advances.....	200
7.4	Future work	202
	Appendices	205
	Appendix A.....	206
	Appendix B.....	222
	Appendix C.....	243
	Bibliography.....	256

List of Figures

Figure 1.1: An overview of mechanisms involved in the disintegration of tablets (Markl & Zeitler, 2017).	5
Figure 1.2: Factors affecting the disintegration and performance of IR tablets.	9
Figure 1.3: Schematic representation of liquid uptake of particles, wicking-driven liquid uptake (left) and swelling-driven liquid uptake (right).	14
Figure 1.4: A summary of the potential mechanisms of physical changes during the storage of IR tablets.	27
Figure 1.5: Schematic of the distribution of water molecules in materials.	29
Figure 1.6: Classification of moisture sorption isotherms.	33
Figure 1.7: Schematic of a DVS system (Surface Measurement Systems, 2025).	35
Figure 1.8: Characteristics of APS studies.	44
Figure 2.1: Schematic representation of the multi-scale experimental and modelling framework used in this thesis. The study progresses from particle-level excipient characterisation through increasing formulation complexity to final tablet performance. Moisture uptake and swelling data collected at the powder level are used to inform predictive models that link short-term behaviour to long-term storage outcomes.	53
Figure 3.1: Example of DVS profile demonstrating the change in mass for MCC particles with time. The DVS profile's sectional analysis reflects the various RH conditions used.	62
Figure 3.2: Tablet storage set-up during the stability study.	69
Figure 4.1: Powder dispersion and storage set-up for the particle size analysis.	81
Figure 4.2: Equilibrium moisture content of excipients at 25°C (A) and 50°C (B), presented relative to the mass at 30% RH.	84
Figure 4.3: Kinetic rate constants of the tested excipients for moisture sorption and desorption at both 25°C (A and B) and 50°C (C and D) as a function of % RH steps. (A) and (C) represent moisture sorption, while (B) and (D) represent moisture desorption.	87

Figure 4.4: Relative Change in EMC (%) from 25°C to 50°C at 75% RH.	90
Figure 4.5: Illustration of the effect of temperature on the EMC of insoluble particles (left) and soluble particles (right).	92
Figure 4.6: Relative Change in sorption (A) and desorption (B) kinetic rate constants from 25°C to 50°C when moving from 30-75% RH.....	93
Figure 4.7: Relative change in volume-based diameter D50 of the studied excipients after storage at (A) 50°C/30% RH, (B) 25°C/75% RH, and (C) 50°C/75% RH over time. Values represent the average relative change in D50 for three samples on each time point at 50°C/75% RH, and one sample at 25°C/75% RH and 50°C/30% RH (Corresponding SDs are provided in Table A.3 in Appendix A).	96
Figure 4.8: The change in volume-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 50°C/75% RH for 1, 3, and 14 days. The examples shown at each time point represent one of the samples analysed at this time point. The CED was smoothed over 50 points.....	98
Figure 4.9: Average relative change in volume-based size parameters after 14 days of storage at 50°C/75% RH (n = 3, mean ± SD).....	99
Figure 4.10: Relative change in particle shape parameters after 14 days of storage at 50°C/75% RH (n = 3, mean ± SD).....	103
Figure 4.11: The Irreversibility in particle size change of (A) CCS, (B) SSG and (C) MCC particles after 14 days of storage at 50°C/75% RH and 28 days out of storage. Particle images with their corresponding CED, as taken from particle size analysis right after removal from storage and 28 days later, out of storage. The data shown represent one sample from each excipient.	105
Figure 5.1: The flowchart illustrates the process of calculating the porosity of tablets, divided into two main phases: before storage (represented by symbols with 'b') and after storage (represented by symbols with 'a'). Measurements for particles and tablets are indicated by 'p' and 't', respectively. The flowchart begins with the calculations before storage on the left, proceeds to the calculations after storage on the right, and uses a dotted arrow to indicate the transition between these two phases.....	115
Figure 5.2: Moisture sorption properties of the powder. (A, B) represent the EMC(%) relative to the mass at the end of 30% RH, while (C, D) represent the sorption kinetic rate constant, at 25°C (A, C) and 50°C (B, D).	118
Figure 5.3: Moisture uptake of tablets at 25°C (A, B) and 50°C (C, D), presented as the EMC(%) relative to the mass at 30% RH. (A) and (C) represent MCC tablets, while (B) and (D) represent MCC-CCS (8%) tablets.	120

Figure 5.4: Sorption kinetic rate constant of the tested tablets at 25°C (A, B) and 50°C (C, D). (A) and (C) represent MCC tablets, while (B) and (D) represent MCC-CCS (8%) tablets.....	121
Figure 5.5: The relationship between tablet properties, RH level, and moisture behaviour. (A) The average EMC of tablets over incremental RH levels above 30% RH, (B) A correlation between average tablets' porosities and sorption kinetic rate constants, extrapolated to include powder data. Data points were fitted using linear regression analysis. Some error bars are not visible due to their small size.	123
Figure 5.6: Correlation between MCC and MCC-CCS (8%) powder and their corresponding tablets' EMC (%) relative to the mass at the end of 30% RH at 50°C. (0,0) represents the 30% RH baseline EMC. Averaged values of tablets' EMC at each RH level are shown.	125
Figure 5.7: Sorption kinetic rate constants of the tested tablets at 50°C/75% RH. The sorption kinetic rate constants were calculated using the kinetic rate constant model (Eq. 3.1). Additional details on the model's predictive performance are provided in Table B.3 in Appendix B. Only data shown where the fitting resulted in an $R^2 > 0.85$. The 10% MCC formulation was excluded from this figure as the fit resulted in an R^2 of 0.72..	127
Figure 5.8: The average relative change in tablets' volume (%) after storage at 50°C/75% RH over time relative to the tablets' volume before storage (each point represents an average of 3 different tablets).	128
Figure 5.9: Tablets' porosity before and after storage at 50°C/75% RH for 42 days (n = 3, mean $\pm$ SD).	130
Figure 5.10: Tensile strength analysis of tablets: (A) Average tensile strength of tablets before and after storage at 50°C/75% RH (0-time point represents initial values); (B) Average relative change in tensile strength after storage relative to initial values for MCC and MCC-CCS tablets. (Each point represents an average of 3 different tablets).	132
Figure 5.11: The relationship between (A) MCC and (B) MCC-CCS (8%) tablets tensile strength and porosity, before and after storage at 50°C/75% RH for 42 days. The line represents a fit to the Ryshkewitch-Duckworth model (Eq. 3.7) (n = 3, mean $\pm$ SD).	134
Figure 5.12: The relative change in (A) refractive index and (B) loss coefficient of tablets after storage at 50°C/75% RH across different time points. (Each point represents an average of 3 different tablets).	137
Figure 5.13: A framework for predicting moisture sorption in tablets under real storage scenarios. The upper section illustrates the length-scale and time-scale correlations between powder and tablet DVS data and the real-storage data, establishing the scaling factors. The lower section demonstrates how these correlations can be applied to estimate tablet moisture sorption in real storage scenarios.	142

Figure 5.14: Mass increase for (A and C) MCC and (B and D) MCC-CCS (8%) tablets at different porosities. Model predictions (lines) based on a single DVS powder measurement (A and B), and based on tablets' DVS measurements (C and D), compared to jars-storage experimental data (points).	143
Figure 6.1: The relationship between tablet tensile strength and porosity. The line represents a fit to the Ryshkewitch-Duckworth model (Eq. 3.7) ($n = 3$, mean $\pm$ SD). 158	
Figure 6.2: Effect of porosity and formulation composition on tablet disintegration and liquid uptake/swelling behaviour. (A) Disintegration time; (B) liquid absorption rate constant (k); (C) linearity of liquid absorption (m); (D) swelling onset time ($St, 0$); (E) maximum swelling area (S_{∞}); and (F) initial swelling rate ($1/A$), as functions of tablet porosity. The disintegration time of pure MCC tablets was not measured.	160
Figure 6.3: DVS analysis of tablets and powders at 50°C and 30-75% RH. (A) Equilibrium moisture content as a function of porosity. (B) The relationship between tablet porosity and the sorption rate constant, extended to 100% porosity to represent the powder state, and calculated using the kinetic rate constant model. Additional details on the model's predictive performance are provided in Table C.4 in Appendix C.....	165
Figure 6.4: The average relative change in tablet weight (%) after storage at 50°C/75% RH over time relative to the tablets' mass before storage (each point represents an average of 3 different tablets).	167
Figure 6.5: Sorption kinetic rate constants of jar-stored tablets stored at 50°C/75% RH, calculated using the kinetic rate constant model. Details of the model performance are provided in Table C.5 in Appendix C. Data are reported only where the fit achieved $R^2 > 0.85$	168
Figure 6.6: The average relative change in tablets' volume (%) after storage at 50°C/75% RH over time relative to the tablets' volume before storage (each point represents an average of 3 different tablets).....	169
Figure 6.7: Effect of storage time on tensile strength of tablets. Top panel: Tensile strength values over 42 days of storage at 50°C/75% RH ($n = 3$, mean $\pm$ SD). Bottom panel: The percentage change in tensile strength relative to before storage values for the same formulations across porosity levels.	171
Figure 6.8: Kinetic rate constants for tensile strength loss in tablets stored at 50°C/75% RH, estimated using the model applied to tensile strength data (Eq. 6.1). Model fit statistics are summarised in Table C.6 in Appendix C.....	174
Figure 6.9: The disintegration time of tablets of different formulations after storage at 50°C/75% RH over time ($n = 3$, mean $\pm$ SD).....	175

Figure 6.10: Characteristic parameters of the liquid absorption and swelling profiles extracted from the sessile drop profiles using (Eq. 6.3 and Eq. 6.5) after storage at 50°C/75% RH over time (n = 3, mean ± SD).....	178
Figure 6.11: Predicted (lines) and experimental (points) moisture uptake of tablets at 50°C/75% RH using tablet-based DVS-derived scaling.	184
Figure 6.12: Kinetic coupling of moisture uptake and tensile strength loss after storage at 50°C/75% RH.	185
Figure 6.13: Change in mass and disintegration time during storage at 50°C/75% RH. Disintegration times: Grey lines, change in mass: black lines (n = 3, mean ± SD).	187
Figure 6.14: Disintegration times and liquid uptake rate of tablets after storage at 50°C/75% RH over time; disintegration times: Grey lines, liquid absorption rate: black lines (n = 3, mean ± SD).....	188
Figure 6.15: Disintegration times and tensile strength of tablets after storage at 50°C/75% RH over time; disintegration times: Grey lines, tensile strength: black lines (n = 3, mean ±SD).	189
Figure 6.16: Summary of humidity-induced changes in IR tablet formulations, presented as a timeline of structural/interfacial changes and performance outcomes. (*Bauhuber et al., 2021; Marshall et al., 1991; ◇ Rapp et al., 1995; ▫Calahan, 2020; Yamamoto et al., 2017).....	190
Figure A.1: Equilibrium moisture content of excipients at (A) 25°C and (B) 50°C, presented relative to the dry reference mass at 0% RH. (0-30% RH represents an average of 4 measurements).....	208
Figure A.2: Moisture sorption and desorption- time profile of (A) MCC and (B) CCS at 25°C.....	209
Figure A.3: Moisture sorption and desorption of MCC and CCS at 25°C over time as predicted by the model vs. experimental measurements.	210
Figure A.4: Absolute change in kinetic rate constant from 25°C to 50°C of the tested excipients in (A) moisture sorption and (B) desorption as a function of % RH steps.	213
Figure A.5: Field of view images of swelling excipients studied using 10X lens.	214
Figure A.6: The average relative change in volume-based diameter D50 of the studied excipients after storage at 50°C/75% RH, showing all time points: 1, 3, and 14 days (n = 3).....	215

Figure A.7: The change in number-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 25°C/75% RH for 1 and 14 days. (The example shown at each time point represents one of the samples analysed for this time point, CED smoothed over 50 points).	217
Figure A.8: The change in number-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 50°C/30% RH for 1 and 14 days. (The example shown at each time point represents one of the samples analysed for this time point, CED smoothed over 50 points).	218
Figure A.9: The change in number-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 50°C/75% RH for 1,3 and 14 days. (The example shown at each time point represents one of the samples analysed for this time point, CED smoothed over 50 points).	219
Figure A.10: Measures to evaluate the Reliability of Morphologi4 in particle size Analysis. (A) Demonstrating the repeatability of measurements for the same sample. (B) Utilising PVC powder as a control material after storage at 50°C/75% RH for 3 days. (C) Investigating the threshold effect on CCS particle size analysis to assess the robustness of the study under storage conditions.	220
Figure A.11: The time needed to establish the required 75% RH inside jars (data shown were extracted from a data logger inside one of the jars intended for 1-day storage)..	221
Figure B.1: EMC (%) of the two formulations at (A)25°C and (B) 50°C relative to the dry mass of the powder at the end of 0% RH.	226
Figure B.2: Moisture uptake of tablets at 25°C (A and B) and 50°C (C and D), presented as EMC (%) relative to the dry mass of tablets at the end of 0% RH. (A) and (C) represent MCC tablets, while (B) and (D) represent MCC-CCS (8%) tablets.	227
Figure B.3: Equilibration of tablet's weight after removal from storage at 50°C/75% RH compared to the weight of tablets before storage. A and B represent MCC and MCC-CCS (8%) tablets of different porosities, respectively (n = 3).	230
Figure B.4: Average relative change in tablet weight at the time of analysis, relative to the weight of tablets before storage (n = 3).	231
Figure B.5: Moisture sorption profile of MCC tablets at 10% porosity (30–75% RH, 50°C). (A) Experimental dataset showing a single anomalous day-3 average (normalised to the initial masses of all tablets before storage, M_0 , intended to be stored across all time points), resulting in reduced model fit ($R^2 = 0.72$). (B) Improved regression ($R^2 = 0.991$) obtained when the day-3 point is excluded, confirming that the poor initial fit was due to an averaging artefact rather than inconsistent behaviour.	233

Figure B.6: Equilibration of tablet's volume after removal from storage at 50°C/75% RH compared to the volume of tablets before storage. A and B represent MCC and MCC-CCS (8%) tablets of different porosities, respectively (n = 3).	234
Figure B.7: The average relative change in tablets' bulk density (%), relative to the bulk density of tablets before storage (n = 3).	235
Figure B.8: The absolute change in inter-particle porosity of the tested tablets after storage at 50°C/75% RH for 42 days (n = 3).	236
Figure B.9: The true density of formulations before and after storage at 50°C/75% RH. (The numbers in squares represent the average relative change in the true density after storage).	237
Figure B.10: Linear correlation between the refractive index and tablet porosity (A) before storage and (B) after storage. The point (100,1) represents the powder of the same composition as the tablets. Additionally, (C) shows the linear correlation between the refractive index and bulk density of tablets before storage, while (D) compares the bulk density derived from the refractive index to the bulk density calculated using the tablets' dimensions.	238
Figure B.11: The average relative change in tablet weight after removal from storage compared to DVS measurements (n = 3).	239
Figure B.12: Moisture loss observed during the transfer of tablets from the DVS for weight measurement. (The above diagram is for illustration purposes only).	240
Figure B.13: Sorption kinetic rate constants of the tested tablets at 50°C/75% RH, including powder data estimated using the scaling factor from DVS data.	241
Figure C.1: Sessile drop images of the (A) MCC, (B) MCC-CCS (3%), (C) MCC-CCS-MgSt, and (D) MCC-CCS-MgSt-Lac, 17% porosity tablets as a function of time.	251
Figure C.2: Predicted (lines) and experimental (points) moisture uptake of tablets at 50°C/75% RH using powder-based DVS-derived scaling.	254

List of Tables

Table 1.1: Hygroscopicity classification schemes.....	17
Table 1.2: Summary of the impact of moisture exposure on the tablet performance characteristics.	25
Table 1.3: ICH stability guidelines, codes, and titles.	39
Table 1.4: Storage conditions recommended by the ICH Q1A guideline for stability testing of a drug product intended for storage at room temperature.	42
Table 3.1: Materials used, their suppliers and abbreviations used in this study.	57
Table 3.2: The various % RH levels investigated in the DVS study.....	60
Table 3.3: Method used for image analysis.....	66
Table 4.1: Accelerated stability storage conditions of raw materials.....	80
Table 4.2: Size and shape characteristics of excipient particles before storage.	95
Table 5.1: Tablet formulations, thickness, compaction pressure, and porosity of the manufactured tablets.....	112
Table 5.2: Calculated scaling factors for (A) moisture uptake and (B) sorption kinetic rate constants, bridging the gap between DVS observations and real storage at 50°C/75% RH.	141
Table 6.1: Compositions and abbreviations of the studied formulations.	152
Table 6.2: Scaling factors for EMC and sorption rate constant at 50°C/75% RH, showing the correction required to translate DVS data to real storage across formulations and porosities.....	182
Table A.1: The recorded datalogger storage conditions (mean $\pm$ SD) (The 25°C/30% RH represents the Laboratory equilibration condition).	207
Table A.2: The Prediction performance of the moisture sorption kinetic rate constant model at 25°C.....	211
Table A.3: Relative change in volume-based diameter (D50)of the studied excipients after storage at 50°C/30% RH (n = 3).	216

Table B.1: The average values of mass, volume, tensile strength, terahertz measured refractive index and loss coefficient with standard deviation(SD) of MCC and MCC-CCS tablets before and after storage (n = 3).....	223
Table B.2: The Prediction performance of the moisture sorption kinetic rate constant model at 25°C and 50°C.....	228
Table B.3: The Prediction performance of the moisture sorption kinetic rate constant model for tablets stored at 50°C/75% RH.	232
Table B.4: The Prediction performance of the moisture sorption kinetic rate constant model to predict the tablet mass at each time point after storage at 50°C/75% RH.....	242
Table C.1: The true density (ρ_{true}) of the excipients used in the study.....	244
Table C.2: The average values of mass and volume of tablets* before and after storage at 50°C/75% RH (n = 3).....	245
Table C.3: EMC of powder blends determined by DVS at 50°C and 30-75% RH.....	247
Table C.4: Prediction performance of the moisture sorption kinetic rate constant model for tablets and powder blends analysed by DVS at 50°C and 30-75% RH. The 100% porosity corresponds to powder blend measurements.....	248
Table C.5: Prediction performance of the moisture sorption kinetic rate constant model for tablets stored at 50°C/75% RH using the jars method.....	249
Table C.6: Prediction performance of tensile strength kinetic rate constant model for tablets stored at 50°C/75% RH using the jars method.	250
Table C.7: Prediction performance of the moisture sorption kinetic rate constant model using a single rsor-scaling factor derived from MCC across all formulations to predict the tablet mass at each time point after storage at 50°C/75% RH.....	252
Table C.8: Prediction performance of the moisture sorption kinetic rate constant model to predict the tablet mass at each time point after storage at 50°C/75% RH.....	253
Table C.9: Prediction performance of the tensile strength kinetic rate constant model to predict the tensile strength at each time point after storage at 50°C/75% RH.	255

Abbreviations

AF	Acceleration factor
API	Active pharmaceutical ingredient
APS	Accelerated Predictive Stability
ASAP	Accelerated stability assessment program
BCS	Biopharmaceutics classification system
BET	Brunauer-Emmett-Teller model
CCS	Croscarmellose sodium
CED	Circle Equivalent Diameter
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
DCP	Dibasic calcium phosphate
DCPA	Dibasic calcium phosphate anhydrous
DVS	Dynamic vapour sorption
EMA	European Medicines Agency
EMC	Equilibrium moisture content
FDA	Food and Drug Administration
FCC	Functionalised calcium carbonate
GAB	Guggenheim-Anderson-de Boer model
ICH	International Council for Harmonisation
IND	Investigational New Drug
IR	Immediate-release
Lac	Lactose
LHPC	Low-substituted hydroxypropylcellulose
Man	Mannitol
MCC	Microcrystalline cellulose
MgSt	Magnesium stearate
NDAs	New Drug Applications
PVC	Polyvinyl chloride
R&D	Research & Development
R²	Coefficient of determination
RH	Relative humidity
RMSE	Root mean square error
SD	Standard deviation
SSG	Sodium starch glycolate
TCP	Tribasic calcium phosphate
TIM	TNO gastrointestinal model
THz-TDS	Terahertz time-domain spectroscopy
USP	United States Pharmacopoeia
WHO	World Health Organisation

Nomenclature

A	Reciprocal of initial swelling rate (Schott model)
A_p	Area of the particle
AR	Aspect ratio
B	Width of the particle
b	Bonding capacity factor
C_{HS}	High sensitivity circularity
c	The speed of light in a vacuum
D	Diameter
D_{10}	Particle diameter at which 10% of the particle's volume (or mass) is smaller
D_{50}	Particle diameter at which 50% of the particle's volume (or mass) is smaller
D_{90}	Particle diameter at which 90% of the particle's volume (or mass) is smaller
F	breaking force
f	Tablet porosity
H	Tablet thickness
k	Liquid absorption rate constant
L	Length of the particle
m	Linearity of liquid absorption
M_0	The mass at $t = 0$
$M_{\max}$	The maximum mass during sorption
$M_{\min}$	The minimum mass during desorption
$M(t)$	The mass at time t
n_{eff}	Effective refractive index
N_p	Number of particles
P	Actual perimeter of the particle
$Q_{\max}$	Maximum absorption ratio
r_{des}	The desorption kinetic rate constant
r_{sor}	The sorption kinetic rate constant
$r_{\text{sor-DVS}}$	Sorption kinetic rate constant obtained using DVS
$r_{\text{sor-real}}$	Sorption kinetic rate constant obtained under real storage (Jars method)
r_{TS}	The tensile strength kinetic rate constant
S_0	Initial liquid droplet size
S_t	Liquid droplet surface area
$s(t)$	Swelling at time t
S_{∞}	Swelling at infinite time (Schott model)
t	Time
t_r	Delay time
TS_0	Initial tensile strength (before storage)
$TS(t)$	Tensile strength at time t
TS_{∞}	Tensile strength at infinite time (plateau after storage)

$S_{t,0}$	Swelling onset time
$V_{p,a\ total}$	Total volume of particles after storage
V	Volume
V_{pores}	Total volume of pores
W	Weight
X_b	Property measured before storage
X_a	Property measured after storage
X_t	Tablet-level property
X_p	Particle-level property
ρ_{bulk}	Tablet bulk density
ρ_{true}	True density
σ_t	Tablet tensile strength at a given porosity
σ_0	Extrapolated tensile strength at zero porosity
Δm	Change in mass
dm/dt	Mass change per unit time (DVS equilibrium criterion)
ε	Deformation factor

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Research outputs

Publications

1. **Ibrahim, I.**, Carroll, M., Almudahka, A., Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., Markl, D., 2025a. Particle-based investigation of excipients stability: the effect of storage conditions on moisture content and swelling. RSC Pharm. <https://doi.org/10.1039/D4PM00259H>
2. **Ibrahim, I.**, Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., Markl, D., 2025. Linking powder to tablet stability: Length- and time-scale prediction of moisture sorption. International Journal of Pharmaceutics 126154. <https://doi.org/10.1016/j.ijpharm.2025.126154>
3. **Ibrahim, I.**, Mann, J., Winge, F., Davis, A., Hens, B., Khadra, I., Markl, D., 2025. From simplicity to complexity: how excipients shape stability and disintegration of immediate-release tablets. (Under internal review)

Oral and poster presentations

1. Carroll, M., **Ibrahim, I.**, Maclean, N., Mann, J., Abbott, A., Davis, A., Khadra, I., & Markl, D. Predicting Long-term Stability of Oral Solid Dosage Forms. EPSRC CMAC Open Days, 2022, Glasgow. **Poster presentation.**
2. **Ibrahim, I.**, Carroll, M., Mann, J., Abbott, A., Davis, A., Khadra, I., & Markl, D. Understanding Long-term Physical Stability of Oral Solid Dosage Forms. EPSRC CMAC Summer School, 2022, Glasgow. **Poster presentation.**

3. **Ibrahim, I.**, Carroll, M., Mann, J., Abbott, A., Davis, A., Khadra, I., & Markl, D. Predicting long-term stability of oral solid dosage forms. Strathclyde research visit to AstraZeneca, 2022, Macclesfield. **Oral presentation.**
4. **Ibrahim, I.**, Carroll, M., Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. Particle-based Investigation: The Influence of Storage Conditions on Tablets' Physical Stability. Eu-Pat 11th pan-European Meeting conference, 2023, Glasgow. **Poster presentation.**
5. **Ibrahim, I.**, Carroll, M., Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. Particle-based Investigation: The Influence of Storage Conditions on Tablets' Physical Stability. EPSRC CMAC Summer School, 2023, Glasgow. **Poster presentation (2nd Place Prize).**
6. **Ibrahim, I.**, Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. Exploring Storage-Induced Physical Instability: Correlating Powder with Tablet Behaviour. EPSRC CMAC Open Days, 2023, Glasgow. **Poster presentation (1st Place Prize).**
7. **Ibrahim, I.**, Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. Understanding long-term physical stability of oral solid dosage forms to enable prediction of time-dependent physicochemical changes. Community for Analytical Measurement Science conference (CAMS) 4th Annual Conference and Networking Event, 2024, London. **Oral presentation.**

8. **Ibrahim, I.**, Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. Exploring Storage-Induced Physical Instability: Correlating Powder with Tablet Behaviour. EPSRC CMAC Summer School, 2024, Glasgow. **Poster presentation (2nd Place Prize).**
9. **Ibrahim, I.**, Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. From Powder to Tablet: Predicting Moisture Sorption and Understanding Physical Stability Changes. EPSRC CMAC Open Days, 2025, Glasgow. **Poster presentation.**

1.Introduction

Chapter summary

This chapter introduces the concept of physical stability in immediate-release tablets and establishes the scientific context for the research presented in this thesis. It reviews the literature on the factors governing the performance and stability of immediate-release tablets, discussing the mechanisms of disintegration and dissolution and how these are influenced by raw material properties, formulation composition, manufacturing parameters, and storage environment. Particular emphasis is placed on moisture-solid interactions and their role in driving physical changes that affect tablet performance. The chapter concludes with an overview of stability testing frameworks and predictive approaches, highlighting current understanding and the knowledge gaps that form the basis for this research.

1.1 Pharmaceutical development

The development of a new pharmaceutical product is a highly resource-intensive and time-consuming process, involving multiple stages from initial discovery through preclinical testing, clinical trials, and ultimately regulatory approval. Recent analyses highlight the substantial investment required to bring a new drug to market. Wouters et al. (2020) estimated the median cost at \$985 million and the average at \$1.3 billion based on a sample of drugs approved between 2009 and 2018. A more recent study by Sertkaya et al. (2024) analysing data from 151 New Drug Applications (NDAs) approved between 2014 and 2018, reported a median capitalised cost of \$1.1 billion and an out-of-pocket cost of approximately \$442 million. These findings reflect both the complexity of the process and the financial challenges encountered along the development pipeline (Sertkaya et al., 2024; Wouters et al., 2020). Out of thousands of candidate compounds screened for potential therapeutic benefit, only a select few reach clinical evaluation, and fewer still achieve approval, making the process not only lengthy but also commercially high-risk (Ende, 2010). To reduce these risks and improve the efficiency of development, considerable emphasis has been placed on early-stage pre-formulation studies. These investigations aim to characterise the physicochemical properties of drug candidates and excipients, enabling the prediction of stability, manufacturability, and eventual performance in the dosage form. By identifying issues early, such approaches support better candidate selection and formulation optimisation, ultimately reducing the likelihood of failure in later development stages (Kalaria et al., 2020).

Among the critical assessments carried out at this stage is the evaluation of the dissolution behaviour of the active pharmaceutical ingredient (API). Dissolution rate and extent are major determinants of oral bioavailability and are routinely used to inform decisions on solid form development. Even minor changes in dissolution behaviour can influence clinical outcomes, delay approval, or result in reformulation or withdrawal from the market (Gray et al., 2009; Huang, 2004). In the later stages of drug development, dissolution testing also plays a key role in evaluating formulation quality, ensuring batch-to-batch consistency, verifying the stability and efficiency of the manufacturing process and establishing regulatory specifications (Amidon et al., 1995; Gray et al., 2009; Lehto et al., 2009).

1.2 Oral solid dosage forms (OSDFs)

Oral drug administration is the most common and preferred route of drug delivery. Common oral dosage forms include tablets, capsules, pills, and powders. Among these, tablets account for the vast majority of orally administered formulations used worldwide. Tablets are compacted solid dosage forms composed of a blend of API and excipients, and are typically designed to deliver drugs systemically via the gastrointestinal tract (Darji et al., 2018). Their widespread use can be attributed to several factors, including ease of large-scale manufacturing, dose accuracy, convenient handling, low production cost, and relatively high chemical, physical, and microbiological stability over time when compared to liquid and semi-solid formulations (Jivraj et al., 2000; Juban et al., 2017). Despite these advantages, tablets also present some challenges, such as time- and labour-intensive manufacturing processes and the poor aqueous solubility of many new drug

candidates emerging from discovery pipelines, which can hinder dissolution and limit bioavailability when formulated as solid dosage forms. In addition, some drug compounds are unstable in the aqueous environment of the gastrointestinal tract, undergoing hydrolysis or degradation after dissolution, which further complicates formulation design and affects therapeutic performance (Savjani et al., 2012).

Tablets can be formulated to release the drug either immediately after ingestion (immediate-release tablets) or in a controlled manner (delayed-, sustained-, or extended-release systems). While research into controlled-release and targeted delivery systems continues to grow, the majority of commercial tablets are still intended to disintegrate rapidly in the gastrointestinal tract and release their APIs promptly (Awad et al., 2021). This is particularly important for drugs with low solubility or those requiring a fast onset of action, such as analgesics. To facilitate this process, disintegrants are commonly included in tablet formulations to promote the rapid breakup of the compact into smaller fragments, thereby accelerating the dissolution (Markl and Zeitler, 2017).

1.3 Performance of immediate-release tablets (IR)

The performance of a tablet is typically assessed by the extent and rate of drug dissolution, as these parameters indicate both bioavailability and therapeutic effectiveness. For IR tablets, rapid dissolution must be preceded by fast disintegration, during which the compacted tablet breaks apart into smaller fragments. This increases the surface area available for drug release, accelerating the dissolution rate (Kalný et al., 2021). Disintegration requires the breakdown of inter-particulate bonds formed during compaction, which define the tablet's internal microstructure. These cohesive forces must

be overcome by repulsive stresses generated internally upon contact with liquid (Quodbach and Kleinebudde, 2016). In the absence of proper disintegration, only the surface-exposed API would dissolve, resulting in a slower and limited release profile. Markl and Zeitler (2017) outlined the main stages of the disintegration process, beginning with capillary liquid uptake (wicking), followed by swelling, either omnidirectional or unidirectional, and ending in the rupture of particle-particle bonds (Figure 1.1).

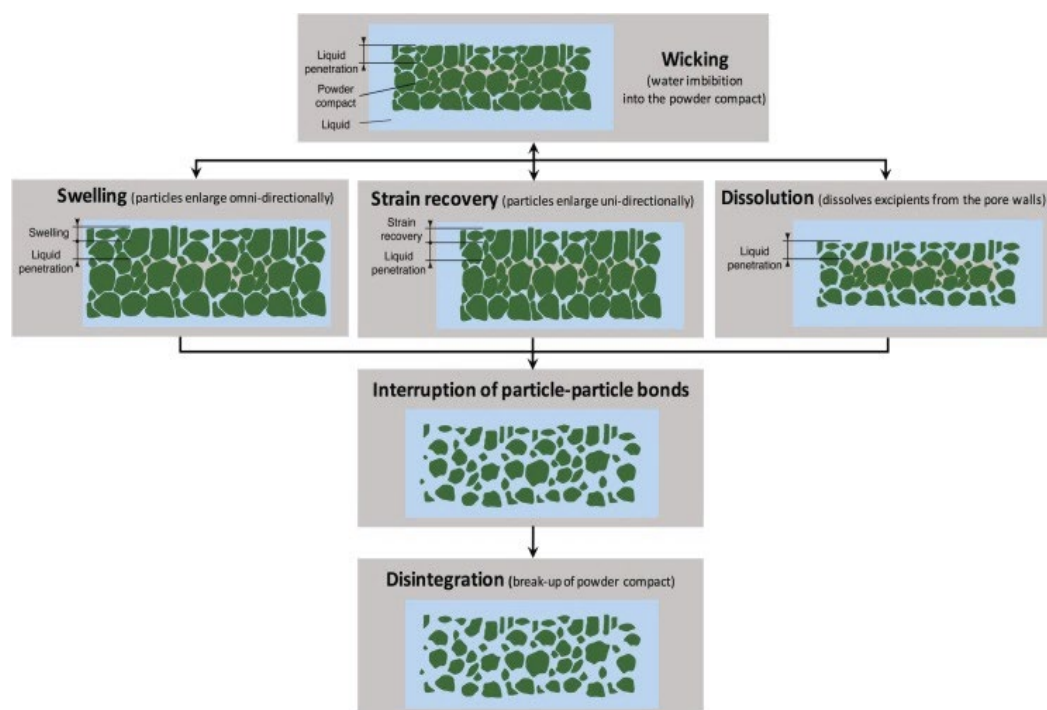


Figure 1.1: An overview of mechanisms involved in the disintegration of tablets (Markl & Zeitler, 2017).

The process is initiated by liquid penetration into the tablet's porous structure via capillary action. While this does not itself produce the mechanical stress required for disintegration, it is a necessary precondition for activation (Desai et al., 2016).

Among the mechanisms involved, particle swelling is generally regarded as the primary contributor to tablet disintegration (Markl and Zeitler, 2017). Upon water uptake, certain

excipients known as disintegrants expand in volume, generating internal stress within the compact. When this stress exceeds the cohesion between particles, the tablet breaks apart. The swelling may occur in all directions (omnidirectional) or be confined to a single axis (unidirectional), depending on the mechanical properties of the material and its behaviour under compaction (Quodbach and Kleinebudde, 2016). Swelling is the term used to describe the omnidirectional particle expansion due to moisture sorption. However, some materials will only expand in one direction due to their reversible elastic deformation during compaction. For these materials, the expansion primarily occurs against the direction of the compression force due to the elastic recovery of the material's original shape (Berardi et al., 2022; Desai et al., 2016). Importantly, the efficiency of shape-recovery mechanisms is strongly influenced by compaction pressure. At higher compression pressures, more energy is stored, enhancing the "spring-like" rebound effect upon wetting. Conversely, tablets compressed at low pressures may fail to disintegrate if insufficient energy is stored for shape recovery (Amayreh et al., 2019; Quodbach and Kleinebudde, 2015).

In addition to disintegrants, other formulation components, such as hydrophilic fillers or binders like lactose, can also promote disintegration. These materials may dissolve upon wetting, disrupting the matrix and further aiding the breakdown of the tablet (Berardi et al., 2021). Native starch and microcrystalline cellulose (MCC) have traditionally been considered to possess disintegrant properties. However, more recently developed disintegrants, referred to as superdisintegrants, are designed to be effective at lower concentrations. These include sodium starch glycolate (SSG), croscarmellose sodium

(CCS), and crospovidone (XPVP), which are chemically modified forms of starch, cellulose, and povidone, respectively (Desai et al., 2016; Markl and Zeitler, 2017; Quodbach and Kleinebudde, 2016; Zarmpi et al., 2017). They are typically used in formulations at levels of 2-8% w/w for SSG, 0.5-5% w/w for CCS, and 2-5% w/w for XPVP (Zarmpi et al., 2017). Their high efficiency at low concentrations arises from their crosslinked structure, which enables rapid water uptake and extensive swelling without dissolving. However, at concentrations above the optimal range, the superdisintegrant particles can absorb excessive fluid and form a local gel-like barrier that impedes further water ingress, leading to slower disintegration (Zarmpi et al., 2017), while simultaneously weakening the tablet structure (Desai et al., 2014). In this thesis, unless otherwise specified, disintegrant refers to both conventional and superdisintegrant materials.

Following a successful disintegration, and for a dosage form to be effective, the API must first be released from the solid structure and dissolved in solution before it is absorbed into the circulatory system for further travelling to its active sites. *In vitro* dissolution testing is commonly employed to evaluate the extent and rate of API release from the dosage form. However, conventional compendial tests often use simple media that may not fully replicate physiological conditions. Therefore, biorelevant dissolution methods and advanced dynamic models such as the TNO gastrointestinal model (TIM) have been developed to better simulate the complex environment of the gastrointestinal tract, providing more predictive insight into *in vivo* drug release and absorption behaviour (Havenaar and Bellmann, 2022; Minekus et al., 1995).

Although disintegration and dissolution are closely linked in IR formulations, they represent fundamentally distinct processes and should not be assumed to be interchangeable performance indicators. Disintegration is a prerequisite for effective drug release, as it governs the generation of surface area and access of the dissolution medium to drug particles. Dissolution, by contrast, is a molecular process controlled by physicochemical properties of the API, including solubility, wettability, particle size, and diffusion within the boundary layer (Gupta et al., 2009; Markl and Zeitler, 2017). Consequently, rapid disintegration does not necessarily guarantee rapid or complete dissolution.

In certain formulations, disintegration can act as a practical surrogate for dissolution testing. This assumption is most likely to hold for highly soluble drugs, particularly those classified as Biopharmaceutics Classification System (BCS) class I or III, where dissolution is fast once sufficient surface area is generated. Under these conditions, tablet breakup becomes the rate-limiting step, and improvements in disintegration performance are commonly reflected in faster dissolution profiles. Regulatory guidance therefore permits the use of disintegration testing as a surrogate for dissolution in selected cases, provided strict formulation and solubility criteria are met (Gupta et al., 2009; Uebbing et al., 2017).

However, there are important limitations and exceptions to this assumption. For poorly soluble drugs, dissolution may remain limited by intrinsic solubility or diffusion even after complete disintegration has occurred (Gowthamarajan, 2010). Similarly, formulation factors such as the presence of hydrophobic lubricants or gel-forming

excipients can impede wetting and liquid penetration, resulting in delayed dissolution despite rapid tablet breakup (Markl and Zeitler, 2017). Conversely, incomplete or slow disintegration does not always imply poor dissolution performance. In formulations containing soluble matrices or erosion-dominated systems, drug release may proceed through gradual matrix dissolution rather than discrete tablet breakup (Siepmann and Siepmann, 2013). In such cases, dissolution and disintegration occur concurrently or through overlapping mechanisms, and classical disintegration time may no longer be a reliable predictor of drug release rate.

1.4 Factors affecting the performance of IR tablets

The mechanisms underlying tablet disintegration are influenced by multiple factors, including the physicochemical properties of the raw materials, the formulation composition, the manufacturing method and storage conditions (Maclean et al., 2021; Markl and Zeitler, 2017). Figure 1.2 provides an overview of the key variables that affect the wicking, swelling, and breakup processes involved in the disintegration process.

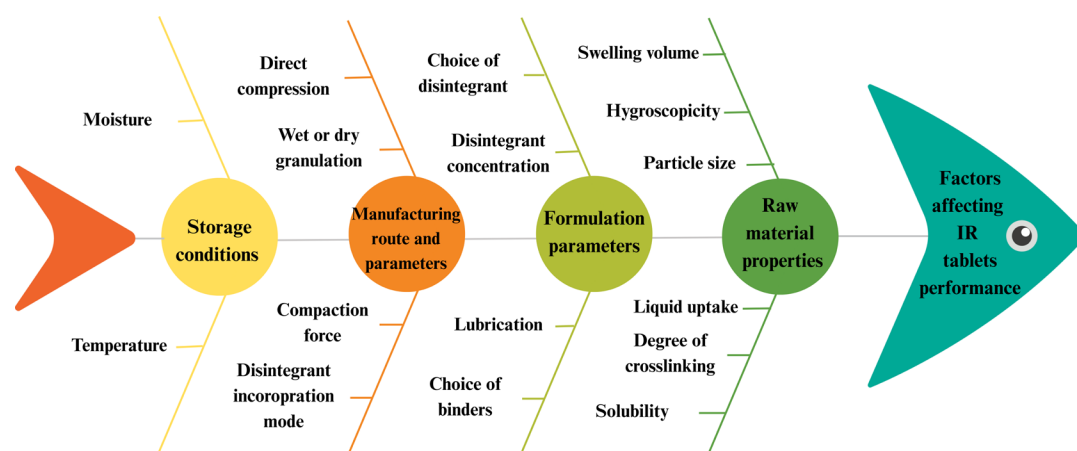


Figure 1.2: Factors affecting the disintegration and performance of IR tablets.

While the schematic highlights the main groups of variables, it is worth noting that additional factors, such as the viscosity, pH, and surface tension of the dissolution medium, as well as tablet-related characteristics including pore structure and surface wettability, can also influence the rate and extent of disintegration and subsequent dissolution.

To design a robust and reliable formulation, it is essential to understand how these factors interact and influence tablet performance, particularly in terms of disintegration and dissolution behaviour.

1.4.1 The effect of raw material properties

The intrinsic physicochemical properties of excipients play a fundamental role in determining the disintegration and dissolution performance of OSDFs. In the case of disintegrants, official pharmacopeial monographs specify particular tests to ensure compliance with established quality and functionality criteria. Quality-related tests focus on verifying the identity, purity, and physicochemical consistency of the material, typically including identification, loss on drying or water content, pH of dispersion, degree of substitution, residue on ignition, and microbial limits. In contrast, functional-related characteristics include swelling capacity, water uptake, viscosity, and particle size distribution (Berardi et al., 2022; Kristensen, 2007). However, beyond these standard evaluations, a wide range of material characteristics have been investigated for their impact on tablet performance (Berardi et al., 2022). These characteristics may be directly related to the properties of the particles themselves or may involve their interaction with the surrounding liquid medium. Both aspects can influence the effectiveness of

disintegration by affecting how the compact structure responds to fluid ingress and the generation of internal stress.

1.4.1.1 Particle size

Although particle size is an essential parameter for all formulation components, it plays a critical role for disintegrants. The functionality of disintegrants can be negatively influenced by particle size in two primary ways. Firstly, at a specific concentration within a formulation, larger disintegrant particles are fewer in number compared to smaller ones, resulting in a less homogeneous distribution. This sparse distribution reduces the likelihood of forming a continuous network of disintegrant particles, which is necessary for efficient water transport, especially at low concentrations. This, in turn, hinders liquid penetration through the tablet matrix and delays disintegration (Bauhuber et al., 2021). Secondly, larger particles have a lower surface area-to-volume ratio, which slows down their rate of liquid absorption compared to smaller particles (Shah and Augsburger, 2002). Conversely, particle size may also exert a positive influence. Larger particles have been reported to exhibit a higher rate and degree of swelling, producing larger cracks in the tablet structure than those formed by smaller particles, thereby facilitating disintegration (Mishra and Sauer, 2022; Shah and Augsburger, 2002; Zhao and Augsburger, 2006a).

Indirectly, the particle size of CCS and SSG may influence dissolution behaviour by affecting the viscosity of the surrounding medium. Smaller particles have been associated with the formation of more viscous gel layers upon hydration, which can hinder drug diffusion and thereby delay dissolution (Zarmpi et al., 2017). In the case of XPVP, particle size correlates with intra-particle porosity. Larger particles generally exhibit

higher porosity, resulting in improved liquid uptake and faster disintegration in tablets containing insoluble fillers. However, even among XPVP grades of similar size, variations in porosity produced distinct disintegration times (i.e. more porous grades disintegrated faster), indicating that porosity, rather than particle size alone, is the more critical factor in disintegration (Shah and Augsburger, 2001).

Furthermore, it has been observed that the particle size distribution of all excipients and APIs affects disintegrant activity. In polydisperse systems, smaller particles can occupy the voids between larger ones, reducing the overall pore volume and obstructing liquid ingress. This can significantly prolong the disintegration time. Additionally, the increased particle-particle contact area in polydisperse formulations can enhance bonding during compression, potentially increasing tablet mechanical strength and further delaying disintegration (Markl and Zeitler, 2017; Smullenbroek et al., 1981).

1.4.1.2 Polymer crosslinking

Crosslinking is a critical step in the production of superdisintegrants, aimed at enhancing their water uptake and swelling behaviour. Without crosslinking, hydrophilic polymer chains tend to dissolve, increasing the medium's viscosity and forming gels that inhibit water diffusion through the tablet. This impairs disintegrant activation, slowing the disintegration process. Optimising the degree of crosslinking is essential; excessive crosslinking may reduce swelling capacity, while insufficient crosslinking may lead to excessive solubility and gelling, both of which can negatively affect performance (Berardi et al., 2022; De Wit, 2015; Rudnic et al., 1985).

1.4.1.3 Swelling volume

Swelling volume refers to the maximum amount of water required to fully hydrate a given mass of dispersed disintegrant particles, providing an estimate of their capacity to accommodate absorbed moisture. Although a higher swelling volume is generally assumed to facilitate faster disintegration, a direct correlation between swelling volume and disintegration time is not always observed. This is because multiple interdependent factors influence disintegration, and no single property can predict its overall kinetics.

For instance, based solely on swelling volume (ranked as SSG > CCS > XPVP) (Bauhuber et al., 2021), SSG would be expected to consistently result in the fastest disintegration, followed by CCS and then XPVP. However, this trend does not always hold true in practice. One explanation is that swelling volume reflects only one aspect of performance and does not account for other critical mechanisms, such as liquid penetration (wicking). Swelling, while necessary, is not necessarily the rate-limiting step in tablet disintegration (Bauhuber et al., 2021; Berardi et al., 2022). This is further supported by observations that individual particles of SSG and CCS can reach approximately 80% of their maximum swelling capacity within one second upon contact with water (Soundaranathan et al., 2020). Given how rapidly swelling can occur, the delay in tablet disintegration is more likely governed by the rate of fluid ingress into the tablet matrix. In this context, wicking and fluid accessibility within the internal tablet structure play a more critical role in determining the overall disintegration time than swelling volume alone.

1.4.1.4 Liquid uptake

Liquid uptake refers to the disintegrant's ability to absorb fluid and is considered a useful indicator of the disintegration performance. Generally, both the rate and extent of liquid uptake provide insight into how quickly a disintegrant can become activated within the tablet matrix.

Liquid absorption is not solely the result of a single mechanism, but rather the combined effect of swelling and wicking. However, despite their complementarity, these two processes may sometimes act in opposition. For instance, while swelling enables expansion and stress generation, it can simultaneously hinder further liquid penetration. This occurs when swollen particles close off interparticulate pores, restricting liquid flow into deeper regions of the tablet and thus limiting overall uptake (Figure 1.3). This phenomenon has been demonstrated in MCC-based tablets containing CCS. At higher

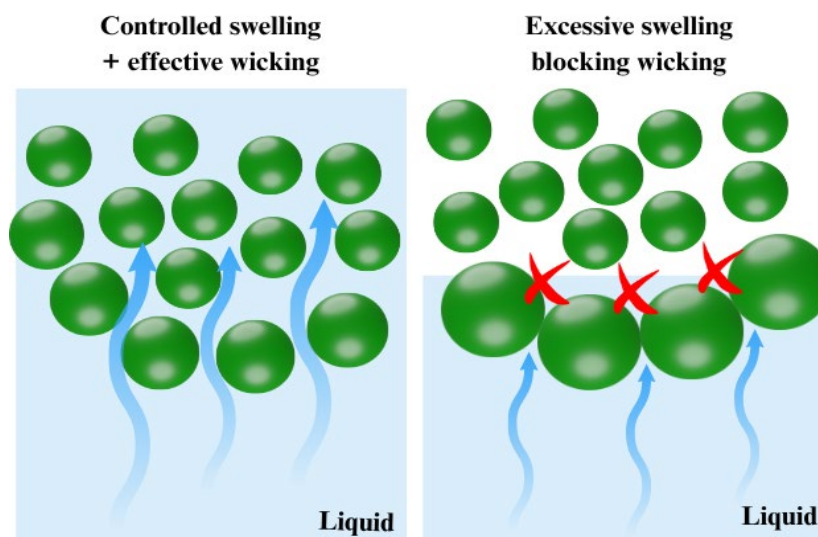


Figure 1.3: Schematic representation of liquid uptake of particles, wicking-driven liquid uptake (left) and swelling-driven liquid uptake (right).

temperatures, CCS was observed to swell more rapidly and begin to gel, resulting in partial closure of the tablet's internal pores. Consequently, the liquid uptake was reduced as the fluid transport was physically blocked by the swollen and gelled disintegrant particles (Basaleh et al., 2020; Yassin et al., 2015).

1.4.1.5 Solubility and intrinsic dissolution rate

The solubility of formulation excipients plays a complex role in tablet disintegration behaviour. It has been observed that tablets formulated with insoluble excipients tend to disintegrate more rapidly than those containing soluble ones (Johnson et al., 1991). This effect is primarily attributed to the interaction between liquid penetration, dissolution, and the availability of water to activate disintegrants. In tablets composed predominantly of soluble materials, the initial liquid ingress occurs through capillary action, followed by the dissolution of excipients near the wetted surface. As the particles dissolve, porosity increases progressively, which may facilitate further liquid penetration and promote disintegration. However, this process is not always advantageous. The dissolution of soluble ingredients can consume significant amounts of water, thereby limiting the availability of free liquid for disintegrant activation deeper within the tablet core (Ekmekciyan et al., 2018). Consequently, disintegration may be delayed, particularly when water availability becomes a limiting factor. This phenomenon helps explain why formulations with insoluble hydrophilic fillers often disintegrate more readily than those containing soluble fillers, such as lactose (Maclean et al., 2021).

Building on this, Maclean et al. (2021) further explored the role of intrinsic dissolution rate by comparing the disintegration performance of MCC/mannitol and MCC/lactose

tablets. Although both mannitol and lactose are soluble fillers with similar aqueous solubilities, tablets containing mannitol disintegrated significantly faster. The difference was attributed to mannitol's higher intrinsic dissolution rate, which enhanced water penetration and accelerated disintegration. In contrast, lactose, with its comparatively lower dissolution rate, slowed water ingress and delayed the disintegration process. These findings suggest that, in formulations containing high levels of soluble excipients, it is not solubility alone but rather the intrinsic dissolution rate that governs the extent and speed of liquid uptake (Maclean et al., 2021).

1.4.1.6 Hygroscopicity

Hygroscopicity refers to the ability of solids to interact with water vapour from the surrounding air at a constant temperature in response to changes in the relative humidity (RH) (Newman et al., 2008). Callahan et al. (1982) proposed a classification of degree of hygroscopicity into four categories, very, moderate, slight, and non-hygroscopic, based on both the quantity and rate of water uptake over different RH ranges, as presented in Table 1.1. In contrast, the European Pharmacopoeia employs a simplified method, measuring water uptake at 25°C and 80% RH, and classifying materials accordingly (Ph.Eur., 2008). The selection of these particular thresholds for water content and the fixed 80% RH appears somewhat arbitrary, and the differences between the two systems are such that the same material might be assigned different classifications depending on the method used.

The hygroscopic nature of excipients can influence disintegration and dissolution by altering the distribution and availability of water within the tablet matrix during liquid

uptake. Hygroscopic materials tend to attract and hold water from their surroundings upon contact with dissolution media, which may interfere with the efficient activation of disintegrants, especially those embedded deeper within the compact. This is particularly relevant when highly soluble or swellable disintegrants compete with hygroscopic excipients for the limited volume of penetrating liquid (Johnson et al., 1991). Gordon and Chowhan (1987) observed that formulations with higher overall hygroscopicity exhibited slower dissolution rates, potentially due to reduced availability of free water needed for effective disintegration (Gordon and Chowhan, 1987).

Table 1.1: Hygroscopicity classification schemes.

Classification	Criteria per Callahan et al. (1982)	Criteria per Ph.Eur. (2008)
Non-hygroscopic	Class I: essentially no moisture increase below 90% RH; less than 20% increase in moisture content above 90% RH in 1 week	0-0.2% (w/w)
Slightly hygroscopic	Class II: essentially no moisture increase below 80% RH; less than 40% (w/w) increase in moisture content above 80% RH in 1 week	0.2-2% (w/w)
Moderately hygroscopic	Class III: moisture content does not increase >5% (w/w) below 60% RH; less than 50% (w/w) increase in moisture content above 80% RH in 1 week	2-15% (w/w)
Very hygroscopic	Class IV: moisture content will increase as low as 40-50% RH; greater than 20% (w/w) increase in moisture content above 90% RH in 1 week	>15% (w/w)

1.4.2 The effect of formulation factors

Incorporating excipients with varying physicochemical characteristics and concentrations within a tablet formulation can influence the performance of disintegrants and, in turn, the disintegration efficiency of IR tablets.

The concentration of the disintegrant is particularly important. For instance, Berardi et al. (2018) found that DCP-based tablets disintegrated more rapidly when 1% of SSG or CCS was used, compared to higher concentrations of 4% or 8%. As DCP is a hydrophilic and readily wettable filler, the authors suggested that lower disintegrant concentrations were sufficient to initiate breakup. In contrast, higher levels may have resulted in the formation of a dense gel-like layer that temporarily hindered disintegration (Berardi et al., 2018). However, in matrices with lower wettability, such as hydrophobic formulations, higher concentrations (e.g. 4%) of SSG, CCS, or XPVP were required to achieve efficient disintegration (Bauhuber et al., 2021). Dvořák et al. (2020) demonstrated that increasing CCS concentration from 1% to 4% in ibuprofen-lactose tablets resulted in smaller fragments upon disintegration, which improved wettability and accelerated both disintegration and dissolution. This effect was less pronounced at lower disintegrant concentrations, where the resulting fragments were larger and disintegration occurred more slowly (Dvořák et al., 2020). Desai et al. (2014) further demonstrated that the optimal concentration of disintegrants can range between 6% and 8%, depending on the drug solubility and formulation design (Desai et al., 2014). This suggests that the commonly cited optimal range of 1-5% (Zarmpi et al., 2017) may not be universally applicable and should be evaluated on a case-by-case basis.

The choice of disintegrant itself is equally important and should be tailored to the overall formulation. For example, in a study using hydrophobic matrices, CCS reduced disintegration time by up to 21-fold compared to XPVP under varying compaction pressures and storage conditions (Bauhuber et al., 2021). These findings underscore the importance of disintegrant type, as their mechanism of action and water demand differ.

Beyond disintegrants, fillers and binders, often included for their compressibility and flow properties, can significantly impact tablet disintegration through their own hydration, swelling, and solubility behaviours. Ekmekciyan et al. (2018) studied the effect of dry binders in directly compressed tablets containing either DCP (an insoluble hydrophilic filler) or lactose (a soluble filler), and SSG, CCS, or XPVP as disintegrants. In DCP-based tablets, the presence of hydrophilic binders slowed disintegration when combined with SSG. This delay was attributed to SSG's slower swelling kinetics, which allowed time for the binder to hydrate and absorb water, which is otherwise needed for the disintegrant to function. In contrast, CCS and XPVP swelled more rapidly, making them less susceptible to this competition for water. At the same time, tablets composed of soluble fillers, such as lactose, disintegrate considerably slower than tablets made from hydrophilic insoluble fillers (Ekmekciyan et al., 2018), supporting the idea that disintegration depends not only on the presence of disintegrants but also on the hydration and water demand of other hydrophilic or soluble excipients.

It is also important to consider that any excipient with swelling capability may contribute to the tablet's overall disintegration behaviour. For example, MCC, a commonly used insoluble filler with inherent swelling properties, can influence disintegration when used

at high concentrations (Desai et al., 2016). Studies comparing MCC and functionalised calcium carbonate (FCC) showed that in MCC-based tablets, both MCC and disintegrants contributed to swelling, with low porosity slowing water ingress due to pore closure from MCC expansion. Conversely, FCC-based tablets, which do not swell, rely entirely on disintegrant action for disintegration, with porosity having a more direct influence on liquid uptake (Al-Sharabi et al., 2020). The classification of MCC in the context of tablet disintegration has been debated in the literature. MCC is well established as a material that absorbs liquids and undergoes swelling upon wetting, generating internal stresses that can contribute to tablet breakup (Desai et al., 2016; Markl and Zeitler, 2017; Quodbach and Kleinebudde, 2016; Soundaranathan et al., 2020). However, the extent of swelling exhibited by MCC is substantially lower than that of classical disintegrants or superdisintegrants (Soundaranathan et al., 2020), and on its own is generally insufficient to drive rapid tablet disintegration. For this reason, MCC should not be considered a disintegrant in the conventional sense. Instead, its highly porous structure and ability to absorb liquid facilitate the activation of co-formulated disintegrants (Lerk et al., 1979).

Another formulation component that can affect the disintegration is the lubricant. Hydrophobic lubricants, particularly magnesium stearate, are known to hinder water penetration by forming a hydrophobic barrier around particles and reducing tablet wettability. Additionally, lubricants may influence mechanical properties, such as tablet hardness, which can indirectly affect the disintegration process. Paul and Sun (2018) compared the effects of different lubricants (magnesium stearate, sodium stearyl fumarate, and stearic acid) on tablet performance. All lubricants delayed disintegration

compared to unlubricated tablets, but sodium stearyl fumarate exhibited the least adverse effect, possibly due to its partial hydrophilic nature. The lubricant particle size and its interaction with other excipients may also determine the extent of this impact (Paul and Sun, 2018). Overall, while lubricants are necessary for manufacturing, their type and concentration must be carefully optimised to avoid compromising disintegration.

1.4.3 The effect of manufacturing route and processing parameters

The method of tablet manufacture and the associated processing conditions play a critical role in determining tablet performance. Among the various methods, direct compression is most commonly employed when assessing the effect of formulation and material-related variables. This approach involves blending excipients and active ingredients shortly before tableting and does not include any intermediate processing steps that could alter material properties. As a result, the disintegration behaviour of such tablets primarily reflects the contributions of the individual excipients and the resulting tablet properties (Quodbach and Kleinebudde, 2016). However, when direct compression is not feasible due to poor flow or compressibility, a granulation step, either wet or dry, may be introduced to improve handling and Tabletability (Hiremath et al., 2019; Shanmugam, 2017).

Tablet porosity, primarily influenced by the applied compression force during tableting, plays a crucial role in determining both the mechanical properties and disintegration behaviour of IR tablets. Compression force alters the compact structure, thereby modulating both pore size and pore distribution. According to the Washburn equation (Washburn, 1921), the penetration rate of a liquid into a porous medium is directly related

to the pore radius and inversely related to the liquid's viscosity and contact angle with the solid. In principle, higher porosity and wider pores would facilitate faster water uptake and enhance disintegration by promoting more efficient wicking (Marais et al., 2003), provided that other variables, such as surface tension and viscosity, remain constant. However, this relationship does not always translate directly into faster disintegration in practice. Disintegration is not only dependent on how quickly water reaches the interior of the tablet, but also on how effectively disintegrant particles can expand and generate sufficient force to disrupt the compact. While higher porosity generally facilitates liquid uptake and disintegration, overly large pores may delay the mechanical action of disintegrants. This is because disintegrant particles may require more time and expansion to reach and press against the pore walls, dispersing some of the swelling energy without translating it effectively into matrix disruption. On the other hand, narrower pores, resulting from higher compaction pressures, can facilitate faster and more direct force transmission from disintegrant swelling to the surrounding matrix, thus accelerating disintegration, particularly for disintegrants that act by swelling rather than shape recovery. However, if the pores become too tight, water penetration may be significantly impeded (Desai et al., 2016; Quodbach et al., 2014). Thus, optimal porosity must be achieved to ensure mechanical strength while preserving disintegration efficiency.

Beyond compression effects, the granulation process itself can significantly influence disintegration. In wet granulation, the addition mode of disintegrant plays a pivotal role. Disintegrants, which are often incorporated intragranularly, can lose some activity due to exposure to granulation fluid and subsequent drying. In contrast, extra-granular addition

preserves disintegrant activity. Combining intra- and extra-granular addition often yields better disintegration performance than using either method alone (Khattab et al., 2011). This observation was further supported by Zakowiecki et al. (2019), who investigated the effect of adding tribasic calcium phosphate (TCP) to acyclovir tablets prepared by wet granulation. Tablets with intra-granular TCP disintegrated more rapidly, whereas those with extra-granular incorporation exhibited higher tensile strength. These findings suggest that highly porous fillers, such as TCP, can enhance wicking and promote disintegration, even when incorporated within the granule structure (Zakowiecki et al., 2019).

Dry granulation via roller compaction is another widely used technique. However, the process can compromise disintegration, particularly for shape-recovery disintegrants. Berkenkemper et al. (2020) found that disintegration was slower in tablets produced by dry granulation than in those made by direct compression, particularly for XPVP. This was attributed to the deformation and misalignment of XPVP particles during roller compaction, which resulted in a less efficient release of stored elastic energy. In contrast, CCS was less affected due to its swelling-based mechanism (Berkenkemper et al., 2020).

1.4.4 The effect of storage conditions

Storage conditions can markedly influence the disintegration behaviour of IR tablets by affecting both excipient functionality and the overall tablet microstructure. They may also indirectly impact disintegration and dissolution through changes in mechanical strength, particularly tensile strength. Among the factors responsible, moisture uptake is the most critical. As summarised in Table 1.2, the literature reports conflicting findings regarding

the impact of high-humidity exposure on tablet performance. Such discrepancies are unsurprising, as study outcomes are often shaped by differences in experimental parameters, including disintegrant type and concentration, compression pressure, diluent type, and storage humidity.

Disintegrants, especially those acting by swelling or shape recovery, may undergo partial activation due to water sorption, thereby compromising their functionality. This phenomenon, often referred to as "pre-activation," results in a diminished expansion force or reduced shape recovery during actual tablet use, leading to slower or incomplete disintegration. Moreover, excipients other than the disintegrant may also contribute to these changes. For instance, certain binders or fillers may soften or harden during storage depending on their hygroscopicity, thereby altering the tablet's mechanical properties and liquid penetration profile (Hersen-Delesalle et al., 2007; Sacchetti et al., 2017).

Table 1.2: Summary of the impact of moisture exposure on the tablet performance characteristics.

Tablet property	Direction of change	Disintegrant involved	Reference(s)
Tensile strength	Increased	CCS, SSG	(Gordon et al., 1993b)
		XPVP	(Gordon et al., 1993b; Hiew et al., 2016)
		Starch	(Shotton and Leonard, 1976)
	Decreased	CCS	(Bauhuber et al., 2021; Chowhan and Yang, 1983; Gordon et al., 1990; Gordon and Chowhan, 1990; Hersen-Delesalle et al., 2007; Maclean et al., 2022; Marais et al., 2003; Pourkavoos and Peck, 1993)
		SSG	(Hersen-Delesalle et al., 2007, 2007; Horhota et al., 1976; Khan and Rhodes, 1975; Pourkavoos and Peck, 1993; Sheen and Kim, 1989)
		XPVP	(Bauhuber et al., 2021; Hersen-Delesalle et al., 2007; Hiew et al., 2016; Pourkavoos and Peck, 1993; Quodbach and Kleinebudde, 2015; Sheen and Kim, 1989; Viljoen et al., 2014)
		Starch	(Chowhan, 1980; Khan and Rhodes, 1975)
	No significant change	CCS, SSG	(Khatab et al., 2011; Sacchetti et al., 2017)
		XPVP	(Khatab et al., 2011)
Disintegration time	Increased	CCS	(Khatab et al., 2011; Sacchetti et al., 2017; Zhao and Augsburger, 2006b)
		SSG	(Khan and Rhodes, 1975; Quodbach and Kleinebudde, 2015; Sacchetti et al., 2017; Zhao and Augsburger, 2006b)
		XPVP	(Hiew et al., 2016; Sacchetti et al., 2017; Viljoen et al., 2014; Zhao and Augsburger, 2006b)

		Starch	(Chowhan, 1980; Khan and Rhodes, 1975; Sheen and Kim, 1989; Shotton and Leonard, 1976)
	Decreased	CCS	(Marais et al., 2003; Sheen and Kim, 1989)
		SSG	(Khattab et al., 2011)
		XPVP	(Khattab et al., 2011; Sheen and Kim, 1989)
	No significant change	CCS	(Quodbach and Kleinebudde, 2015)
		SSG	(Sheen and Kim, 1989)
		XPVP	(Quodbach and Kleinebudde, 2015)
Dissolution rate	Increased	CCS	(Gordon et al., 1990; Marais et al., 2003)
		Starch	(Chowhan and Yang, 1983)
	Decreased	CCS	(Gordon et al., 1993b, 1993a; Gordon and Chowhan, 1990; Khattab et al., 2011; Maclean et al., 2023)
		SSG	(Gordon et al., 1993b, 1993a; Gordon and Chowhan, 1990; Khan and Rhodes, 1975; Khattab et al., 2011)
		XPVP	(Gordon et al., 1993b, 1993a; Gordon and Chowhan, 1990; Khattab et al., 2011; Li et al., 2004; Sacchetti et al., 2017)
		Starch	(Chowhan, 1980)
	No significant change	SSG	(Horhota et al., 1976)

Changes in disintegration time due to storage are not always unidirectional. Exposure to low RH has been shown to slow disintegration by reducing the moisture available for wetting, while moderate humidity may initially improve disintegration kinetics (Nokhodchi and Javadzadeh, 2007). However, at higher humidity levels, the partial dissolution of soluble excipients followed by recrystallisation upon moisture loss can create rigid interparticle bridges. This solid-bridge formation can significantly increase tablet hardness, thereby delaying disintegration (Gordon and Chowhan, 1990; Molokhia et al., 1987). Once these structural changes occur, they are often irreversible, even if the tablets are subsequently removed from storage. Figure 1.4 summarises the effects of storage on the performance of IR tablets.

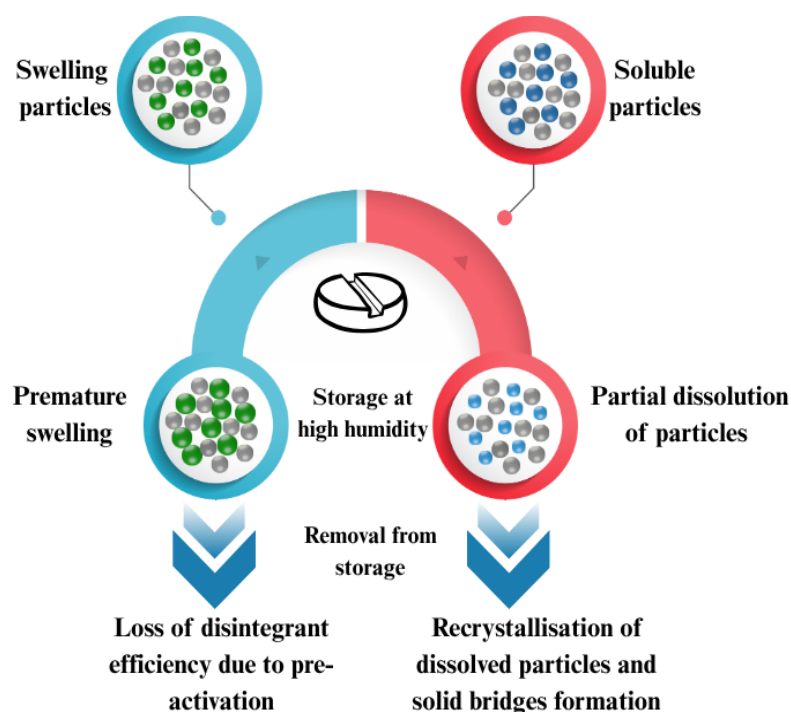


Figure 1.4: A summary of the potential mechanisms of physical changes during the storage of IR tablets.

1.5 Water in oral solid dosage forms

Water is an omnipresent factor in the lifecycle of OSDFs, from raw material handling and manufacturing through to packaging and long-term storage. Its presence is often unavoidable, as many pharmaceutical operations, such as wet granulation, spray drying, and film coating, involve water as a processing medium. Even after drying, residual moisture remains associated with excipients and APIs, while exposure to environmental humidity during storage provides further opportunities for uptake (Airaksinen et al., 2005). The dual role of water, as both a facilitator of desirable properties and a source of instability, makes it one of the most critical parameters in the development of solid dosage forms.

On the one hand, limited amounts of moisture can enhance compressibility, promote binding, and even stabilise certain crystal forms. For example, granules with slightly higher water content tend to exhibit better compressibility, resulting in stronger tablets with lower friability (Chowhan and Chow, 1981). Similarly, residual moisture can contribute to solid bridging and recrystallisation, improving tensile strength after compression. On the other hand, excessive or uncontrolled moisture uptake can have highly detrimental consequences, ranging from hydrolytic degradation of sensitive APIs to compromised disintegration and dissolution behaviour, as discussed in the previous section 1.4.4.

1.5.1 Mechanisms of water-solid interactions

Water can associate with pharmaceutical solids through several distinct mechanisms, each with unique thermodynamic and kinetic implications.

1.5.1.1 Adsorption and absorption

Adsorption refers to the binding of water molecules to the external surface of a solid. It is primarily a surface phenomenon, dependent on the polarity of surface chemical groups, hydrogen bonding capacity, and available surface area. At low RH, water molecules form a monolayer covering polar sites; with increasing RH, multilayers are formed on top of this primary layer (Figure 1.5) (Ahlneck and Zografi, 1990). While bulk properties are often unaffected, surface adsorption can significantly alter powder flow, surface energy, and interparticle interactions, particularly in high-surface-area materials such as finely milled excipients or amorphous solids (Newman et al., 2008).

Absorption, in contrast, involves penetration of water molecules into the bulk of the solid (Figure 1.5). This occurs predominantly in amorphous phases, where molecular disorder provides free volume and energetically favourable sites for water incorporation. Water plasticises the amorphous structure, lowering the glass transition temperature and enhancing molecular mobility (Ahlneck and Zografi, 1990). These changes accelerate

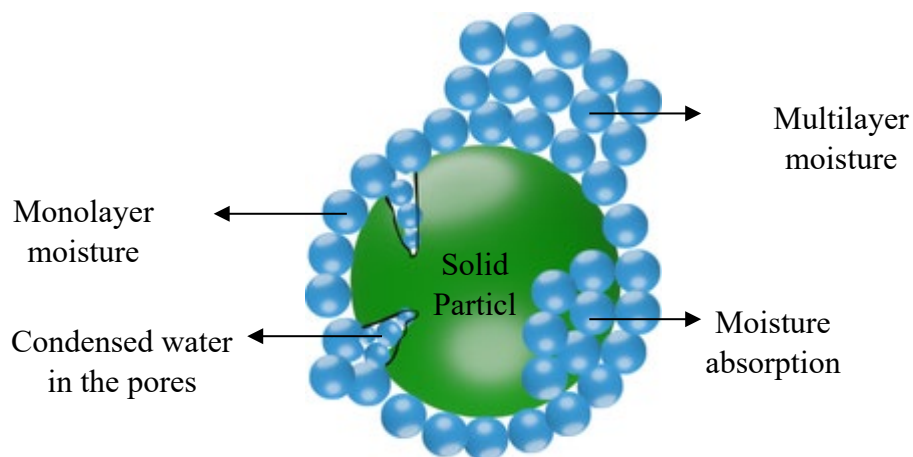


Figure 1.5: Schematic of the distribution of water molecules in materials.

physical transformations and chemical degradation processes. Even small amounts of amorphous material in an otherwise crystalline sample can markedly increase water uptake and compromise stability. Crystalline materials are generally resistant to bulk absorption, but structural defects introduced by processes such as milling, spray drying, or compaction can create pathways for water penetration (Waterman et al., 2002).

While adsorption and absorption differ in terms of the location and local environment of the sorbed molecules, they do not differ in the fundamental thermodynamic criterion that defines equilibrium. From a thermodynamic perspective, both adsorption and absorption are driven by minimisation of the Gibbs free energy of the system and reach equilibrium when the chemical potential of the sorbing molecules is equalised across phases. In gas–solid adsorption, equilibrium is achieved when the chemical potential of the adsorbed molecules associated with the solid equals that in the surrounding vapour phase (Myers and Monson, 2014; Sacchetti, 1998). Similarly, for absorption into a bulk solid or porous matrix, equilibrium corresponds to equality between the chemical potential of the sorbed molecules within the material and that in the external vapour. The distinction between adsorption and absorption is therefore mechanistic rather than thermodynamic, reflecting whether the sorbed phase is localised at an interface or distributed throughout the bulk, rather than a difference in the governing equilibrium condition (Pourhakkak et al., 2021; Sacchetti, 1998).

Although absorption is often described kinetically using diffusion concepts, such as Fick's law and diffusion coefficients, these descriptions relate to the rate at which equilibrium is approached rather than the equilibrium state itself. Diffusion governs how

rapidly concentration or activity gradients within a material are eliminated, whereas the direction of spontaneous change and the final equilibrium condition are determined by gradients in chemical potential (Ma et al., 2022).

1.5.1.2 Crystal hydrate formation

Certain crystalline materials can incorporate water molecules into their lattice structure to form crystal hydrates. These can be either stoichiometric, where water molecules are included in fixed ratios (e.g. α -lactose monohydrate contains one mole of water per mole of lactose), or non-stoichiometric, where water occupies lattice channels or cavities without fixed proportions. Hydrate formation often results in significant changes in solubility, dissolution rate, and stability. Generally, hydrates are more thermodynamically stable but less soluble than their anhydrous counterparts, leading to slower dissolution and, in the case of APIs, reduced bioavailability (Tian and Rantanen, 2011).

1.5.1.3 Deliquescence

Deliquescence occurs when a crystalline solid absorbs sufficient moisture from the atmosphere to dissolve in its own sorbed water, forming a saturated solution on the surface. This transformation happens when environmental RH exceeds the compound's critical relative humidity (RH_0) (Kontny and Zografi, 1985; Mauer and Taylor, 2010). The process is particularly problematic for highly soluble excipients (e.g. sugars, salts) and APIs, as surface dissolution not only alters physical appearance but also promotes chemical instability and recrystallisation (Van Campen et al., 1983).

1.5.1.4 Capillary condensation

In porous solids or granular assemblies, water can condense within fine pores at RH values below saturation. This capillary condensation creates localised regions of high moisture content, which can alter the mechanical strength and dissolution properties of compacts. While most pharmaceutical solids are not highly porous at the nanometre scale, interparticulate voids and defects can still provide sites where capillary condensation occurs (Newman et al., 2008).

1.5.2 Moisture sorption isotherms

Moisture sorption isotherms describe the equilibrium relationship between the water content of a material and the RH of its surrounding atmosphere at a constant temperature. They are fundamental for characterising water-solid interactions in pharmaceutical systems. Most pharmaceutical excipients and APIs display Type II (sigmoidal) or Type III sorption isotherms (Veronica et al., 2022). Type II profiles show initial monolayer adsorption, followed by multilayer adsorption and eventual bulk condensation. Type III profiles are characterised by weaker interactions, with more abrupt increases in uptake at higher RH (often due to deliquescence of soluble crystalline excipients). Figure 1.6 illustrates the different types of moisture sorption isotherms (Brunauer et al., 1940).

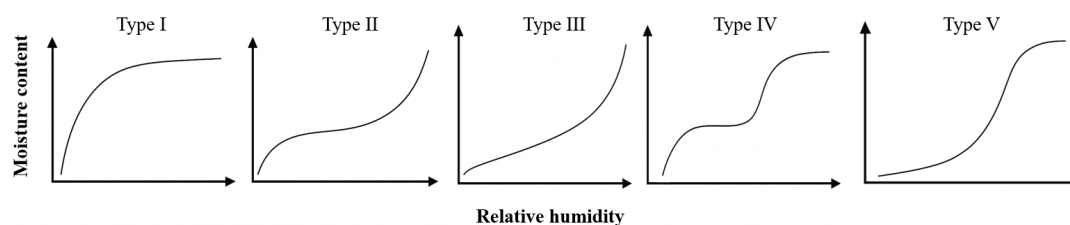


Figure 1.6: Classification of moisture sorption isotherms.

A common phenomenon observed in pharmaceutical solids is hysteresis, where the desorption isotherm does not retrace the adsorption path. This difference arises from structural rearrangements, clustering of water molecules, and non-equilibrium effects (Newman et al., 2008). Hysteresis is particularly pronounced in porous excipients and in materials that undergo amorphisation or swelling during sorption-desorption cycles. The presence and magnitude of hysteresis provide essential clues about the strength of water binding and potential irreversible structural changes (Hiew, 2017).

Quantitative analysis of isotherms is achieved through the use of mathematical models. The Brunauer-Emmett-Teller (BET) model is one of the earliest and most widely applied models. It estimates monolayer moisture content, which represents the water level at which a single molecular layer of water saturates the solid surface. This parameter has often been linked to the stability, since water in the monolayer is bound too tightly to promote degradation. In contrast, multilayer and bulk water are more mobile and reactive (Kontny and Zografi, 1985). However, the BET equation is only valid in the low RH range (typically < 0.3) (Brunauer et al., 1938), limiting its utility for excipients that continue to sorb significant water at higher RH. The Guggenheim-Anderson-de Boer (GAB) model extends the BET framework by incorporating multilayer sorption, making

it suitable for describing a wider RH range (up to 0.9). The GAB model is widely applied in food and pharmaceutical systems to estimate both monolayer and multilayer contributions (Al-Muhtaseb et al., 2002).

1.5.3 Experimental aspects of water vapour sorption analysis

Accurate determination of moisture sorption behaviour is essential for quantifying water-solid interactions and constructing sorption isotherms. Several experimental methods are available, ranging from traditional static approaches to modern automated techniques.

The most established static technique is the desiccator method, in which pre-weighed samples are equilibrated over saturated salt solutions that impose a fixed RH. The samples are periodically removed, weighed, and returned until a constant mass is achieved. This method is reliable for establishing equilibrium values, but it requires gram-scale amounts of material, is labour-intensive, and equilibration may take several days or even weeks (Callahan et al., 1982; Newman et al., 2008).

Dynamic methods overcome many of these limitations. Among these, dynamic vapour sorption (DVS) has become the gold standard in pharmaceutical research. In a DVS experiment, a milligram-scale sample is placed on a high-precision microbalance and subjected to a programmed sequence of RH steps, generated by blending dry and humidified carrier gas streams (typically nitrogen or air). The change in sample mass is continuously recorded as the RH is increased or decreased, allowing real-time monitoring of sorption and desorption (Zelinka et al., 2024). A schematic of a DVS system is shown in Figure 1.7.

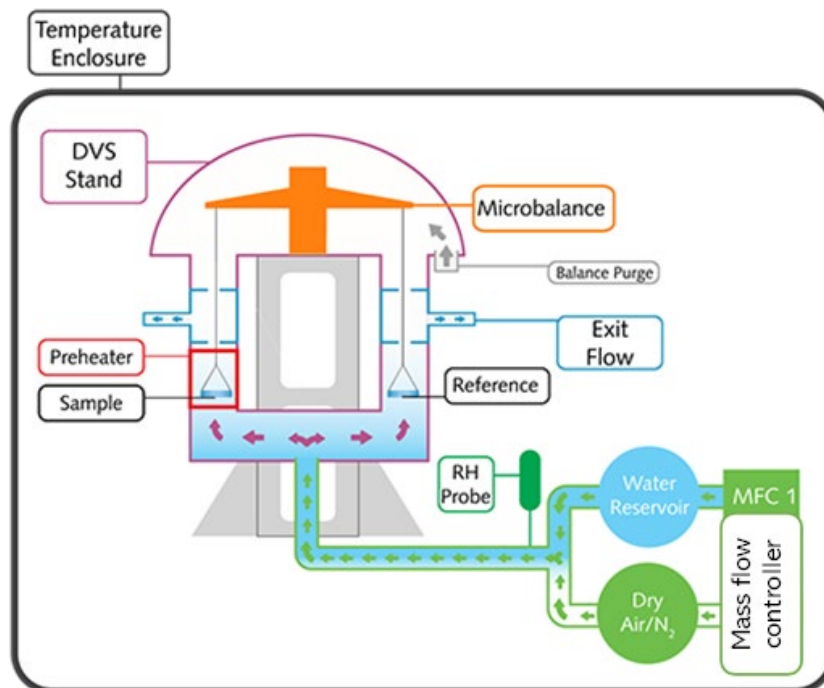


Figure 1.7: Schematic of a DVS system (Surface Measurement Systems, 2025).

DVS is advantageous because it requires only small amounts of material, provides high sensitivity, and enables fully automated RH cycling. Complete adsorption-desorption isotherms can thus be generated in days rather than weeks, making DVS particularly valuable in early development when API supply is often limited (Arlabosse et al., 2003; Newman et al., 2008; Stubberud, 1995). The ability of DVS to provide continuous kinetic data is a major strength, distinguishing it from static approaches that only measure endpoint equilibria. DVS has been used to detect hydrate formation (Burnett and Thielmann, 2012), to monitor crystallisation from amorphous solids (Burnett et al., 2006, 2004; Sheokand et al., 2014), and to identify subtle differences in excipient batches. Furthermore, DVS can capture the impact of processing steps such as milling or spray-

drying, which may increase disorder and accelerate moisture uptake (Newman et al., 2008).

Despite these advantages, careful experimental design is essential to avoid misinterpretation. The choice of equilibration criteria strongly influences the accuracy of the resulting isotherms. If mass-stability thresholds are set too loosely or maximum dwell times too short, the sample may not achieve true equilibrium (Glass et al., 2018, 2017).

DVS itself is a gravimetric technique that measures the net change in sample mass as a function of relative humidity and time. The measured mass change reflects the net uptake or release of vapour by the sample and is commonly expressed in the form of sorption–desorption isotherms. Importantly, the term “sorption” is used deliberately in this context, as DVS does not distinguish between adsorption of vapour at external or internal surfaces and absorption of vapour into the bulk or pore network of the material. Instead, the gravimetric response represents the combined contribution of all vapour–solid interactions occurring within the sample (Sheokand et al., 2014). From a thermodynamic perspective, relative humidity imposes the water activity and thus the chemical potential of water in the vapour phase. Moisture uptake proceeds until the chemical potential of water associated with the solid equals that of the surrounding vapour, at which point equilibrium is reached (Myers and Monson, 2014). Each point on a DVS sorption isotherm therefore represents a thermodynamic equilibrium defined by equality of chemical potential, rather than a specific sorption mechanism.

Although moisture uptake in DVS experiments is frequently described using classical sorption isotherm models, it is important to recognise the assumptions underlying these

models. The BET equation and its extension, the GAB model, were originally derived to describe multilayer adsorption on solid surfaces and therefore rely on surface adsorption concepts and well-defined adsorption sites. When applied to water vapour sorption in hygroscopic and porous solids, these models are commonly used in a phenomenological manner, as bulk absorption, pore filling, and swelling may contribute significantly to the measured uptake (Shimizu and Matubayasi, 2021).

1.6 Stability of oral solid dosage forms

Stability is a critical quality attribute that governs whether a drug product can be released to the market and remain effective throughout its shelf life. It refers to the ability of a pharmaceutical product, in a specified packaging, to maintain its identity, strength, quality, purity, and safety within predefined limits over time under the influence of various environmental conditions (González-González et al., 2022; Veronica et al., 2022). The stability of a drug product comprises chemical, physical, microbiological, therapeutic, and toxicological aspects. Chemical stability relates to the rate and extent of API and excipient degradation into products that may be less effective or potentially harmful. This degradation not only leads to a reduction in drug potency but may also introduce safety risks. Physical stability involves changes in the physical characteristics of the dosage form, including organoleptic properties, disintegration time, dissolution rate, tensile strength, porosity, moisture content, and phase transitions, all of which can significantly affect the performance and bioavailability of the drug. Microbiological stability refers to a product's ability to resist microbial contamination and maintain sterility throughout its shelf life (González-González et al., 2022; Guo et al., 2013).

A wide array of intrinsic and extrinsic factors influences the overall stability of OSDFs. These include the chemical properties of the API, excipient compatibility, manufacturing process, packaging system, transportation and handling conditions, and exposure to environmental factors such as temperature, RH, light, and oxygen (Bajaj et al., 2012; Bott and Oliveira, 2007).

1.6.1 Stability testing and regulatory frameworks

Stability testing is a critical component of pharmaceutical development, serving multiple roles from guiding formulation selection to determining appropriate packaging and storage conditions (Qiu, 2018). In early stages, accelerated studies conducted under elevated temperature and humidity are often employed to identify potential degradation pathways and predict long-term stability. Conversely, studies under standard or milder environmental conditions help estimate shelf life and establish expiration dates (Bajaj et al., 2012). Formulations sensitive to environmental stress, such as moisture, may require specific packaging strategies, like the inclusion of desiccant. As development advances, stability testing continues to validate the product's robustness post-packaging and during use. It also plays a vital role in regulatory submissions, from Investigational New Drug (IND) applications to post-approval changes, by ensuring that modifications in formulation or manufacturing do not compromise product quality (Qiu, 2018).

To ensure that optimally stable drug substances and products are manufactured, distributed, and administered to patients, regulatory authorities worldwide have established mandatory requirements for the submission of stability data as part of the drug approval process. The primary objective of these regulations is to harmonise testing

procedures across manufacturers, ensuring consistency in the evaluation of quality, safety, and efficacy over the product's shelf life.

The foundation of modern pharmaceutical stability assessment was laid in the early 1990s and 2000s with the introduction of a comprehensive set of technical guidelines by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), in collaboration with the World Health Organisation (WHO). These guidelines (ICH Q1A, Q1F, Q3A-B, Q5C, and Q6A-B) standardised the regulatory expectations for the stability testing of both APIs and finished pharmaceutical products, particularly in terms of data generation, storage conditions, and documentation required for global submissions (ICH, 2003). A brief outline of the ICH Q1 guidelines is given in Table 1.3.

Table 1.3: ICH stability guidelines, codes, and titles.

ICH code	Guideline title
Q1A	Stability Testing of New Drug Substances and Products
Q1B	Photostability Testing of New Drug Substances and Products
Q1C	Stability Testing for New Dosage Forms
Q1D	Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
Q1E	Evaluation of Stability Data
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV

To facilitate mutual drug approvals across major markets (the European Union, Japan, and the United States), the ICH introduced climate zone-based guidance, outlining required storage conditions that reflect the environmental challenges in different regions (ICH, 2003).

In addition to the ICH framework, the Committee for Proprietary Medicinal Products (CPMP), operating under the European Medicines Agency (EMA), has developed complementary guidance on stability testing. These documents support regulatory submissions in the EU by addressing specific concerns such as storage declarations, in-use stability, and the impact of manufacturing variations on shelf-life (Bajaj et al., 2012).

Building on these foundations, a new draft revision of the ICH Q1 guideline (2025) has recently been released for public consultation. This draft reflects the ongoing evolution in scientific understanding and regulatory expectations, offering enhanced flexibility for incorporating predictive stability tools and providing clearer guidance for products destined for international markets. Although still under review, the proposed updates highlight a growing trend toward streamlined, risk-based stability strategies that align with advances in modelling, analytics, and global harmonisation (ICH, 2025).

1.6.1.1 Conventional ICH stability studies

ICH guidelines categorise stability studies into three categories based on the intended storage duration and purpose: long-term, intermediate, and accelerated. Each category specifies unique combinations of temperature, humidity, and testing timelines to reflect different storage and distribution realities (WHO, 2018). These studies must account for the entire shelf life of the product and consider environmental conditions, particularly

temperature and humidity, that are typical in the countries where the drug will be distributed. Globally, four climatic zones (I-IV) are recognised based on their average annual temperature and humidity profiles, and the appropriate storage conditions must be selected according to the destination market (González-González et al., 2022). Country-specific long-term conditions are provided in the WHO "Stability conditions for WHO Member States" and may change over time (WHO, 2021).

Real-time (long-term) stability testing should span the shelf life proposed in the product submission and include the retest period for the API. Supplementary data from accelerated and intermediate stability studies are often included to simulate potential excursions, such as those that may occur during shipping and handling. If any deviations arise under accelerated conditions, a clear justification must be provided. These excursions should also be analysed to evaluate the resilience of the product beyond the labelled storage recommendations (González-González et al., 2022). Table 1.4 presents the ICH-recommended storage conditions for long-term, intermediate, and accelerated stability testing. It is worth mentioning that alternative storage conditions can also be used if justified by scientific rationale (ICH, 2003).

Data for stability studies is collected at strategically spaced intervals. For instance, a drug product with a proposed shelf life of at least one year should be tested every three months during the first year, biannually in the second year, and annually thereafter until its expiry date (ICH, 2003).

Table 1.4: Storage conditions recommended by the ICH Q1A guideline for stability testing of a drug product intended for storage at room temperature.

Study	Storage conditions	Minimum study duration covered for submission
Long-term	25°C ± 2°C/60% ± 5% RH or 30°C ± 2°C/65% ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% ± 5% RH	Six months
Accelerated	40°C ± 2°C/75% ± 5% RH	Six months

1.6.1.2 Accelerated predictive stability studies

The rigid timelines of ICH studies, often requiring six months or more, can delay early-stage formulation decisions. In response to this, Accelerated Predictive Stability (APS) studies have emerged as an efficient alternative, offering quicker insights into the long-term stability behaviour of drug substances and products (McMahon et al., 2021; Qiu, 2018). Unlike conventional ICH protocols, APS methodologies are designed to intentionally stress pharmaceutical products by exposing them to elevated temperature and humidity conditions, thereby accelerating degradation processes and identifying the underlying kinetic mechanisms driving these changes (González-González et al., 2022).

APS studies offer a versatile platform that supports multiple applications within pharmaceutical development, including formulation screening, container closure evaluation, shelf-life estimation, and verification of formulation changes. These studies are particularly advantageous in preclinical development, where the timely selection of stable excipients and packaging components is essential to support downstream decisions.

The foundation of APS testing was laid by Waterman et al. (2007), who introduced the Accelerated Stability Assessment Program (ASAP) using a moisture-modified Arrhenius model to simulate degradation kinetics under exaggerated stress conditions (Waterman et al., 2007). This protocol typically involves exposing samples to extreme temperature and humidity levels, often exceeding 40°C, for durations as short as 3 to 4 weeks. These conditions are sufficient to identify degradation pathways and estimate shelf-life behaviour under standard ICH conditions through extrapolation (Qiu, 2018; Williams, 2018). Unlike conventional ICH-guided studies, which typically evaluate products in their final packaging, APS experiments involve exposing the bulk drug substance or dosage form directly to the environmental conditions inside the chamber. This direct exposure enables a faster and more sensitive assessment of stability behaviour under stress conditions (Qiu, 2018). The distinguishing features of APS studies are summarised in Figure 1.8.

By accelerating stability evaluations and generating early degradation profiles, APS studies support faster and informed decision-making. This is particularly important when introducing new molecular entities to the market, where development timelines are often compressed (Waterman et al., 2007). APS also facilitates the prediction of degradation behaviour during transport or storage excursion conditions that may not be fully captured in conventional studies.

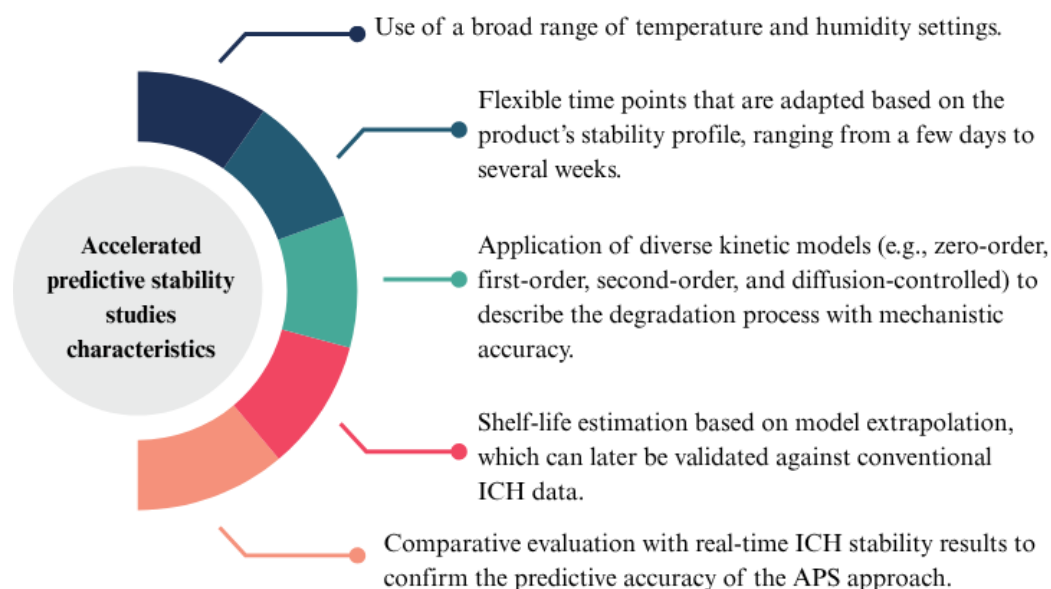


Figure 1.8: Characteristics of APS studies.

APS methods have become well-established tools for assessing chemical degradation; however, their application to physical attributes, such as tensile strength, disintegration, dissolution, and changes in solid-state properties, remains relatively underexplored (Williams, 2018). This is a significant limitation, particularly as delayed dissolution performance can have a direct impact on bioavailability. Evidence suggests that dissolution slowdown during storage is often driven by physical, rather than chemical, processes, especially given the dominant role of RH compared to temperature and the relatively rapid onset of such effects (González-González et al., 2022).

1.6.2 Prediction and modelling approaches

Traditional stability testing methods, though robust, are time-consuming and labour- and resource-intensive. As the pharmaceutical industry shifts toward more efficient and science-driven development practices, predictive modelling approaches are gaining

traction for estimating the long-term stability of drug products. These tools aim to reduce development timelines, support risk-based decision-making, and complement empirical data.

One of the most widely used approaches for predicting chemical degradation is the ASAP, along with its corresponding software, ASAPprime[®]. Initially developed by Waterman et al. (2007). The method is based on the concept of isoconversion time, which is the time required for a product to reach a predefined degradation threshold under specific combinations of temperature and humidity. This threshold could relate, for example, to potency loss or the emergence of degradation products. The model incorporates a moisture-corrected Arrhenius equation to project long-term stability outcomes, often under conventional storage conditions such as 25°C and 60% RH (Waterman, 2011). While ASAP has demonstrated strong predictive capability for chemical degradation pathways that conform to Arrhenius kinetics, extending its use to physical stability attributes (such as disintegration or dissolution) presents additional challenges. These processes often involve more complex, non-linear mechanisms not easily captured by traditional kinetic models. Nonetheless, recent studies have successfully applied the ASAP framework to predict dissolution behaviour, reporting a strong alignment between model projections and empirical data from long-term stability testing (Li et al., 2016).

In an alternative modelling strategy, Scrivens (2019) proposed that the shape of dissolution profiles remains fundamentally unchanged over time. By fitting these profiles to a Weibull function, they introduced the concept of an "acceleration factor" (AF), calculated from the ratio of the dissolution rate constants before and after storage. The

temporal progression of this AF was described using an exponential decay model, and predictive equations were established through multiple linear regression to account for different storage conditions (Scrivens, 2019).

A more mechanistically driven approach was later proposed by Tsunematsu et al. (2020), who investigated how changes in the available surface area influence dissolution behaviour. Their model employed surface area-time profiles to calculate parameters such as T22.1 and T63.2, representing the time required to dissolve 22.1% and 63.2% of the surface area, respectively. These kinetic markers provided insight into whether the release mechanism was dominated by disintegration or erosion, and enabled predictive modelling using both linear and non-linear regression, taking into account temperature-dependent effects. (Tsunematsu et al., 2020).

In support of these approaches, the Step 2b, 2025 draft revision of the ICH Q1 guideline offers new flexibility and clarity around the use of predictive modelling in stability studies. It recognises that modelling and simulation, when supported by scientifically sound data, may be used to support shelf-life claims and retest periods. The draft highlights that kinetic models based on chemical degradation mechanisms, such as those following Arrhenius-type behaviour, are acceptable provided they are justified with relevant data and aligned with product-specific understanding. Furthermore, the use of predictive tools during product development is encouraged, especially when they can guide formulation and packaging decisions or anticipate the impact of excursions outside labelled storage conditions. However, it is also emphasised that model-based predictions

should complement, rather than replace, the empirical data, particularly in regulatory submissions (ICH, 2025).

This evolving regulatory perspective marks a significant shift toward science-based, model-informed stability strategies. By combining validated models with supportive long-term data, pharmaceutical developers can enhance the efficiency and accuracy of stability projections. These innovations not only shorten development timelines but also deepen understanding of degradation behaviour, both chemical and physical, across various dosage forms and storage environments.

1.7 Summary of the knowledge gaps

The physical stability of OSDFs remains insufficiently understood, with several key gaps persisting in relation to predictive, formulation-relevant metrics under realistic storage conditions. A key knowledge gap lies in understanding the relationship between stability rate processes at the particle and tablet scales. These processes typically occur much faster at the particle level than in tablets, providing an opportunity to accelerate stability assessments and develop predictive understanding early in formulation development. This thesis aims to bridge these gaps through a multi-scale experimental investigation that integrates particle- and tablet-level analyses under controlled storage conditions. The key gaps addressed are:

1. Understanding moisture-induced excipient changes under vapour exposure (storage-relevant conditions).

The majority of existing studies on excipient swelling focus on direct exposure to liquids (e.g., water immersion), which does not reflect actual storage conditions. Consequently, the behaviour of excipients under vapour-phase humidity remains poorly characterised and understood. There is also limited information on the rate at which these changes develop during storage, which could be critical for early detection of instability. This thesis examines the impact of RH on swelling, particle size, and morphology, offering insights that are more relevant to real-world stability scenarios (Chapter 4).

2. Unclear link between excipient moisture uptake and tablet-level stability.

Although moisture sorption studies using DVS are common, their relevance in predicting tablet behaviour under realistic storage conditions remains underdeveloped. The literature lacks a quantitative framework that connects moisture sorption behaviour at the excipient level with that at the tablet level. Furthermore, the predictive relationship between particle-level and tablet-level responses, spanning different length scales, has not been established. This thesis addresses these gaps by proposing a systematic framework that correlates excipient and tablet moisture sorption behaviour using DVS and demonstrates how moisture-related changes at the particle level can inform predictions of tablet stability (Chapters 5 and 6).

3. Porosity as a dynamic property and its predictability from particle swelling.

Porosity is often treated as a static property determined at the point of compaction, overlooking its potential to evolve during storage. This thesis challenges that assumption

by demonstrating that porosity can change within hours of storage due to moisture-induced particle swelling and tablet expansion. Furthermore, it shows that these porosity shifts can be predicted from particle-level swelling behaviour measured using a static imaging technique. By establishing a quantifiable link between particle swelling and porosity evolution, this work bridges the length scale between particles and tablets, enabling early prediction of structural changes that impact disintegration and performance (Chapter 5).

4. Neglect of porosity-dependent storage effects across formulations.

While tablet porosity is known to influence moisture penetration and disintegration, few studies have systematically examined how porosity modulates storage-induced changes in performance across different formulations. This thesis fills that gap by using tablets of four distinct porosity levels across all formulations, facilitating a clearer understanding of moisture-driven behaviour within varying structural constraints (Chapters 5 and 6).

5. Limited characterisation of liquid uptake and swelling kinetics under storage.

Existing studies often report only equilibrium or endpoint changes, ignoring how the *rate* of liquid uptake and swelling evolves with storage. The absence of kinetic data makes it difficult to explain changes in disintegration behaviour. This thesis captures the dynamic swelling kinetics, including the initial rate and maximum swelling, before and after storage, demonstrating how these kinetic parameters shift and influence disintegration behaviour (Chapter 6).

6. Limited understanding of the time frame over which moisture-induced physical changes occur during storage.

Stability studies typically report changes at standard, often widely spaced timepoints (e.g., 1, 2, 4, or 6 weeks), which may overlook rapid changes that occur shortly after exposure to humid conditions. The specific time frame over which critical changes, such as porosity evolution, strength reduction, or disintegration delays, remains poorly defined in the literature. This thesis addresses this gap by adopting a time-resolved storage design with shorter timepoints (1, 3, 7, 14, and 42 days), enabling the investigation of when key physical changes begin and how they evolve over time. This approach provides a more detailed understanding of the temporal profile of physical instability and supports the refinement of conventional stability testing protocols to include shorter, formulation-relevant timepoints (Chapters 4, 5, and 6).

7. Absence of complementary predictive tools to support or substitute physical stability studies.

Standard physical stability studies depend on real-time or accelerated storage to monitor changes in tablet properties over extended periods. However, the literature lacks predictive tools that can bridge the time scale between rapid, short-term characterisation methods and long-term physical outcomes. In particular, there is no established approach for using short-term moisture uptake data, such as that generated by DVS, to predict tablet behaviour during prolonged storage. This thesis addresses this gap by proposing a predictive framework that uses scaling factors to relate short-term DVS moisture sorption data to long-term storage ones. By establishing this time-scale connection, the work

enables early estimation of storage-induced moisture sorption and offers a potential complementary strategy to conventional stability testing (Chapters 5 and 6).

8. Limited understanding of individual excipient contributions in multi-component systems.

Although multi-component formulations are common, the overlapping effects of different excipients often hinder clear interpretation of individual contributions. This thesis addresses this limitation through a sequential formulation strategy, progressing from simple binary systems to more complex blends incorporating magnesium stearate and lactose. This approach enables the isolated evaluation of each excipient's role in modulating storage-induced changes, which is essential for developing predictive models that generalise across formulation complexity (Chapters 5 and 6).

2.Aim and Objectives

As highlighted in the previous chapter, IR tablets face challenges related to their physical stability under storage, particularly in how moisture and temperature affect tablet properties and, consequently, tablet performance. Understanding the physical stability of tablets requires an in-depth examination of how individual excipients respond to storage conditions and how those responses translate into performance changes in the final dosage form.

The overarching aim of this thesis is to investigate how storage-induced particle-level changes in pharmaceutical excipients influence the physical performance of IR tablets manufactured by direct compression, with a specific emphasis on disintegration. The research further seeks to establish predictive connections between early material responses and long-term tablet outcomes, thereby supporting a multi-scale understanding of physical stability from powder to tablet. A visual summary of the research framework is presented in Figure 2.1.

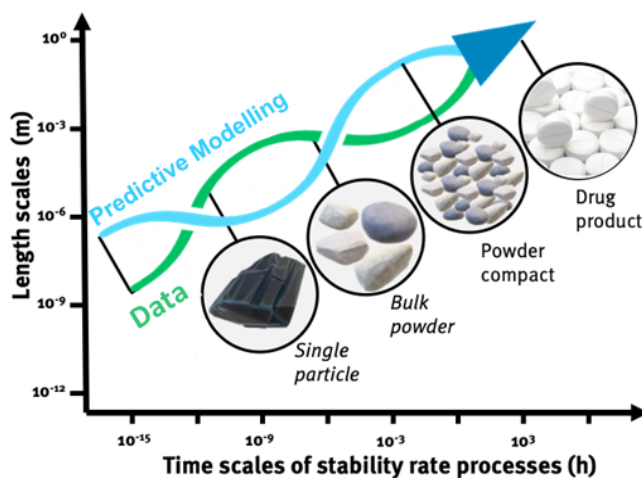


Figure 2.1: Schematic representation of the multi-scale experimental and modelling framework used in this thesis. The study progresses from particle-level excipient characterisation through increasing formulation complexity to final tablet performance. Moisture uptake and swelling data collected at the powder level are used to inform predictive models that link short-term behaviour to long-term storage outcomes.

Building on this framework, the study is structured around the following objectives:

1. **Investigate the stability of the pharmaceutical excipients at the particle scale.**
This involved analysing the moisture sorption and desorption kinetics, as well as the swelling behaviour, of common pharmaceutical excipients. DVS was employed to simulate storage and determine the equilibrium moisture content and rate constants under controlled humidity and temperature conditions. Complementary particle imaging over a 14-day accelerated storage period was used to quantify swelling dynamics and assess reversibility.
2. **Establish links between particle-level changes and tablet behaviour.** Two directly compressed tablet systems with swelling properties (MCC and MCC with 8% CCS) were produced at four porosity levels and stored under accelerated conditions (50°C/75% RH) for up to 42 days with dense early sampling. Structural and mechanical properties, including porosity, dimensions, and tensile strength, were monitored. A predictive framework was then developed to account for particle swelling when estimating porosity changes in stored tablets. Meanwhile, moisture uptake data from the DVS were compared with jar storage results to test the translation of short-term sorption data into long-term storage outcomes.
3. **Investigate the impact of formulation complexity on both the progression and mechanisms of tablet changes during storage.** Using a formulation staircase approach, MCC, CCS, MgSt, and lactose were incrementally combined and compressed into tablets at defined porosities. These were subjected to the same accelerated storage regime (50°C/75% RH, up to 42 days) and analysed for changes

in mass, dimensions, tensile strength, disintegration time, surface liquid absorption, and swelling kinetics. This enabled evaluation of excipient interactions, lubricant effects, and the extent to which the predictive framework established for simpler systems remains valid in more complex formulations.

Collectively, these objectives establish a pathway for connecting particle-level moisture and swelling behaviour with tablet-level performance, demonstrating how early material responses can be extrapolated to explain and predict long-term changes in stored tablets.

3. Materials and Methods

Chapter summary

This chapter outlines the materials and experimental procedures employed across the thesis. It covers the general methods used for raw material characterisation, tablet manufacturing, sample storage, and subsequent analysis of tablet properties. Where necessary, additional methods specific to individual studies are provided within the relevant experimental chapters.

3.1 Materials

3.1.1 Excipients

A full list of excipients studied is detailed in Table 3.1, including CCS, XPVP, L-HPC, and SSG as disintegrants, MCC, mannitol, lactose, and DCPA as fillers, and MgSt as the lubricant.

Table 3.1: Materials used, their suppliers and abbreviations used in this study.

Material	Grade	Supplier	Abbreviation
Croscarmellose sodium	AcDiSol	FMC International	CCS
Crospovidone	Kollidon® CL	BASF Pharma	XPVP
Low-substituted hydroxypropyl cellulose	LH-21	Shin-Etsu Chemical Co.	LHPC
Sodium starch glycolate	Primojel®	DFE Pharma	SSG
Microcrystalline cellulose	Avicel® PH-102	FMC International	MCC
Mannitol	Pearlitol® 200 SD	Roquette	Man
Lactose monohydrate	FastFlo® 316	Foremost Farms USA	Lac
Dibasic calcium phosphate anhydrous	Anhydrous Emcompress®	JRS Pharma	DCPA
Magnesium stearate	Hyqual®5712	Mallinckrodt	MgSt

For the stability study, sodium chloride and magnesium chloride (Merck Life Science, UK) were used to prepare saturated solutions to maintain humidity levels during storage

at 75% RH and 30% RH, respectively. Polyvinyl chloride (PVC) (Sigma-Aldrich, USA) was used as a negative control material due to its non-hygroscopic nature, ensuring that it would not absorb moisture and consequently would not change in size upon exposure to storage conditions (Suherman et al., 2010).

The excipients used in this study were the most commonly used in the pharmaceutical industry for manufacturing directly compressed tablets (Maclean et al., 2021). Choosing different materials with a wide range of physicochemical properties was necessary to understand how this would affect their moisture sorption characteristics. MCC is a hygroscopic and insoluble filler that undergoes swelling upon contact with liquid. DCPA, on the other hand, is a non-hygroscopic and insoluble filler. Both lactose and mannitol serve as soluble fillers (Maclean et al., 2022). Among the disintegrants, CCS, L-HPC, and SSG are classified as swelling disintegrants, while XPVP functions through a shape recovery mechanism (Quodbach and Kleinebudde, 2014).

3.1.2 Saturated salt solution

Saturated salt solutions were prepared using sodium chloride and magnesium chloride to maintain specific humidity levels during storage at 75% RH and 30% RH, respectively (Greenspan, 1977). Excess salt was added to purified water, which was heated to approximately 70°C on a hot plate with continuous stirring to facilitate dissolution and to ensure saturation under conditions relevant to elevated-temperature storage. Salt was added incrementally until no further dissolution was observed. It is essential to be aware that a salt solution that is saturated at ambient temperature may not be saturated at the higher temperatures involved in ASAP studies, as the solubility of some salts rises

dramatically with increasing temperature (Williams, 2018). At this stage, more salt was added to the solution to ensure an excess of solid salt was present. Additional solid salt was added to each vial of the saturated solution to ensure that the solution would remain saturated during storage at high temperatures.

3.2 Methods

3.2.1 Raw material characterisation

3.2.1.1 Moisture sorption and desorption analysis

A dynamic vapour sorption apparatus (DVS, Surface Measurement Systems Ltd., London, UK) was used to understand the dynamics of moisture sorption for the studied raw materials and tablets during storage, i.e., to measure how quickly and how much moisture is sorbed (adsorbed and absorbed). The device features an SMS UltraBalance with a mass resolution of $\pm 0.1 \mu\text{g}$ to monitor the intake and loss of vapour gravimetrically, and a temperature-controlled incubator to maintain a constant temperature at a level of $\pm 0.1^\circ\text{C}$. 10 mg of each powder was placed into the sample pan of the DVS. Then, samples were preconditioned to a constant mass under a stream of dry nitrogen at 0% RH, which was recorded as the sample reference mass. Data was saved every second to help calculate the moisture sorption and desorption rate.

Although moisture isotherms are typically constructed by implementing a series of steps across the entire RH range, this approach will impact the EMC and the rate at which EMC is reached due to pre-moisture exposure from the RH steps used. To address this concern, the rate and extent of water uptake in a one-step simulation were assessed, covering the

range of 30%-75% RH. This method more accurately mimics real-world storage conditions by exposing a sample, intended for a specific RH storage level, to a single-step transition from baseline humidity. The process begins at 30% RH, as measured in the laboratory, and adjusts to the target RH level. For instance, to obtain the sorption/desorption isotherm at 75% RH, the instrument initiated conditioning the sample at 0% RH, then made a direct jump from 30% RH to 75% RH, and subsequently returned to the 30% RH baseline. Moisture sorption/desorption data were analysed at temperatures of 25°C and 50°C. The different conditions studied are summarised in Table 3.2.

Table 3.2: The various % RH levels investigated in the DVS study.

Initial % RH	Target sorption % RH	Target desorption % RH
30	40	30
30	50	30
30	60	30
30	75	30

Two equilibrium criteria (stop criteria) were used to determine when equilibrium had been reached. The first criterion is the rate of change in sample mass with time, dm/dt , which is the change in sample mass (dm) with respect to the time interval (dt). The second is the minimum time during which the sample mass remains stable. In this study, equilibrium was assumed to be attained when the weight change was less than or equal to 0.002%/min over a 10-minute window. If this criterion was not met, the analysis would be continued for a maximum of 6 hours. After that, the equilibrium is assumed to be complete, and the experiment proceeds to the next programmed humidity stage. The

percentage change in mass will be recorded relative to the mass at 30% RH to simulate the case of storing excipients at humidities over 30% RH (which was considered the baseline). A new sample was used for each RH point to minimise any moisture or temperature history effects, with one sample tested per condition. This experimental design was considered appropriate given the ultra-high mass resolution of the DVS system, equipped with a microbalance capable of detecting mass changes as small as 0.1 μg , together with its high baseline stability under tightly controlled temperature and humidity conditions. Preliminary validation experiments confirmed minimal run-to-run variability, demonstrating that a single measurement was sufficient to capture representative sorption kinetics and equilibrium behaviour. In addition, the experimental design encompassed a wide range of conditions, including multiple relative humidity steps and temperature, and tablets compressed at four distinct porosity levels, with each DVS experiment requiring a separate tablet. The primary objective of this work was to establish and validate the concept of scaling DVS-derived moisture uptake kinetics to real storage behaviour across formulation and structural space. Within this proof-of-concept framework, emphasis was placed on systematic comparison across materials, porosities, and conditions rather than statistical replication within individual conditions. Accordingly, the use of a single measurement per condition was sufficient to demonstrate the robustness and applicability of the proposed scaling approach while enabling efficient exploration of multiple formulation and tablet variables. Because of this design, statistical analysis was not conducted or required.

Figure 3.1 shows the DVS profile from (30-75% RH), demonstrating the steps involved in the analysis.

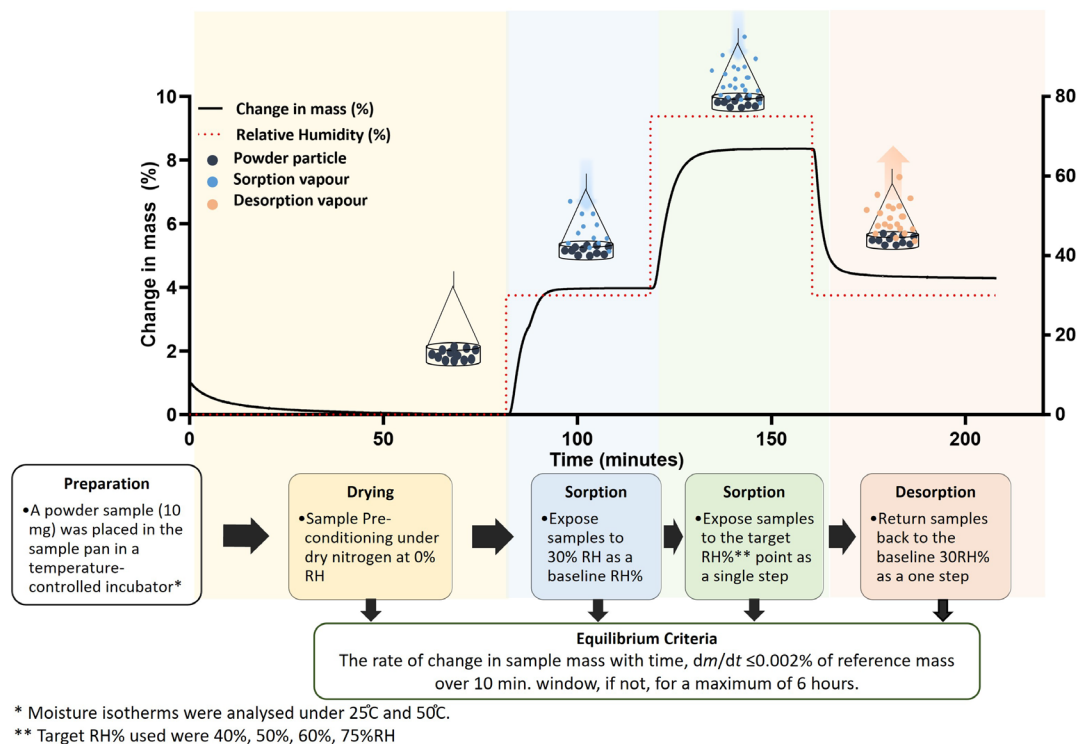


Figure 3.1: Example of DVS profile demonstrating the change in mass for MCC particles with time. The DVS profile's sectional analysis reflects the various RH conditions used.

3.2.1.2 Moisture sorption and desorption rate constant model

DVS sorption and desorption time data were used to calculate the moisture sorption/desorption rate constant ($r_{\text{sor/des}}$) to understand the dynamics of moisture sorption/desorption and the effect of RH level and temperature on the rate of

sorption/desorption. A model was developed to calculate the kinetic rate constants by fitting the temporal sample mass at a specified temperature and humidity:

$$M(t) = M_0 e^{-r_{\text{sor/des}} t} + M_{\text{max/min}} (1 - e^{-r_{\text{sor/des}} t}) \quad \text{Eq. 3.1}$$

Where $M(t)$ is the mass at a time (t), M_0 is mass as $t = 0$, $r_{\text{sor/des}}$ is the kinetic rate constant for sorption (r_{sop}) and desorption (r_{des}), and $M_{\text{max/min}}$ is either the maximum mass during sorption EMC or the minimum mass during desorption. Model fitting and data analysis were performed using Python 3.9.7 (Python Software Foundation, Virginia, USA) using the SciPy "curve_fit" function. Model performance was evaluated using the coefficient of determination (R^2) and the root mean square error (RMSE). CIs were calculated but omitted from results for clarity when their values were negligible ($<9 \times 10^{-4}$).

Eq. 3.1 adopts a single exponential, pseudo-first order form, in which the rate of change in moisture content is proportional to the difference between the instantaneous value and the equilibrium moisture content. While DVS measurements capture the combined gravimetric contribution of both surface adsorption and bulk absorption, the mathematical form of this equation corresponds to adsorption-type kinetics, characterised by a single dominant time constant. Absorption-related processes such as diffusion into the bulk, moisture redistribution within pores, swelling, and structural relaxation are therefore not explicitly resolved by the model, even though they may contribute to the observed mass change.

This interpretation implicitly relies on a number of simplifying assumptions. Moisture concentration within individual particles is assumed to be spatially uniform at any given time, implying that internal diffusion is effectively instantaneous relative to the overall sorption timescale. Consequently, the rate-limiting step is assumed to be moisture transport across the solid-vapour interface rather than diffusion within the particle or pore network. In addition, a linear relationship is assumed between the sorption driving force and the difference between instantaneous and equilibrium moisture content, consistent with pseudo-first order kinetics. Particle and tablet volume are also assumed to remain constant during the sorption step, such that swelling, structural relaxation, or changes in internal structure do not explicitly influence the fitted kinetics.

As a result, the extracted rate constant should be interpreted as an effective sorption rate constant, representing the kinetics of moisture sorption processes rather than a mechanistic parameter associated with a specific transport phenomenon. This simplified approach is used to enable consistent comparison across materials, formulations, and conditions, while avoiding over interpretation of the rate constant as a fundamental material property.

The kinetic model used to determine the rate constants was originally developed by Mark Carroll for the manuscript "Particle-based investigation of excipients stability: the effect of storage conditions on moisture content and swelling."¹

¹ All experimental data collection, model fitting, and analysis of the kinetic models presented in this thesis were performed by the author.

3.2.1.3 True density

True density (ρ_{true}) measurements of raw materials were conducted using gas pycnometry (MicroUltrapyc 1200e, Quantachrome, USA) with nitrogen gas. Measurements were taken in triplicate for each sample.

3.2.1.4 Particle size analysis

Particle size analysis of swelling excipients was determined using the Morphologi4® particle characterisation system (Malvern PANalytical, UK). It is a wholly automated static-image analysis-based particle characterisation device that provides particle size and shape information. The technique can measure the size and shape of particles down to less than 0.5 μm in size by using a variety of lenses. As a result of the system's ability to capture every particle, it can give information on particle size and shape in terms of both volume (geometric) and number (arithmetic) (Gamble et al., 2011).

Particle imaging was conducted using a 10X magnification lens with z-stacking enabled to take four planes above the initial point of focus to account for the changes of the sample in z-direction due to swelling. Z-stacking also reduced the blurring observed around the particles after removal from storage due to moisture diffusion. The threshold of particle detection was adjusted to ensure the detection of the whole parts of the particle, as well as dark and bright particles. Morphological filtering was applied manually to the raw image data to eliminate partially imaged or overlapping particles. All samples were analysed according to the method summarised in Table 3.3.

Table 3.3: Method used for image analysis.

Parameter	Set value
Sample volume	5 mm ³
Solid dispersion unit settings	Injection pressure: 1 bar (for CCS and MCC) and 2 bar for SSG Injection time: 20 ms Settling time: 60 s
Illumination	Diascopic (bottom light) bright field
Optics selection	10X
Light intensity	80%
Focus	Manual focus
Trash size	10 pixels
Z-stacking	4 planes, equivalent to 48.9 μm

The circle equivalent diameter (CED) was used as the primary particle size descriptor, which is the diameter of a circle with the same area as the 2D image of the particle. The CED is calculated by:

$$CED = \frac{\sqrt{4 A_p}}{\pi} \quad \text{Eq. 3.2}$$

where A_p is the projected area of the particle (Malvern Panalytical, 2021). Shape descriptors including convexity, high sensitivity-circularity (C_{HS}), and aspect ratio (AR) were also extracted to provide additional information on particle morphology:

$$C_{HS} = \frac{4A_p\pi}{P^2} \quad \text{Eq 3.3}$$

$$AR = \frac{B}{L} \quad \text{Eq. 3.4}$$

Where P is the particle perimeter, B is the width, and L is the length. A value between 0 and 1 was assigned to each particle; typically, the aspect ratio and circularity values approach 1 for spherical particles and 0 for elongated particles. Convexity, on the other hand, is a measure of the surface roughness of a particle where a perfectly smooth shape is characterised by a convexity of 1, whereas a more 'spiky' or irregular object tends to have a convexity closer to 0 (Malvern Panalytical, 2021).

3.2.2 Tablet manufacturing

Powder blends (200 g per batch) were prepared in a 0.5 L blending vessel using a Turbula T2GE blender (Willy A. Bachofen, Switzerland) at 35 rpm for 5 minutes, with an additional 1-minute blending step after adding MgSt. Powder was then introduced into the die using a hopper. Round, flat-faced tablets were manufactured using direct compression via a compaction simulator (HB50, Huxley-Bertram Engineering, Cambridge, UK), equipped with 5 mm round, flat-faced punches, to produce tablets with a target weight of 50 mg. While the diameter and weight remained consistent, the thickness was adjusted to achieve varying levels of tablet porosity to achieve tablets with four different porosities of 10%, 17%, 22%, and 29%. Following manufacturing, tablets were allowed to equilibrate and relax for a week at a controlled room temperature of $(25.1 \pm 0.2^\circ\text{C})$ and humidity of $(30.2 \pm 3.5 \% \text{ RH})$ before measuring the final thickness, from which porosity was calculated using Eq. 3.5.

$$f_b(\%) = \left(1 - \frac{4 W_{t,b}}{D_b^2 H_b \pi \rho_{\text{true}}} \right) \times 100 \quad \text{Eq. 3.5}$$

To calculate the porosity of tablets before storage (f_b), the weight ($W_{t,b}$), diameter (D_b), and thickness (H_b) of the compacted tablet were measured (Bawuah et al., 2021). The true density of the tested formulations was calculated as the weighted harmonic mean, considering the true density and the weight fraction of each component (Sun, 2004). Porosity before storage was then determined as the average of 10 tablets per formulation. Throughout this thesis, the subscript b denotes parameters measured before storage, while a refers to measurements taken after storage.

3.2.3 Tablet storage

Each tablet was placed in an open vial, along with a vial filled with a saturated sodium chloride solution to establish the required humidity level. The vials were then placed inside airtight glass jars sealed with parafilm and stored in temperature-controlled chambers at 50°C for the specified duration.

Figure 3.2 represents the experimental set-up utilised for tablet storage during the stability investigation. To ensure precise monitoring of temperature and humidity, iButton data recorders (DS1923 Hygrochron iButton, Measurement Systems Ltd, UK) were added to each jar. These data loggers recorded temperature and humidity data at 10-minute intervals throughout the storage period, enabling consistent monitoring of environmental conditions. Tablets were subjected to accelerated storage conditions at 50°C and 75% RH to evaluate their stability. Time points for sample collection were carefully selected, as

storage conditions were expected to influence particles more rapidly than tablets. The selection of time points in this study was informed by the findings of Maclean et al. (2022), who reported that most changes in tablet physical properties occurred within the first two weeks of storage before reaching a steady state (Maclean et al., 2022). Stability analysis of the tablets was conducted at six different time points: initial, 1, 3, 7, 14, and 42 days. A fresh tablet was used for each time point. After storage, three weeks were allowed for sample stabilisation under ambient conditions before analysis. This waiting period ensured accurate tablet measurements by minimising potential fluctuations due to residual moisture absorbed during storage. However, tablet weights and dimensions were monitored throughout this equilibration period. Triplicate analyses were performed for each time point and each test to ensure the reliability and consistency of results. The recorded storage and resting conditions were ($49.8^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ / $77.7\% \pm 1.3\%$ RH) and ($25.1^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ / $30.2\% \pm 3.5\%$ RH), respectively.

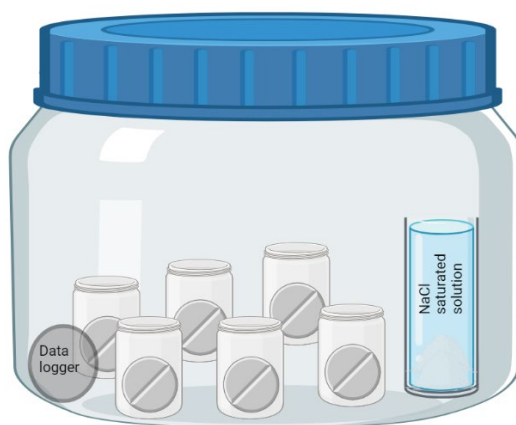


Figure 3.2: Tablet storage set-up during the stability study.

3.2.4 Tablets Characterisation

Tablet characterisation was conducted on every tablet, both before and after storage, enabling the tracking of the same tablet throughout the study, except for destructive tests such as tensile strength assessment. New tablets were also used at each time point.

3.2.4.1 Moisture sorption dynamics and capacity

To assess the impact of tablet porosity and raw material addition on their moisture sorption capacity and rate, the DVS method, previously used for powder moisture sorption analysis, was employed on tablets under the same conditions (3.2.1.1 and 3.2.1.2). For each RH condition, a new tablet was utilised, with one tablet tested per condition. Findings were documented as a percentage change in mass (EMC (%)), referencing the tablet's mass at the end of the (0-30% RH) stage.

To facilitate comparison between DVS and real storage conditions, the equilibrium moisture content obtained from DVS measurements was compared to the weight changes observed in tablets stored under real laboratory conditions at 50°C and 75% RH using the jar method. Additionally, the model used to calculate the sorption rate constant in (Eq. 3.1) was fitted to the real storage data to determine the sorption rate constant. To differentiate between data obtained under real storage and DVS conditions, the subscripts "real" and "DVS" were used for tablet data throughout Chapters 5 and 6. Accordingly, $r_{\text{sor-real}}$ and $r_{\text{sor-DVS}}$ refer to the sorption rate constants obtained from real storage (jars method) and DVS experiments, respectively.

3.2.4.2 Weight, dimensions, and tensile strength

The weight of each tablet was measured with precision to the nearest 0.01 mg using an analytical balance (Sartorius Quintix-124-1S, UK). Subsequently, the diameter and thickness of each tablet were measured using a micrometre (RS Pro Electronic Micrometre 0-25 mm; RS Components Ltd., Corby, UK) and recorded to the nearest 0.01 mm.

Tablet tensile strength was assessed using a hardness tester (Kraemer Elektronik Hardness Tester, GmbH, Darmstadt, Germany). Tensile strength (σ_t), calculated using breaking force (F), diameter (D), and thickness (H) of the tablet with Eq. 3.6 (Fell and Newton, 1970).

$$\sigma_t = \frac{2 F}{\pi D H} \quad \text{Eq. 3.6}$$

The relationship between tablet porosity (f) and σ_t , known as compactibility, was explored using the Ryshkewitch-Duckworth equation (Eq. 3.7) (Duckworth, 1953) to determine the slope and intercept, referred to as the bonding capacity factor (b), and the tablet tensile strength at zero porosity (σ_0).

$$\sigma_t = \sigma_0 e^{-b f} \quad \text{Eq. 3.7}$$

The reported values for tablet weight, porosity, and tensile strength before storage represent the average measurements obtained from ten tablets for each formulation, while those after storage represent the average of three tablets at each time point.

3.2.5 Data analysis and visualisation

All data analysis and graphical visualisations were performed using GraphPad Prism (version 10.6.0; GraphPad Software, San Diego, USA). The software was used to perform linear regression analysis and generate all plots, including scatter plots, fitted trend lines with regression equations, and heat maps used for data comparison and visual representation.

The primary aim of this thesis was to establish mechanistic understanding and predictive frameworks linking moisture sorption behaviour to time-dependent changes in tablet properties, rather than to perform inferential hypothesis testing between populations. Independent tablet samples were analysed at each storage time point and compared with their initial values before storage, rather than repeatedly measuring the same sample over time. While this approach enables assessment of the progression, magnitude, and timing of storage-induced physical changes, the study was not designed to support statistical comparisons between discrete time points. As the formulation space and storage conditions investigated were intentionally limited, and many reported parameters, including moisture content and sorption rate constants were derived from single-sample measurements characterised by high instrumental precision, classical statistical hypothesis testing was not applied. Differences between formulations, porosities, and storage times are therefore interpreted in terms of consistent directional change and temporal evolution, rather than statistical significance.

For all statistical modelling and prediction exercises, R^2 , RMSE, and corresponding CIs were calculated and are reported in the relevant appendices.

4. Particle-based investigation of excipients' stability: the effect of storage conditions on moisture content and swelling

Chapter summary

This chapter examines the moisture sensitivity of eight widely used excipients in OSDFs using DVS to characterise moisture sorption/desorption under controlled humidity conditions representative of storage environments. Equilibrium moisture content, sorption/desorption kinetics, and humidity-induced particle swelling are characterised, revealing irreversible swelling for CCS and SSG and partial reversibility for MCC. These findings advance the understanding of excipient-moisture interactions.

This chapter is based on the following publication:

Ibrahim, I., Carroll, M., Almudahka, A., Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., & Markl, D. (2025). Particle-based investigation of excipients stability: The effect of storage conditions on moisture content and swelling. *RSC Pharmaceuticals*, 10.1039.D4PM00259H. <https://doi.org/10.1039/D4PM00259H>.

Isra' Ibrahim's contribution to the peer-reviewed paper:

- a. Responsible for the entire experimental work and data analysis, which includes the design of the experimental procedure, creation and subsequent analysis of all samples and presentation of data.
- b. Wrote the entire manuscript and implemented any corrections and comments provided by the co-authors and the reviewers.

4.1 Introduction

Excipients are essential components incorporated into pharmaceutical formulations for various purposes, ranging from facilitating manufacturing processes and sustaining product stability to enhancing bioavailability, as well as improving patient acceptability and compliance (Darji et al., 2018). Although excipients are considered pharmacologically inactive, they are far from inert within a formulation. Instead, they play an active role in the physical aspects of the dosage form, as they comprise a significant majority of the final formulation. It has become widely recognised that the performance of a dosage form is closely linked to the physical and chemical properties of all its ingredients (Chamarthy et al., 2009; Viljoen et al., 2014). Consequently, excipient properties affect various quality attributes of the drug product, including drug release, friability, tensile strength, appearance, and stability. Among these attributes, stability stands out as a particularly crucial aspect for a drug product to be released to the market (Veronica et al., 2023).

Stability testing is a routine part of drug development, traditionally focusing on chemical stability and loss of potency. Equally important is the assessment of physical stability, which is influenced by the physicochemical characteristics of the components, including particle size, morphology, moisture content, and polymorphic form (Guo et al., 2013; Williams, 2018). Pharmacopeial monographs, manufacturers, and researchers examine different material properties that affect performance and stability (Berardi et al., 2022). Among the many influencing factors, temperature and moisture are the main drivers of instability in tablets (Bajaj et al., 2012).

Water plays a crucial role in various stages of pharmaceutical product manufacturing, directly contributing as a component in processes like wet granulation or coating. Environmental moisture during packaging, transportation, storage, and usage also indirectly affects drug product attributes (Veronica et al., 2022). Moisture is adsorbed in the form of monolayers or multilayers, or it may exist as condensed water on the surface. The presence of moisture will not only change the pharmaceutical and mechanical properties of the final product. Still, it may also pose a risk of physicochemical instability, ultimately affecting the effectiveness of the drug as well (Rajabi-Siahboomi et al., 2015). The interaction of moisture with different materials is connected to the chemical affinity of their particles, their physical properties such as particle size, specific surface area, and porosity, and on the ambient RH and temperature of the environment (Ahlneck and Zografi, 1990; Airaksinen et al., 2005; Garr and Rubinstein, 1992). Consequently, every element in a formulation possesses a distinct affinity for moisture, so it is crucial to understand their specific interactions with moisture concerning their behaviour at various RH levels and the resulting influence on the performance of the product. In a study conducted by Dalton and Hancock (1997), notable variations in the water sorption tendencies of formulations were observed, primarily due to the considerable differences in how the excipients absorbed water (Dalton and Hancock, 1997). Starch and cellulose excipients, commonly used in OSDFs, are particularly affected by the hydrogen bonding between water and solid molecules (Rajabnezhad et al., 2020).

To characterise water associated with these excipients, moisture sorption isotherms are established. This provides valuable insights into the equilibrium moisture levels and

moisture retention capacities of materials under specific temperature and humidity conditions. Hysteresis, observed with starch and cellulose-based excipients, occurs during desorption, where some water molecules remain within the powder and cannot be dissociated at the same equilibrium RH level, attributed to the particles' swelling and changes in the conformational structure. This alters the accessibility of binding sites for water molecules, leading to incomplete removal of water molecules during desorption (Caurie, 2007; Rajabnezhad et al., 2020; Salmén and Larsson, 2018). As a result, the moisture affinity of a material can be influenced by its prior exposure to moisture or its history of moisture exposure (Veronica et al., 2023). Analysing sorption isotherms can uncover information about water interactions with particles and understand water adsorption and desorption extents under different RH levels. This is of practical importance, as it can directly affect the performance and stability of the drug product.

Among the excipients significantly affected by water sorption are disintegrants. The swelling of their particles when they come into contact with a physiological fluid is essential for disrupting interparticulate bonds within the tablet, thereby enhancing tablet disintegration, promoting dissolution, and facilitating drug release (Omidian and Park, 2008; Quodbach and Kleinebudde, 2016). In addition to disintegrants, other excipients, such as MCC, which is typically used as a diluent, filler, or binder, can also experience swelling, thereby playing a role in the tablet swelling process (Desai et al., 2016). The swelling of these particles primarily relies on two key factors: the water diffusion coefficient and the maximum absorption ratio ($Q_{\max}$), which is the ratio of the mass of hydrated particles to the mass of dry particles. While $Q_{\max}$ can be experimentally

measured through straightforward weighing methods, determining the diffusion coefficient directly is often more challenging (De Richter et al., 2022). These excipients are considered inert in the dry tablets. Still, they should cause the tablet matrix to swell and disintegrate rapidly in the patient, accelerating the dissolution of the drug particles. Any prior exposure of these agents to moisture or liquid will impact their moisture affinity and physical properties, potentially leading to a loss of disintegrant power due to the possibility of "pre-activation" of the disintegrant swelling and influencing the performance and stability of the dosage form (Berardi et al., 2021; Maclean et al., 2022).

Considerable research efforts have been directed toward quantifying the swelling behaviour of particles in response to liquid water. Soundaranathan et al. (2020) used an optical microscope paired with a custom flow cell and utilising a single particle swelling model to quantify the swelling characteristics of different disintegrants (SSG, CCS, and LHPC) along with five grades of MCC (Soundaranathan et al., 2020). They demonstrated that the swelling behaviour varied among the different excipients, with CCS exhibiting the highest diffusion coefficient and SSG showing the highest maximum absorption ratio. Zhao and Augsburger (2005) utilised laser diffraction to quantify the intrinsic swelling of disintegrants in a suspension, finding that SSG exhibited a superior swelling capacity compared to CCS (Zhao and Augsburger, 2005a). Rojas et al. (2012) evaluated the swelling properties and water uptake capabilities of SSG, CCS, and MCC powders in simulated gastric and intestinal fluids, finding that SSG exhibited the highest water uptake ability and swelling value, followed by CCS and MCC (Rojas et al., 2012).

Investigations into the behaviour of excipients in response to humidity have predominantly concentrated on the impact of water at or near its saturation point. To the best of the authors' knowledge, none of these studies has explored the swelling of particles induced by moisture in the gaseous phase during storage. It is noteworthy that the variations in water absorption observed below 96% RH may not align with findings at 99.98% RH (Lovikka et al., 2018). This limits the relevance of research outcomes derived from fully saturated conditions for stability studies at lower RH levels. Furthermore, there is also a gap in the literature regarding how moisture affects the particle size of these swelling excipients, as the bulk of research efforts have been devoted to exploring the effects of storage conditions on tablets containing these excipients.

The primary objective of this study is to thoroughly investigate the impact of storage conditions, both moisture and temperature variations, on the intrinsic properties of eight commonly used excipients in OSDFs. Specifically, this study focuses on the moisture content and moisture sorption kinetics in a manner that reflects the dynamic simulation of moisture sorption in practice, using DVS paired with a mathematical model. The temporal effect of sorbed moisture on the particle size distribution of potential swelling excipients MCC, CCS, and SSG is also discussed.

4.2 Materials and methods

4.2.1 Materials

All materials used in this study are described in Section 3.1.

4.2.2 Moisture sorption and desorption analysis

Moisture sorption/desorption isotherms for each excipient were collected as described in Section 3.2.1.1.

4.2.3 Sorption and desorption kinetic rate constants

The model used to calculate the rate constants for moisture sorption/desorption kinetics was described in Section 3.2.1.2.

4.2.4 Storage-induced particle size changes

The experimental method was carefully designed to accurately quantify the micro-scale changes to particles stored for a specific time under accelerated humidity and temperature conditions. The primary consideration was to ensure that individual particles are exposed to storage conditions, rather than the bulk of a powder, where particles close to the surface experience a different exposure to the environment compared to those in the core of the bulk. This study focused on swelling particles only: CCS, SSG, and MCC.

4.2.4.1 Excipients dispersion and powder storage

Powders of raw materials were thoroughly mixed in the primary container by hand rolling and inversion before taking samples to ensure a representative sample was obtained. Samples of 5 mm³ were scooped using special spoons designed for the instrument and then dispersed as a thin layer on glass Petri dishes using the Morphologi 4[®] (Malvern PANalytical, UK), which features a sample dispersion unit that utilises a laboratory's compressed air supply. The general objective was to achieve a dispersion with as many particles as possible in each frame without physically touching each other so that all

particles experience the same environment. A low-pressure value of 1 bar was used to disperse MCC and CCS, ensuring that air dispersion would not affect the particles in any way. In contrast, a pressure of 2 bar was used for the dispersion of SSG due to the possible appearance of aggregates. Powders dispersed over plates were subsequently analysed for their particle size and shape parameters. This will serve as a reference for comparison after removal from storage.

4.2.4.2 Powder storage

Powder of swelling excipients was stored at three different temperature and humidity conditions (Table 4.1) to assess the effect of accelerated storage conditions on their particle size parameters. Temperature and humidity were tracked in each jar while the powders were stored using iButton data recorders as described in Section 3.2.3. The actual storage conditions, as recorded by dataloggers, are provided in Table A.1 in Appendix A.

A single plate of each powder, along with a vial filled with a saturated salt solution to establish the required humidity level, was placed inside an airtight glass jar. Jars were then stored in temperature-controlled ovens at 25°C or 50°C for the designated storage duration. Figure 4.1 illustrates the experimental set-up employed for storing powder samples throughout the stability study.

Table 4.1: Accelerated stability storage conditions of raw materials.

Temperature (°C)	Humidity (% RH)	Time points (days)
25	75	1, 14
50	30	1, 14
50	75	1, 3, 14

Particle size distribution analysis was carried out in triplicate for each time point under 50°C/75% RH condition, indicating that three separate samples were analysed at each time point. In contrast, a single sample was utilised for each time point under 25°C/75% RH and 50°C/30% RH. The corresponding time points are listed in Table 4.1.

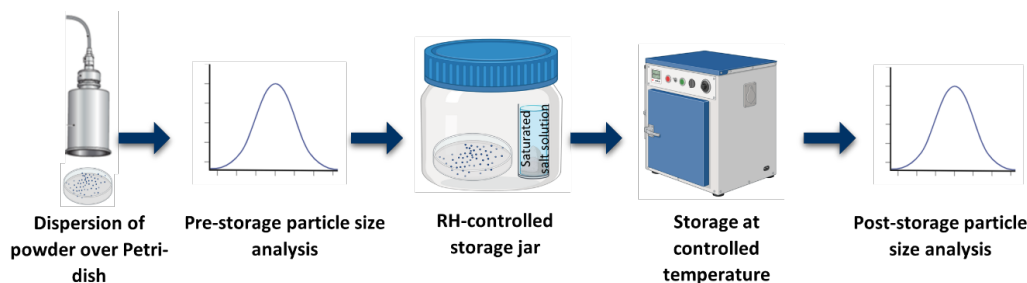


Figure 4.1: Powder dispersion and storage set-up for the particle size analysis.

4.2.4.3 Particle size analysis

Particle size and shape measurements of excipients before and after storage were conducted according to the method described in Section 3.2.1.4. To study the effect of storage conditions (if any) on the particle size, size distribution, or shape parameters, plates were removed from storage jars at a specific time point to be analysed. For each time point, a new dish was used. Particle size distributions were initially obtained for each excipient before storage, then analysed again after storage, while they were on the same plate without touching the particles to ensure no agglomerates formed due to moisture. This approach facilitated the comparison of the measured particle distribution post-storage with the initial distribution obtained before storage for each dish. Comparing the same sample before and after storage facilitated the tracking of any alterations in particle size distribution attributed to storage. This is because even with good sampling

techniques, differences in size distribution may exist; therefore, this method accounts for such variations during the comparison.

To assess the reliability of this methodology, a careful approach has been followed, incorporating key measures aimed at validating the integrity of the results. Firstly, the experiment was systematically performed on multiple replicates to assess the consistency and reproducibility of findings. Secondly, a controlled material, PVC, characterised by its resistance to moisture-induced swelling, was selected to ensure that variations in particle size are not influenced by external factors other than moisture absorption. Furthermore, a precise adjustment was made to the threshold parameters, creating a controlled variance of $\pm 5\%$. The threshold was adjusted to reflect a level that might reasonably be selected by different operators, in order to assess the sensitivity of the particle size analysis to subjective threshold selection and to ensure that the estimated particle size metrics were not driven by operator-dependent threshold choices. This precautionary measure helped ensure the accuracy of the size analysis by confirming that any detected changes in size distribution were exclusively caused by moisture, and not a consequence of threshold selection and modification. To carefully investigate the reversibility of particle size change following removal from storage, particles were allowed to equilibrate with the controlled laboratory humidity and temperature. The equilibration period lasted between one week and one month, after which the samples were analysed again.

Due to moisture diffusion through the particles during storage under humid conditions, a fraction of the smaller particles became transparent, causing an artefactual increase in

the frequency of larger particles. Therefore, the number of particles was also used to visualise the results of the CED.

4.3 Results and discussion

4.3.1 Effect of RH level on EMC and kinetic rate constant

The moisture sorption/desorption properties of each excipient were measured using the DVS to simulate the conditions used in practice. Figure 4.2 illustrates the EMC at various RH levels for the different excipients under investigation. The data is presented as a percentage change in mass relative to the mass recorded at 30% RH. Additionally, the EMC relative to the dry mass of powder at 0% RH is provided in Figure A1 in Appendix A, with PVC data included as a control.

According to the moisture sorption results, lactose, mannitol, and DCPA are non-hygroscopic and do not absorb moisture substantially; even under high RH conditions, the mass change was less than 1%. On the contrary, disintegrants showed very high hygroscopicity (Figure 4.2A). CCS and SSG absorb approximately 16% moisture in the 30-75% RH range, while XPVP absorbs nearly 20% at the same % RH at 25°C. Moisture sorption results, expressed as a ratio to the dry mass of the powder, are consistent with prior findings (Airaksinen et al., 2005; Maclean et al., 2022; Rowley and Mackin, 2003). The difference in moisture capacities among excipients is attributed to their different interactions with moisture depending on their chemical properties and polarity, as well as on the RH, temperature, particle-size distribution, specific surface area, and porosity of the material (Airaksinen et al., 2005).

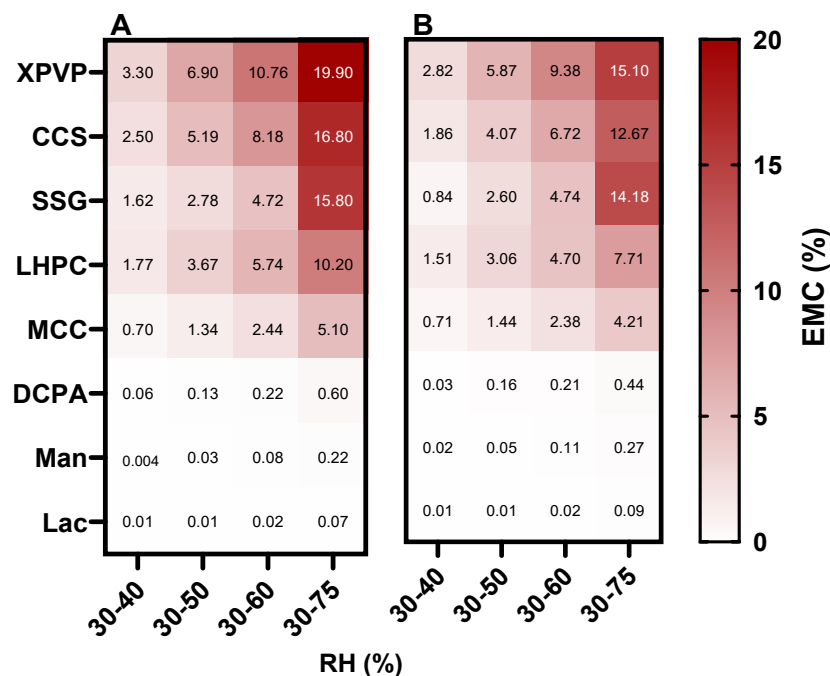


Figure 4.2: Equilibrium moisture content of excipients at 25°C (A) and 50°C (B), presented relative to the mass at 30% RH.

Crystalline, non-hygroscopic excipients, such as lactose and mannitol, exhibit limited moisture gain with no monolayer formation; however, delayed multilayering occurs. At low RH, water is adsorbed onto the crystalline material's surface. As RH increases, weak interaction forces, such as van der Waals forces, cause water molecules to attach at the sugar-vapour interface. This limited water uptake behaviour is attributed to their low surface area and stable crystalline lattice, supported by stable hydrogen bonding networks, which minimise available binding sites for moisture adsorption in these crystalline sugars (Bronlund and Paterson, 2004; Hancock and Shamblin, 1998). A tendency for multilayer sorption is expected as RH increases, and at high humidity (generally over 65% RH), solid water-soluble sugar molecules dissolve, forming a

saturated sugar solution (Airaksinen et al., 2005; Bronlund and Paterson, 2004). Our findings show that the water content of lactose and mannitol remains relatively small at the studied RH ranges. On the other hand, starches and cellulose-based excipients exhibit higher moisture gain, which involves the sequential sorption of a single tightly bound water molecule, followed by less tightly bound water molecules, and additional sorption of free water. They generally demonstrate substantial bulk absorption of water, characterised by a slow diffusion-controlled mechanism (Airaksinen et al., 2005; Zografi and Kontny, 1986).

Increasing humidity levels also resulted in higher moisture uptake, with powders exposed to 75% RH levels exhibiting the most significant moisture uptake compared to those at other RH levels. This observed correlation between moisture uptake and RH is consistent with prior findings (Li et al., 1994; Visalakshi et al., 2005).

DVS isotherms do not indicate a true affinity for water vapour since the data present the total sorption capacity of each excipient in terms of mass change from the dry mass as a function of humidity, with no reference to the timescale. As observed from the moisture uptake results, there can be similarities in sorption capacity between excipients, which suggests that the behaviour of these materials at these humidities towards water vapour is similar. However, in reality, differences in their performance indicate different interactions. To further classify the excipients in terms of their behaviour to water vapour, the DVS sorption time data were used to calculate the rate at which they adsorb or desorb moisture. Figure A.2 in Appendix A compares the change in mass as a function of time

for CCS and MCC, where the time required to achieve equilibrium is higher for CCS compared to MCC, despite using the same sample size and conditions.

Knowing how quickly a material absorbs moisture is essential for predicting its stability during storage. The moisture sorption kinetic rate constant model was applied to all DVS sorption/desorption time data and compared to the measured data, as shown in Figure A.3 in Appendix A. The accurate prediction performance of the moisture kinetic rate constant model is provided in Table A.2 in Appendix A, as indicated by its high R^2 and low RMSE, except for mannitol and lactose at low RH. However, non-hygroscopic excipient data should be interpreted carefully, as the readings are more prone to measurement noise due to minimal changes in mass. A summary of the calculated kinetic rate constants extracted from DVS time data for all excipients tested in this work, during both sorption and desorption, is shown in Figure 4.3.

Generally, CCS, SSG, and XPVP consistently tend to take a longer time to reach equilibrium (Figure 4.3A), but they exhibit greater mass sorption under the studied conditions. In contrast, non-hygroscopic excipients, such as mannitol, lactose, and DCPA, achieve equilibrium more rapidly with a higher rate constant of moisture sorption compared to hygroscopic excipients. This trend extends to desorption (Figure 4.3B), where CCS, SSG, and XPVP exhibit the smallest desorption rate constant, indicating a longer time to return to the 30% equilibrium level, while DCPA and mannitol reach the equilibrium humidity level the fastest. It is noteworthy to mention that similar observations have been documented by Heidemann and Jarosz (1991) with different formulations, showing that excipients exhibiting a higher capacity for moisture sorption

tend to achieve equilibrium more slowly compared to those with lower moisture affinity (Heidemann and Jarosz, 1991).

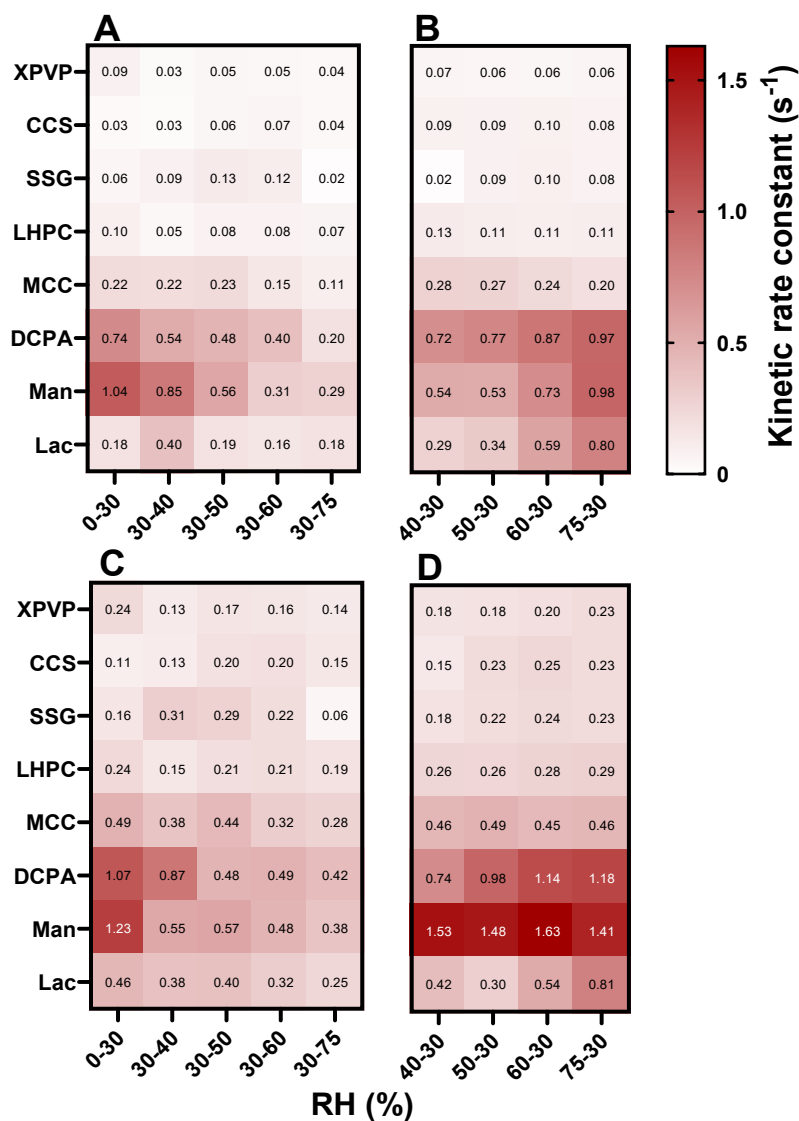


Figure 4.3: Kinetic rate constants of the tested excipients for moisture sorption and desorption at both 25°C (A and B) and 50°C (C and D) as a function of % RH steps. (A) and (C) represent moisture sorption, while (B) and (D) represent moisture desorption.

At a specific humidity level, the desorption rate constants were higher than the sorption rate constants, suggesting faster moisture loss for the studied excipients compared to

moisture gain. A few exceptions were observed with SSG, mannitol, and lactose. Sorption rate constants depend on the target RH, where they are generally higher at lower humidity levels (30% and 40% RH) and smaller humidity increments compared to larger ones (75% RH). This implies that moisture sorption occurred more rapidly at smaller humidity steps and when targeting lower humidity levels, as opposed to larger humidity steps and higher target RH percentages for the tested excipients, which require a longer time to reach equilibrium. This is attributed to the saturation of available binding sites for moisture sorption, which initiates with the rapid formation of a firmly bound monolayer of water molecules on the surface of dry particles with the entry of the initial water molecules into the system. This process depends on surface binding and diffusional forces. As more water molecules are attached to the surface, the moisture-binding sites become saturated, and the diffusional forces begin to outweigh the binding forces. As the moisture starts to diffuse into the bulk, the rate of moisture absorption depends on the difference between the saturation moisture content and the moisture content at a given time. As sorption progresses, the increasing moisture content diminishes the driving force, leading to a gradual reduction in the sorption rate.

Multiple layers of moisture that are less tightly bound to the surface or condensed into the pores, which is associated with swelling in the case of non-rigid porous structures, may also occur. At higher humidity levels, the amount of unbound water increases, which behaves like pure water that is lightly adsorbed and loosely bound to the surface of the particles (Airaksinen et al., 2005; Khazaei, 2008). The process of moisture sorption ceases when the particles reach saturation in moisture content. On the contrary, the

desorption rate constants exhibited less sensitivity to both the humidity level and the humidity step size. Nevertheless, it is noticeable that, at higher RH levels, the rate of moisture desorption was higher. This can be attributed to the presence of more unbound free water molecules, which could be easily removed from the system. In contrast, at lower % RH levels, the available water molecules tend to be tightly bound in monolayers or condensed within pores, requiring a longer time to be removed. In summary, it's crucial to recognise the pivotal roles that both sorption isotherms and sorption kinetics play in fully understanding and characterising materials and predicting their behaviour to moisture under different storage conditions.

4.3.2 Effect of temperature on EMC and the kinetic rate constant

The effect of temperature is a critical factor that must be addressed, particularly in the context of storage conditions. Water molecule mobility and the dynamic equilibrium between the vapour and adsorbed phases could both be influenced by temperature. The effect of increasing the temperature to 50°C on moisture uptake is shown in Figure 4.2B.

At low humidity levels, temperature appears to have minimal impact on excipient moisture content. However, notable differences in EMC emerged at 50°C under high RH levels. Figure 4.4 shows the relative change in moisture content as temperature increased from 25°C to 50°C at 30-75% RH. In general, for the studied excipients, maintaining constant humidity levels while elevating the temperature from 25°C to 50°C resulted in a notable 24-27% reduction in the fraction of sorbed water for DCPA, XPVP, CCS and L-HPC. SSG exhibited the least sensitivity to increased temperature, showing a 10% decrease in the sorbed moisture. However, mannitol and lactose showed exceptions to

this trend, experiencing increases of 23% and 28% in moisture content, respectively. The rise in EMC for lactose and mannitol is relatively small compared to that of disintegrants. However, it is crucial to note this observation, considering that the soluble fillers lactose and mannitol are non-hygroscopic materials; similar effects have been reported in food research for some sugars (Al-Muhtaseb et al., 2002). These differences in EMC are higher when compared to the dry mass of the powder, as shown in Figure A.1 in Appendix A, than from the mass at 30% RH.

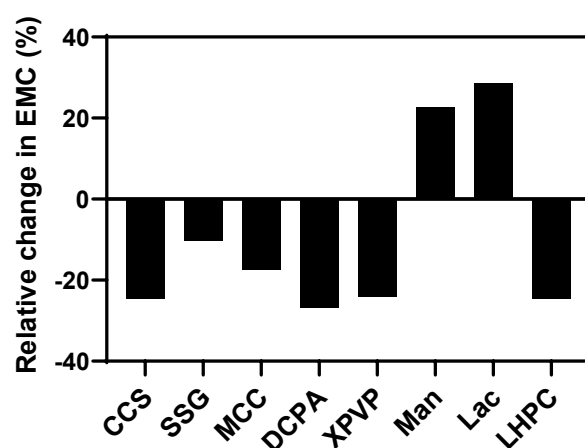


Figure 4.4: Relative Change in EMC (%) from 25°C to 50°C at 75% RH.

The decrease in EMC with an increase in temperature from 25°C to 50°C is attributed to the activation of some water molecules at higher temperatures to energies that enable them to separate from their sorption sites, thus reducing the EMC. This observation is consistent with the findings of Al-Muhtaseb et al. (2004), who noted a similar trend in starches under varying temperatures. They attributed the decrease in EMC with rising temperature to a reduction in the number of active sites for water binding due to physical and/or chemical changes induced by heat (Al-Muhtaseb et al., 2004). Palipane and

Driscoll (1993) also explained that higher temperatures cause water molecules to reach higher energy levels, making them less stable and more likely to detach from water-binding sites (Palipane and Driscoll, 1993). The thermodynamic equation $\Delta G = \Delta H - T\Delta S$ explains this necessity, where ΔG is a measure of the spontaneity of a reaction, ΔH is the enthalpy change, T is the temperature in Kelvin, and ΔS is the entropy change. Since $\Delta G < 0$ (indicating that sorption is a spontaneous process) and $\Delta S < 0$ (suggesting reduced freedom for the sorbed water molecule), ΔH must be negative. Consequently, higher temperatures make conditions less favourable for water sorption (Kapsalis, 1987).

However, lactose and mannitol deviate from this pattern, becoming more hygroscopic at higher temperatures. This is attributed to their ability to dissolve in adsorbed water vapour, forming a solution that causes a rise in moisture content (Figure 4.5). A similar trend is observed with certain sugars (such as glucose), sugar alcohols, and other low-molecular-weight food constituents (like salt), which become more hygroscopic at higher temperatures because they can dissolve in water (Al-Muhtaseb et al., 2002). Conversely, Bronlund and Paterson (2004) demonstrated that crystalline lactose exhibits almost no temperature dependence within the range of 12°C to 37°C, except for amorphous lactose at 12°C, which absorbed less moisture than observed at higher temperatures (Bronlund and Paterson, 2004).

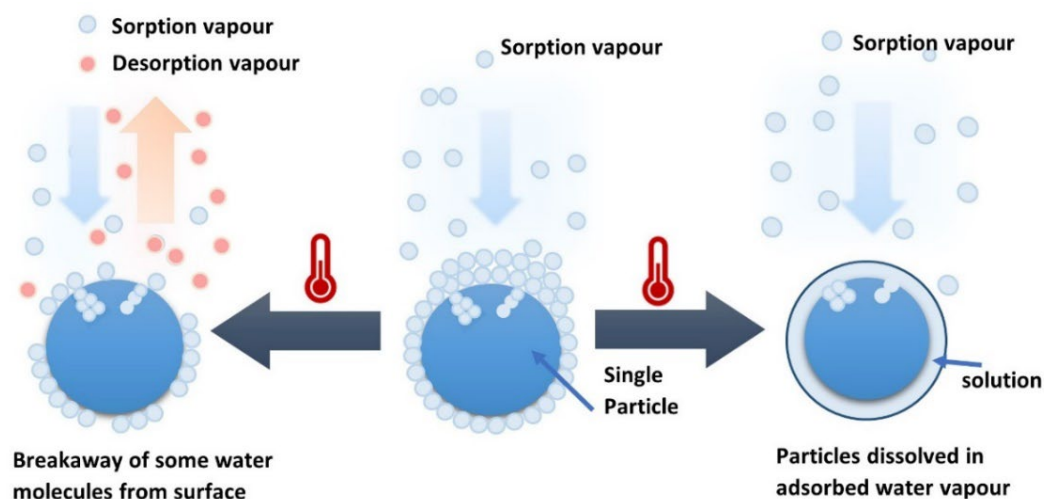


Figure 4.5: Illustration of the effect of temperature on the EMC of insoluble particles (left) and soluble particles (right).

Although the temperature increase impacted the moisture content, its effect on the kinetic rate constant was more significant (Figure 4.3C and D). The sorption and desorption rate constants increased dramatically when the temperature rose from 25°C to 50°C, particularly for hygroscopic excipients. For example, increasing the temperature from 25°C to 50°C has resulted in increased CCS sorption and desorption kinetic rate constants, from 0.04 s⁻¹ to 0.15 s⁻¹ and from 0.08 s⁻¹ to 0.23 s⁻¹, respectively. The effect of temperature on the sorption/desorption rate constant is attributed to the fact that at higher temperatures, the kinetic energy of water molecules increases, causing them to move more quickly and accelerate diffusion, which in turn raises the rate of sorption or desorption. In line with Fick's laws of diffusion, the rate of diffusion is directly proportional to the temperature. From an adsorption perspective, moisture uptake involves thermally activated exchange between adsorbed and vapour-phase water molecules. Increasing temperature reduces the residence time of water on adsorption sites

and accelerates adsorption-desorption kinetics, leading to a faster approach to equilibrium despite a reduction in equilibrium moisture content. As adsorption rate constants typically follow Arrhenius-type behaviour, relatively small increases in temperature can result in disproportionately large increases in the apparent sorption or desorption rate (Adamson and Gast, 1997). It is noteworthy that the effect of temperature on EMC and the kinetic rate constant is material and RH-dependent. Figure 4.6 illustrates the relative change in sorption and desorption rate constants at 30-75% RH from 25°C to 50°C, highlighting that the temperature affected the sorption rate constant more than the desorption, except for XPVP.

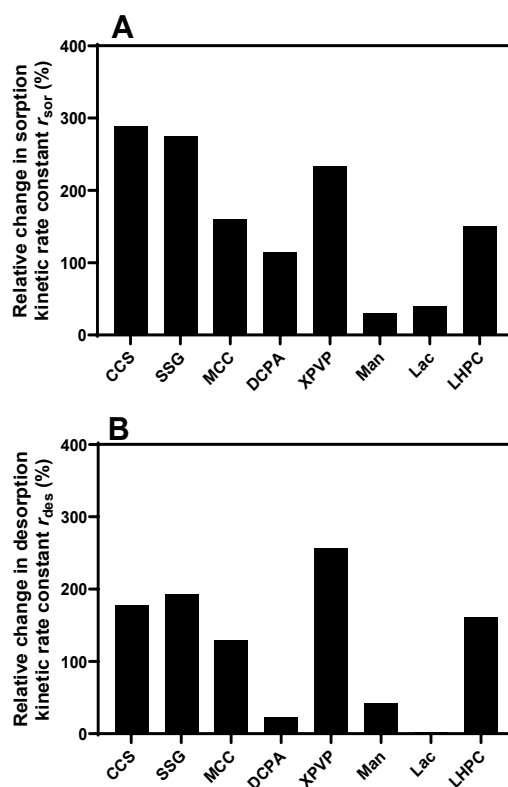


Figure 4.6: Relative Change in sorption (A) and desorption (B) kinetic rate constants from 25°C to 50°C when moving from 30-75% RH.

A substantial increase in the sorption rate constant of approximately 300% was observed for CCS and SSG, compared to a 30% increase for mannitol. On the other hand, the desorption rate constant increases by around 190% for CCS and SSG, compared to 42% for mannitol. While this relative change highlights the impact of temperature on the sorption/desorption process, it is essential to consider the absolute change for a comprehensive understanding (Figure A.4 in Appendix A). In instances where the relative change may seem very high, such as 300% increase for CCS, the absolute change was 0.11 s^{-1} . Presenting the absolute change becomes crucial for understanding the magnitude of the alterations. This is particularly significant when considering the temporal dynamics of the sorption/desorption processes, as equilibrium was reached on the DVS within a day under all conditions.

4.3.3 Particle size analysis

4.3.3.1 Characterisation of particles before storage

Table 4.2 summarises the mean values of some particle size and shape parameters.

According to the CED measurements, DCPA and mannitol have the largest particle size, while SSG and CCS have the smallest. As concluded from circularity results, SSG and mannitol particles are the most spherical, whereas CCS and MCC have a cylindrical-like shape. Figure A.5 in Appendix A shows magnified field images for CCS, MCC, and SSG.

Table 4.2: Size and shape characteristics of excipient particles before storage.

Material	CED (geometric D_{50}) (μm)	circularity mean (-)	Convexity mean (-)	Aspect ratio mean (-)
CCS	45	0.72	0.96	0.61
MCC	94	0.76	0.98	0.61
DCPA	138	0.76	0.99	0.64
XPVP	97	0.78	0.97	0.66
Man	131	0.81	0.98	0.68
SSG	44	0.92	0.99	0.80
Lac	111	0.79	0.98	0.71

4.3.3.2 Effect of storage on particle size/ shape characteristics of swelling excipients

Figure 4.7 presents the changes in the median CED of CCS, SSG and MCC across various time points (The 3-day time point changes are shown in Figure A.6 in Appendix A). Storing these particles at 50°C/75% RH for 14 days resulted in a volume-based median diameter change of approximately 6%, 5.5%, and 2.7% of their initial CED for CCS, SSG and MCC, respectively, indicating an expansion in particle size. Conversely, at 50°C/30% RH, the change in median CED was approximately 0.8% for CCS, 0.5% for SSG, and 0.4% for MCC after 14 days. This indicates that the expansion in particle size is attributed to elevated humidity levels and increased moisture content. The swelling of excipient particles involves the absorption of moisture, resulting in an increase in weight (as evidenced by DVS) and volume (as observed from particle size analysis). Temperature

exhibited minimal influence on particle swelling, with an absolute difference of less than 1% between 25°C and 50°C after 14 days of storage at 75% RH.

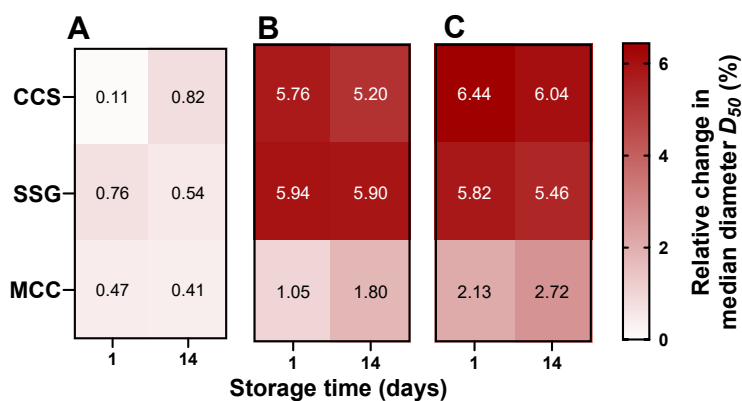


Figure 4.7: Relative change in volume-based diameter D_{50} of the studied excipients after storage at (A) 50°C/30% RH, (B) 25°C/75% RH, and (C) 50°C/75% RH over time. Values represent the average relative change in D_{50} for three samples on each time point at 50°C/75% RH, and one sample at 25°C/75% RH and 50°C/30% RH (Corresponding SDs are provided in Table A.3 in Appendix A).

By comparing the PSD before and after storage, storing CCS, SSG, and MCC particles at 50°C/75% RH consistently induced a shift in the PSD, moving toward a higher particle size across all examined time points (Figure 4.8). The PSD before and after storage for the other storage conditions are presented in Appendix A (Figure A.7 and Figure A.8). Because of the large number of smaller particles (<10 μm) and to reduce the sensitivity to them, volume-based size distribution has been used to assess the changes in PSD. Changes in the PSD using the number of particles were also used to visualise the change (Figure A.9 in Appendix A). Figure 4.9 illustrates the relative changes in various volume-based size parameters for particles after 14 days of storage at 50°C/75%. The fact that the

D_{10} , D_{50} , and D_{90} all experienced a positive relative change suggests an overall increase in the particle size distribution of the three excipients studied.

It is noteworthy, as shown in Figure 4.7, that while the change in particle diameter followed the order of CCS > SSG > MCC, the minimal difference between CCS and SSG implies comparable effects, considering the potential error introduced due to variations in the threshold and errors resulting from it, as observed in Figure A.10 in Appendix A. This agrees with the results from DVS, which showed that CCS and SSG absorb moisture substantially into their porous structure with moisture uptake of 16.8% and 15.8%, respectively, compared to 5.1% for MCC at 50°C/75% RH. CCS is a crosslinked carboxymethyl cellulose sodium, which is a modified form of cellulose with a considerably larger swelling capacity than MCC.

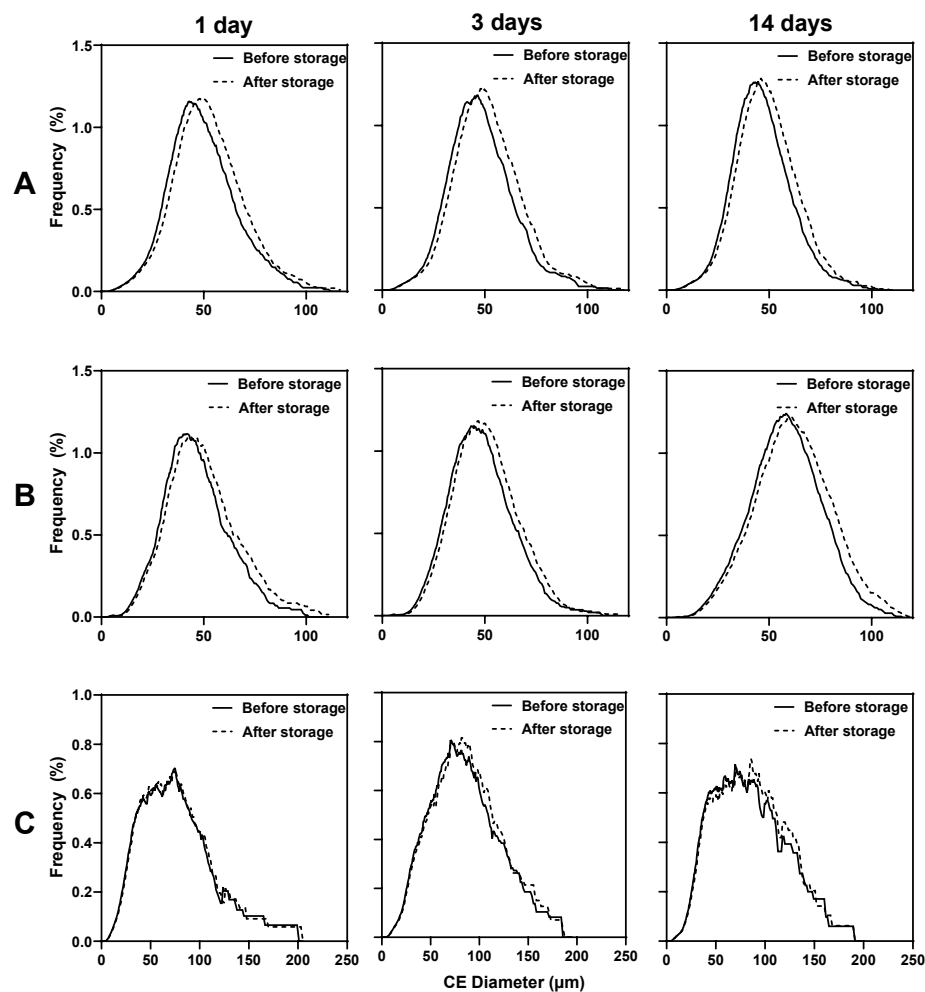


Figure 4.8: The change in volume-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 50°C/75% RH for 1, 3, and 14 days. The examples shown at each time point represent one of the samples analysed at this time point. The CED was smoothed over 50 points.

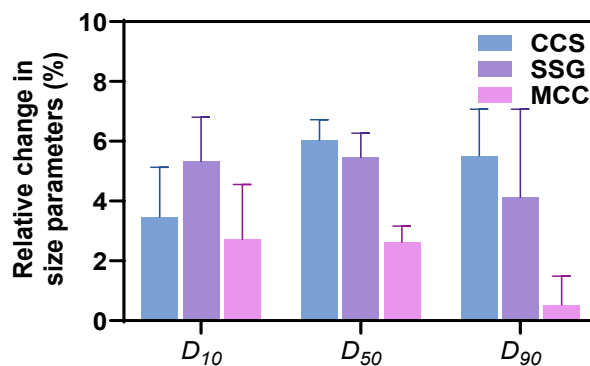


Figure 4.9: Average relative change in volume-based size parameters after 14 days of storage at 50°C/75% RH (n = 3, mean $\pm$ SD).

The results indicate that SSG and CCS exhibited the highest swelling capability, followed closely by MCC. However, prior findings showed a more pronounced change in volume mean diameter during SSG swelling compared to CCS (Desai et al., 2012; Soundaranathan et al., 2020; Zhao and Augsburger, 2005a). SSG, identified as the sodium salt of crosslinked carboxymethylated starch, undergoes modification through two chemical processes; substitution to enhance hydrophilicity and crosslinking to reduce solubility (Desai et al., 2016; Shah and Augsburger, 2002). The exceptional swelling capacity of SSG is attributed to the generous spacing between crosslinked phosphate groups, enabling effective water penetration, swelling, and gel formation (Rojas et al., 2012). In contrast, CCS, which undergoes crosslinking through esterification, exhibits a lack of significant spacing between polymer chains, resulting in a reduced swelling capacity (Zarmpi et al., 2017). Soundaranathan et al. (2020) distinguished between the swelling patterns of SSG and CCS due to contact with water and showed that SSG exhibited a more significant overall swelling than CCS, demonstrating a superior capacity

to absorb water. At the same time, CCS had a greater diffusion coefficient and, thus, a larger diffusion capacity due to its quicker liquid absorption at the surface and quicker initial swelling (Soundaranathan et al., 2020). The difference observed in our study compared to previous literature can be attributed to various factors. A crucial distinction lies in our specific focus on moisture-induced swelling, rather than liquid water, which may introduce unique considerations that may not precisely align with findings from studies that concentrate solely on liquid water-induced swelling. Additionally, the measurement technique used, such as the reliance on circle equivalent diameter, assumes that all particles are spherical, providing the diameter of a circle with the same area as the measured particle. This assumption may not fully capture the complexity of morphological changes and could contribute to differences. Furthermore, the imaging method provides insights into the change in the diameter of the entire particle size distribution, offering a comprehensive overview of the particles' behaviour. However, because of the polydispersed nature of the particle size distribution, high variability in the measured particle size parameters resulted, as smaller particles may behave differently from larger ones. This approach contrasts with some studies in the literature that focused on examining a few individual particles or compacts potentially overlooking the broader variability within the particle size distribution.

All particles achieved their maximum swelling, indicating the attainment of their EMC within the initial day of storage, as shown in Figure 4.7. This means that the changes resulted from storage conditions being too rapid, and this can be explained by the large surface area of particles exposed to these conditions, which leads to the changes

happening faster. Despite the accelerated changes observed within the first day, the prolonged time required to achieve the required RH level inside the jars limited the ability to investigate alterations over shorter durations within this critical period (Figure A.11 in Appendix A). The findings from DVS further supported the prompt attainment of moisture equilibrium within a day after exposure to all studied conditions.

The dynamics of particle swelling involve two key mechanisms: moisture uptake at the particle surface and the intrinsic swelling ability of the particle. Soundaranathan et al. (2020) demonstrated that SSG exhibits a relatively gradual initial swelling, indicating that hydration primarily originates from the interaction between the anionic carboxyl group and water (Zhao and Augsburger, 2005a). In contrast, CCS undergoes fast swelling driven by the hydration of the carboxymethyl group (Zarmpi et al., 2017). However, our results indicated that all studied excipients reached maximum swelling within a day of storage with no differences between them. Taking a closer look at the swelling of these excipients during the first day could reveal more details and differences that might not be evident in the broader day-long observations.

A comprehensive analysis of all possible particle shape descriptors may be just as critical as particle size. Particle shape, however, is often ignored or disregarded. Figure 4.10 provides insights into the morphological changes resulting from storage at elevated humidity and temperature. CCS and SSG experience more pronounced alterations in shape parameters compared to MCC, which exhibits the least impact. Specifically, the circularity of CCS particles undergoes the most significant decrease, approximately 9%, in contrast to the 1% decrease observed for MCC. Similarly, convexity decreases up to

5% for CCS particles, while MCC experiences a more modest 1.3% decrease. This consistent reduction in circularity and convexity across all excipients indicates a trend toward less rounded and rougher surface particle morphologies, aligning with the expected behaviour during particle swelling. Simultaneously, there is an increase in aspect ratio, underscoring changes in particle shapes induced by storage conditions. The observed changes were more pronounced for CCS than SSG and MCC, suggesting that SSG and MCC swelled in all directions. At the same time, CCS expanded mainly along the shorter (width) axis, implying less elongated particles. This aligns with previous studies suggesting that swelling tends to be omnidirectional, with CCS particles primarily expanding from the shorter axis (Berardi et al., 2018; Soundaranathan et al., 2020). It's essential to interpret the AR results cautiously, as these measurements rely on 2D imaging, while the particles' swelling occurs along all directions. Consequently, capturing the precise direction of swelling poses challenges, and the AR results should be considered as an approximation rather than a definitive representation of the swelling direction.

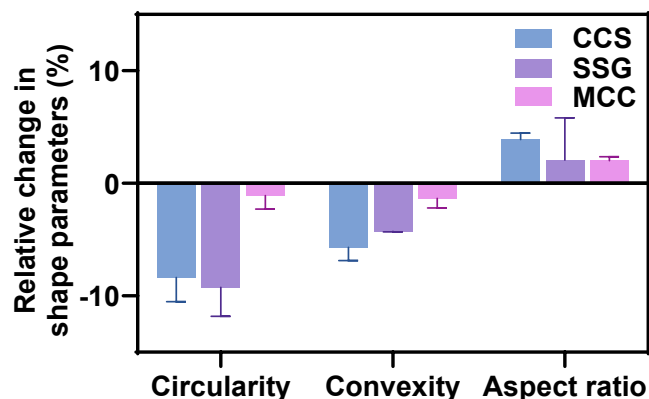


Figure 4.10: Relative change in particle shape parameters after 14 days of storage at 50°C/75% RH (n = 3, mean $\pm$ SD).

The reversibility of particle size swelling was also investigated (Figure 4.11). A comparison of particle size distribution profiles before and after storage revealed nearly identical PSD profiles for CCS and SSG particles after storage and after a subsequent month at laboratory conditions (25°C/30% RH). This implies that there was no obvious shift in the PSD of swollen particles back to their initial state before storage, indicating a persistent alteration in particle size caused by prior exposure to moisture when the particles returned to laboratory baseline conditions. Particle images further supported these findings, suggesting a minimal change in particle size, with a shift of approximately 0.5% in the median diameter for both CCS and SSG. In contrast, partial reversibility in PSD was observed for MCC particles, as evidenced by changes in median diameter decreasing by 1.26% compared to the maximum swelling observed directly after removal from storage (2.68%). This resulted in an overall swelling of 1.38% from the dry particle. However, due to the limited swelling of MCC, these changes should be interpreted cautiously.

Understanding how moisture irreversibly affects the particle size is crucial to understanding how excipients respond to changes during storage conditions, especially when evaluating the stability of materials. The swelling of disintegrants before use, which can occur during storage, plays a pivotal role in inducing physical instability and thereby diminishing their effectiveness. This phenomenon directly influences the release of drugs from dosage forms (Berardi et al., 2021; Maclean et al., 2022). Furthermore, the swelling of these excipients inside the dosage forms due to storage extends beyond affecting the size of the tablets; it also influences porosity and other mechanical properties due to irreversible alteration in their microstructure, thereby impacting their overall physical stability. In a study by Maclean et al. (2022), the impact of storage conditions on different formulations with diverse disintegrants and fillers was compared. Most formulations exhibited an increase in porosity and a decrease in tensile strength after being stored in high humidity, which further influenced disintegration time and was attributed to the premature swelling of disintegrants (Maclean et al., 2022). Hersen-Delesalle et al. (2007) similarly observed that an increase in RH resulted in a reduction in tensile strength (Hersen-Delesalle et al., 2007). This was associated with the formation of cracks on the surface and internal structure of tablets containing CCS, SSG, and XPVP disintegrants, likely caused by the premature activation of disintegrants absorbing moisture from the surrounding air.

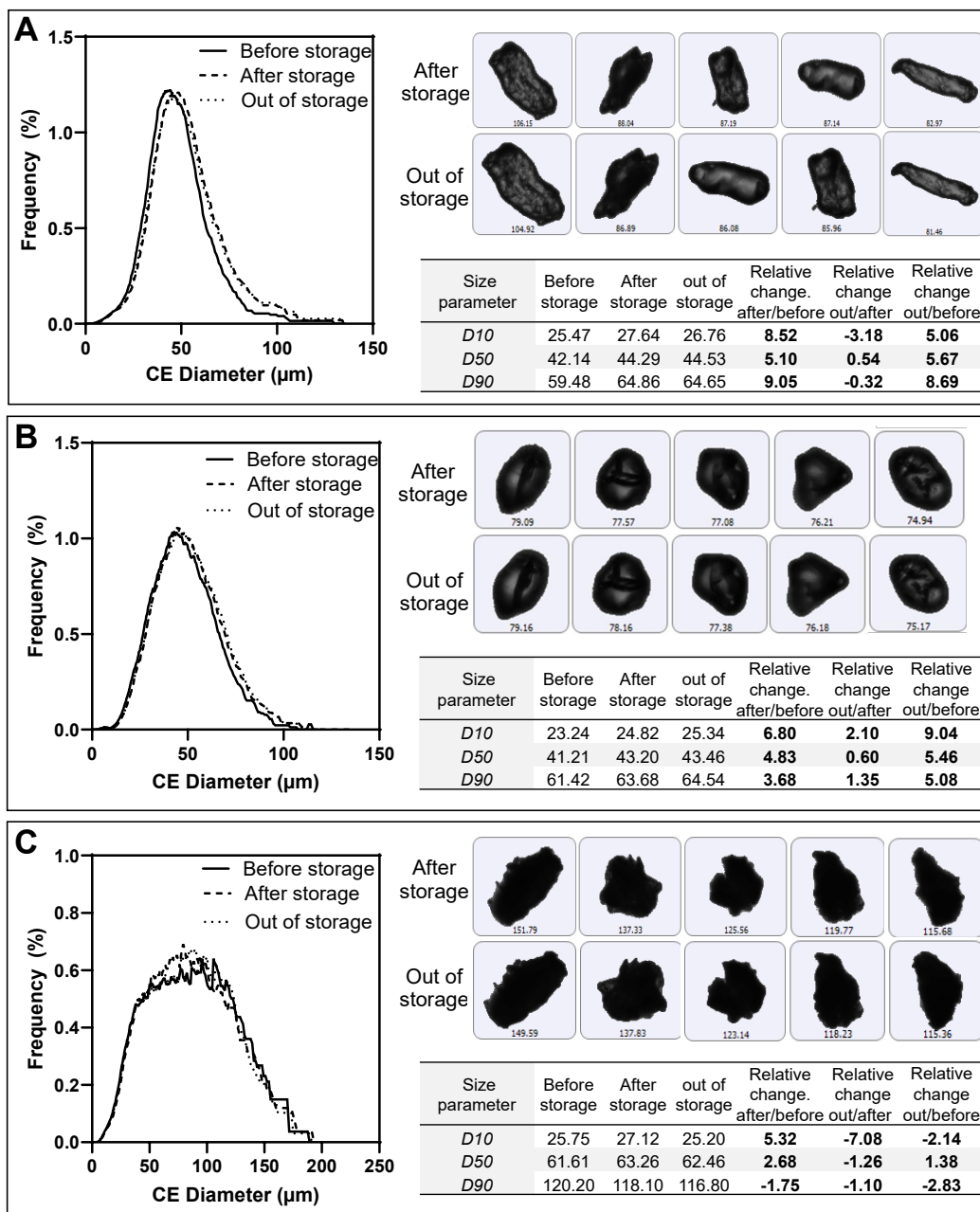


Figure 4.11: The Irreversibility in particle size change of (A) CCS, (B) SSG and (C) MCC particles after 14 days of storage at 50°C/75% RH and 28 days out of storage. Particle images with their corresponding CED, as taken from particle size analysis right after removal from storage and 28 days later, out of storage. The data shown represent one sample from each excipient.

4.4 Conclusion

This study focused on investigating the impact of varying humidity and temperature conditions on the moisture uptake rates and extent of commonly used excipients in IR tablets, as well as the resulting changes in their particle size and shape parameters. This is important for further assessing the effect of material attributes on the performance and physical stability of tablets. DVS results indicated that particles exposed to higher humidity levels exhibited increased moisture adsorption, diffusing into the bulk, yet requiring a longer time to reach the EMC. Temperature played a significant role in moisture dynamics, where increasing temperature increased the sorption/desorption rate constants of all excipients studied, accompanied by a decrease in the EMC, except for mannitol and lactose.

The study also highlighted varying swelling behaviour under accelerated conditions, with excipients following the order CCS > SSG > MCC, with minimal differences between CCS and SSG. This swelling was a result of humidity, not temperature effect. However, all of the excipients reached the maximum swelling within the first day of storage. This change in particle size was permanent, exhibiting partial reversibility for MCC, but no restoration of the initial size for CCS and SSG.

4.5 Future implications

This knowledge supports the prediction and modelling of formulation moisture behaviour and moisture-driven changes in disintegration, which directly influence drug release. Future modelling efforts can build on this by quantitatively linking moisture uptake and particle swelling to dissolution performance. In this context, particle-level sorption

kinetics and swelling behaviour may serve as early screening parameters during excipient selection to identify materials that are more resistant to humidity-induced physical change.

Quantification of particle swelling provides a direct basis for estimating porosity evolution following tablet formation, as particle expansion alters the solid–void balance within the compact. Resulting changes in porosity are expected to affect liquid penetration pathways, stress development during wetting, and the efficiency of tablet breakup, thereby influencing disintegration and dissolution. Incorporating particle swelling parameters into disintegration models therefore offers a route to improved prediction of tablet performance after storage. These findings may also inform future consideration of excipient pre-conditioning or pre-swelling within regulatory and quality-by-design frameworks.

Systematic characterisation of excipient moisture sorption further provides a framework for estimating formulation-level moisture uptake. Particle-scale sorption kinetics and equilibrium behaviour can be used to flag formulations with higher susceptibility to environmental exposure at early development stages, reducing reliance on long-term empirical stability studies. However, translation of particle-level moisture behaviour to tablet-scale response requires consideration of additional factors, including excipient–excipient interactions, tablet microstructure, inter-particle bonding, and liquid absorption kinetics. Addressing these interactions is essential for developing predictive approaches capable of supporting formulation robustness and long-term physical stability.

5. Linking powder to tablet stability: length- and time-scale prediction of moisture sorption

Chapter summary

Building on the excipient-level findings, this chapter examines the influence of tablet porosity and swelling excipients on moisture uptake and stability, linking particle-level interactions with tablet behaviour across short-term DVS and long-term storage. Pure MCC and MCC-CCS (8%) tablets are produced at four porosity levels, and a predictive framework is developed to estimate porosity changes from particle swelling. Correlating powder and tablet DVS data with real-storage results enables the prediction of moisture sorption behaviour over time, supporting faster and more reliable stability assessments.

This chapter is based on the following publication:

Ibrahim, I., Mann, J., Abbott, A., Winge, F., Davis, A., Hens, B., Khadra, I., Markl, D., 2025b. Linking powder to tablet stability: Length- and time-scale prediction of moisture sorption. *International Journal of Pharmaceutics* 126154. <https://doi.org/10.1016/j.ijpharm.2025.126154>.

Isra' Ibrahim's contribution to the peer-reviewed paper:

- a. Responsible for the entire experimental work and data analysis, which includes the design of the experimental procedure, creation and subsequent analysis of all samples, and presentation of data.
- b. Wrote the entire manuscript and implemented any corrections and comments provided by the co-authors and the reviewers.

5.1 Introduction

IR tablets are a popular dosage form due to their convenience and fast onset of action (Awad et al., 2021; Zhao and Augsburger, 2005b). The composition of the formulation plays a crucial role in achieving the desired release characteristics and more generally the quality of the final product. While the properties of each excipient in the formulation can potentially influence the disintegration mechanisms and tablet performance, other factors such as manufacturing processes, environmental conditions and microstructural factors (e.g., porosity, hardness) must be considered in terms of their impact on the rate of liquid penetration and the initial release of the API (Bawuah et al., 2023; Bi et al., 1999; Jange et al., 2023). Specifically, the internal pore structure is crucial in IR formulations, as it directly influences disintegration kinetics by controlling the penetration of liquid into the tablet matrix. Generally, tablets with higher porosity exhibit faster liquid penetration (Al-Sharabi et al., 2020).

The release of IR tablets is closely linked to their physical properties, such as swelling capacity, porosity, and wettability, which can be altered by storage conditions. Results from the previous chapter highlighted that excipients such as CCS, SSG, and MCC exhibit varying swelling behaviour under accelerated storage conditions, with CCS showing the most prominent effect within the first day of storage. Permanent swelling was observed for CCS and SSG, whereas MCC displayed a partial reversibility post-storage. Consequently, even upon removal from storage, the microstructure of the tablet has undergone irreversible changes.

At various phases of the drug development process, stability testing is a standard protocol employed on pharmacological compounds and drug products to explore the reasons or mechanisms behind product instability (Kommanaboyina and Rhodes, 1999). Predictive stability approaches utilise shorter stability tests under accelerated or stressed conditions and are designed to allow for the extrapolation of degradation kinetics back to ambient storage conditions (Williams, 2018). The expense, resources, and time required for pharmaceutical product stability testing during the research and development phases significantly burden the industry. Therefore, it's crucial to find strategic solutions to address these challenges. Previous studies published in the literature have frequently examined complex formulations without a comprehensive understanding of the individual contributions of each constituent towards stability outcomes.

This study aims to establish a direct link between raw material properties and tablet stability, focusing on moisture sorption behaviour and its impact on physical changes over time. It examines how powder properties influence tablet properties and how short-term moisture uptake data from DVS can be used to predict long-term storage behaviour. To achieve this, we assess the moisture sorption dynamics of simplified formulations containing MCC and MCC-CCS, chosen for their characteristic swelling behaviour, by using DVS to quantify equilibrium moisture levels in both powder and tablet forms across different porosities. We also examine structural changes in stored tablets at 50°C/75% RH as a worst-case scenario, using the jar storage method, by monitoring changes in weight, dimensions, porosity, density, and tensile strength. By integrating these elements,

this work provides a predictive approach to understanding moisture-driven physical changes in tablets.

5.2 Materials and methods

5.2.1 Materials

All materials used in this study are described in Section 3.1.

5.2.2 Raw materials characterisation

5.2.2.1 Moisture sorption analysis

Moisture sorption isotherms for MCC and MCC-CCS (8%) blend were collected as described in Section 3.2.1.1.

5.2.2.2 Sorption kinetic rate constant model

The model used to calculate the rate constants of moisture sorption kinetics was described in Section 3.2.1.2.

5.2.2.3 True density

True density measurements of raw materials were conducted as described in Section 3.2.1.3.

5.2.3 Tablet manufacturing

Full details of the tablet manufacturing process are provided in Section 3.2.2. This study discusses two tablet formulations: 100% w/w MCC and a combination of MCC (92% w/w) and CCS (8% w/w). An 8% concentration of CCS was selected as it represents the highest level that would be used in formulations (Berardi et al., 2021). This enables a

better understanding of how the maximum disintegrant level affects tablet stability. No lubricant was incorporated into the formulations or applied to the punches or die during the compression process.

Tablet porosity before storage was calculated as described in Section 3.2.2.

Detailed information regarding tablet formulations, thickness, compression pressure, and porosity values can be found in Table 5.1.

Table 5.1: Tablet formulations, thickness, compaction pressure, and the calculated porosity of the manufactured tablets.

Tablet	MCC (%)	CCS (%)	In-die thickness (mm)	Thickness (mm)	Compaction pressure (MPa)	Porosity (%)
MCC	100	-	1.68	1.82	191 ± 8.73	10
MCC	100	-	1.8	1.97	140 ± 9.43	17
MCC	100	-	1.9	2.1	97 ± 5.26	22
MCC	100	-	2.17	2.3	65 ± 1.94	29
MCC-CCS	92	8	1.68	1.83	197 ± 3.21	10
MCC-CCS	92	8	1.8	1.97	137 ± 1.43	17
MCC-CCS	92	8	1.9	2.09	121 ± 2.56	22
MCC-CCS	92	8	2.17	2.31	61 ± 1.11	29

5.2.4 Sample Storage

Tablets were stored as described in Section 3.2.3, which details the storage setup and time points, at 50°C/75% RH.

5.2.5 Tablet characterisation

Tablet characterisation was performed before and after storage on the same tablets, except for tensile strength. New tablets were used at each time point.

5.2.5.1 Moisture sorption dynamics and capacity

The moisture sorption analysis of tablets to measure the EMC and the moisture kinetic rate constant using DVS is described in Section 3.2.4.1.

5.2.5.2 Weight, dimensions, and tensile strength

The weight, dimensions, and tensile strength before storage and after storage were reported as described in Section 3.2.4.2.

The relationship between tablet porosity (f) and tensile strength was examined using the Ryshkewitch-Duckworth equation as described in Section 3.2.4.2.

5.2.5.3 Porosity of tablets after storage

During storage at 50°C/75% RH, CCS and MCC particles exhibited swelling that increased their initial diameters by approximately 6% and 2.7%, respectively, as reported in the previous chapter. This change affects the true particle density after storage, making the conventional method in (Eq. 3.5) for calculating tablet porosity less accurate.

To address this issue, a new method was developed for determining the porosity of tablets after storage, taking into account the change in true density of particles due to swelling (Figure 5.1). This method depends on estimating the number of particles in each tablet before and after storage. Several assumptions were made to facilitate this calculation, and

these introduce systematic effects that can influence the accuracy of after-storage porosity estimates: (1) particles are approximated as spheres when measuring diameter and calculating particle volume from the circle-equivalent diameter. However, MCC and CCS are not perfectly spherical with sphericity values of 0.72-0.76. For oblate particles, this approach overestimates true volume, reduces the calculated number of particles, and biases porosity downward, whereas for elongated/prolate particles, the reverse can occur, inflating porosity; (2) all particles are assumed to swell uniformly, which neglects potential moisture gradients within the compact. If central particles swell less than those at the edges, the total particle volume increase is overestimated and porosity is underestimated after storage; and (3) the particle number is assumed to remain constant before and after storage, i.e., no fragmentation, agglomeration, or dissolution. A decrease in particle number due to agglomeration would bias porosity upward, whereas an increase in the number of particles from fragmentation would bias porosity downward. Likewise, if part of the tablet mass were lost after storage (e.g., through chipping or dissolution), the reduced mass would lower the calculated particle number, leading to an overestimation of porosity. The calculation of porosity for tablets after storage was applied to the tablets at the last time point only, ensuring that particles had reached their maximum swelling and equilibrium had been reached.

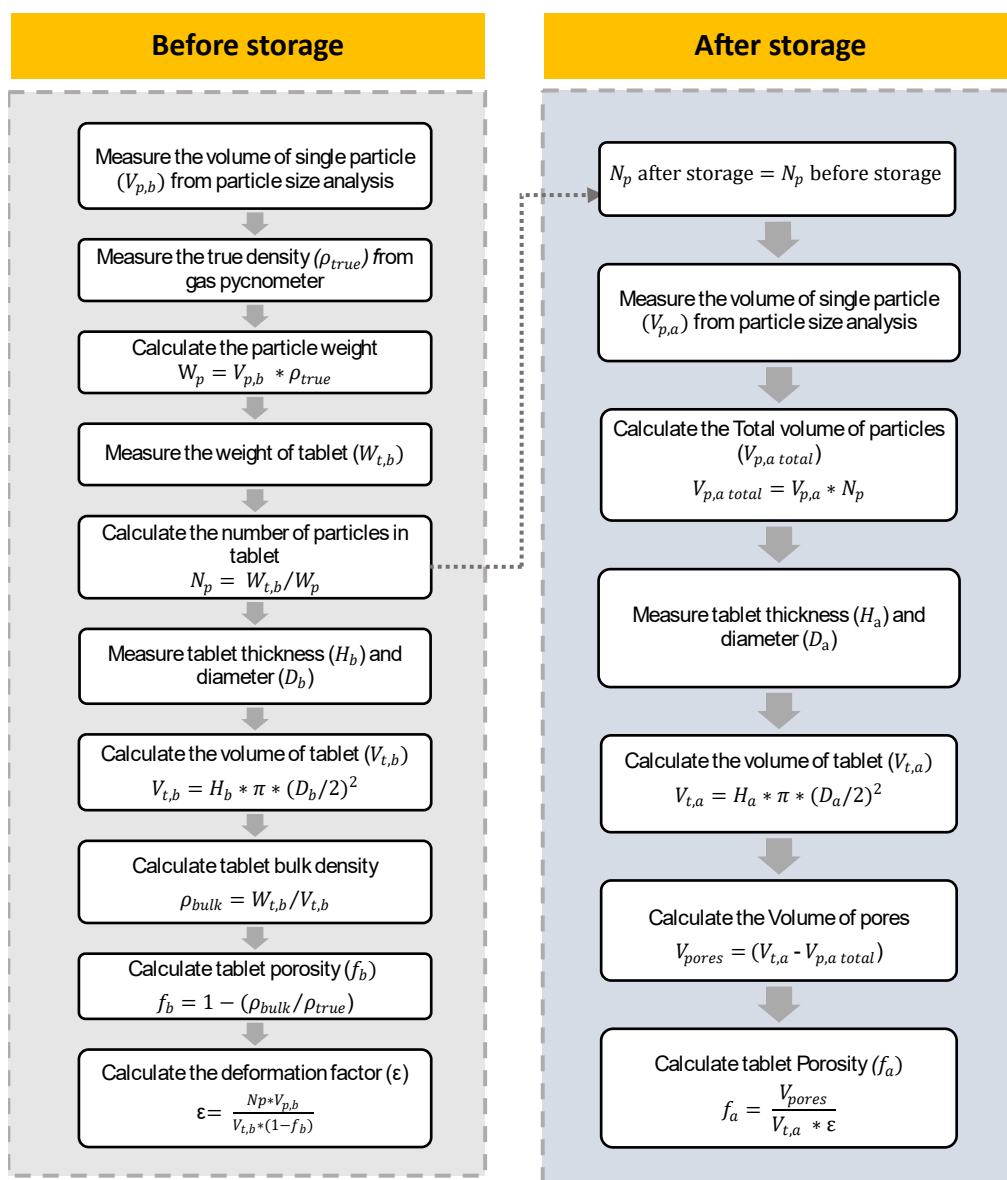


Figure 5.1: The flowchart illustrates the process of calculating the porosity of tablets, divided into two main phases: before storage (represented by symbols with 'b') and after storage (represented by symbols with 'a'). Measurements for particles and tablets are indicated by 'p' and 't', respectively. The flowchart begins with the calculations before storage on the left, proceeds to the calculations after storage on the right, and uses a dotted arrow to indicate the transition between these two phases.

5.2.5.4 Terahertz time-domain spectroscopy (THz-TDS)

THz-TDS measurements of all tablets were carried out using a commercial system (TeraPulse 4000, Teraview Ltd., Cambridge, UK). To ensure accuracy during analysis, the sample chamber was purged with dry nitrogen gas to remove moisture from the air. Samples were examined using an optical delay of 200 ps and an average of 30 measurements. From the terahertz data, both the refractive index and loss coefficient were determined. For comparison of changes in these parameters across different formulations and time points, a frequency of 0.9 THz was selected from the spectra obtained. This frequency was chosen because the materials used do not exhibit spectral features from the tablet components in either formulation.

The effective refractive index (n_{eff}) of a sample can be derived from terahertz measurements by comparing the waveform of a reference (i.e., when no sample is present in the measurement chamber) with that of the sample. The effective refractive index of the tablet is then calculated from the measured thickness of the tablets and the pulse delay between the reference and sample pulses (Eq. 5.1) (Bawuah et al., 2023).

$$n_{\text{eff}} = \frac{c \Delta t}{H} + 1 \quad \text{Eq. 5.1}$$

Where c is the speed of light in the vacuum. The reported values for THz measurement represent the average measurements obtained from three tablets at each time point.

A supplementary table (Table B.1) is provided in Appendix B, showing the mean and standard deviation for all properties measured in the study at each storage time point.

5.3 Results

5.3.1 Raw materials characterisation

Moisture sorption behaviour of the tested formulation powder is shown in Figure 5.2. The EMC relative to the dry mass of powder at the end of 0% RH is provided in Figure B.1 in Appendix B. The addition of 8% CCS to MCC resulted in a higher moisture uptake compared to MCC alone. When exposed to 75% RH at 25°C, the mass of MCC powder increased by 5.1%, while the MCC-CCS powder blend exhibited a 5.7% increase. However, incorporating CCS into MCC resulted in a slight decrease in the sorption kinetic rate constant, indicating a longer time to reach EMC compared to MCC alone. This difference can be attributed to the higher hygroscopicity of CCS compared to MCC, resulting in a higher percentage of moisture uptake and, consequently, slower moisture sorption. A previous study by Heidemann and Jarosz (1991) has shown that excipients with greater moisture sorption capacity tend to reach equilibrium more slowly than those with lower moisture affinity (Heidemann and Jarosz, 1991).

Moreover, increasing humidity levels resulted in higher moisture uptake, with powders exposed to 75% RH exhibiting the highest moisture uptake compared to the other RH levels studied. This observed correlation between moisture uptake and RH is consistent with previous findings (Li et al., 1994; Visalakshi et al., 2005). However, this increase in humidity led to smaller sorption kinetic rate constants, indicating slower moisture sorption with increasing RH. This is due to the saturation of available binding sites for moisture sorption. On the other hand, temperature had a reversible effect on the EMC of the powder across all RH levels. Elevating the temperature from 25°C to 50°C at 75%

RH resulted in approximately an 18% decrease in EMC for both MCC and MCC-CCS powder. Maintaining a constant RH level while increasing the temperature led to an increase in the sorption kinetic rate constant from 0.11 s^{-1} to 0.28 s^{-1} for MCC and from 0.1 s^{-1} to 0.26 s^{-1} for MCC-CCS at 75% RH, indicating faster moisture sorption. This is attributed to the effect of temperature on the kinetic energy of water molecules, causing them to move more rapidly.

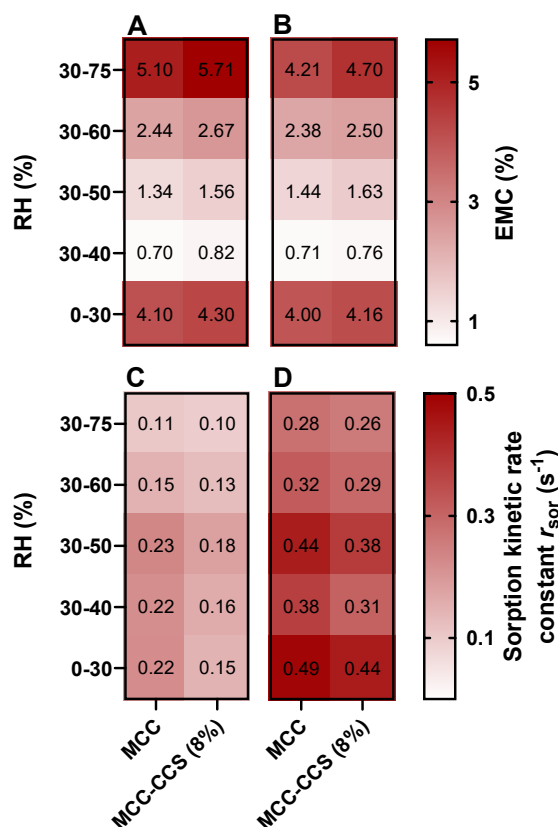


Figure 5.2: Moisture sorption properties of the powder. (A, B) represent the EMC(%) relative to the mass at the end of 30% RH, while (C, D) represent the sorption kinetic rate constant, at 25°C (A, C) and 50°C (B, D).

5.3.2 Tablet characterisation

5.3.2.1 Moisture sorption

5.3.2.1.1 DVS analysed tablets

Figure 5.3 and Figure 5.4 provide a summary of the moisture behaviour of tablets of varying porosities across different RH levels and temperatures. Furthermore, in Appendix B, Figure B.2 illustrates the EMC data relative to the dry mass of the tablet at 0% RH. The predictive performance of the moisture kinetics rate constant model is detailed in Table B.2 in Appendix B, which shows high R^2 values and low RMSE.

The effect of RH level and temperature on tablets' moisture behaviour was similar to that observed in the raw materials. As illustrated in Figure 5.3, increasing RH levels resulted in increased moisture uptake by the tablets, with the highest uptake occurring at 75% RH. For example, at 50°C/75% RH, MCC-CCS tablets with 29% porosity exhibited an average moisture uptake of 5.6%, compared to 2.6% at 60% RH and 0.8% at 40% RH. This aligns with the hygroscopic nature of the tablets' constituents, which tend to sorb moisture from the surrounding environment as RH levels rise. However, despite the variations in RH levels, the sorption kinetic rate constants remained relatively consistent across all humidity levels (Figure 5.4). This suggests that while the tablets sorbed varying amounts of moisture at different RH levels, the rate at which they did remained unaffected. On the other hand, while RH primarily regulates moisture availability for sorption, temperature affects the kinetic energy of water molecules, influencing both the tablets' moisture sorption rate and EMC, except within the range of 0-30% RH. Elevating the temperature to 50°C resulted in a reduction in the tablets' EMC (Figure 5.3C and D),

accompanied by an increase in the sorption rate constant, indicating faster moisture sorption (Figure 5.4C and D). For example, at 75% RH and 25°C, MCC tablets with 29% porosity exhibited a moisture uptake of approximately 4.8% and a sorption rate constant of 0.02 s^{-1} . In contrast, at 50°C, the moisture uptake decreased to 3.5%, while the sorption rate constant increased to 0.09 s^{-1} .

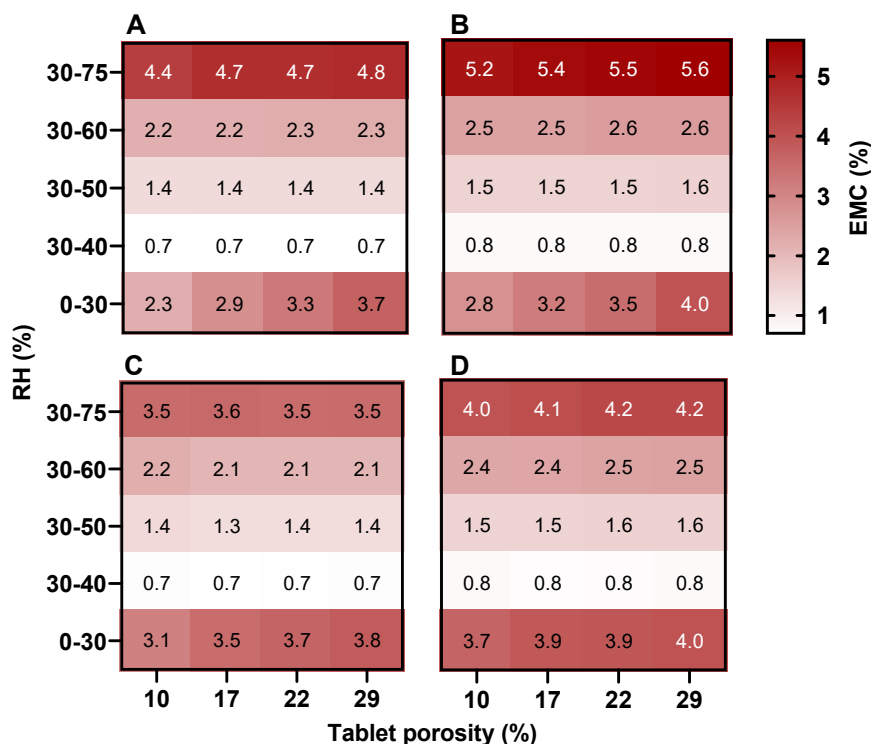


Figure 5.3: Moisture uptake of tablets at 25°C (A, B) and 50°C (C, D), presented as the EMC(%) relative to the mass at 30% RH. (A) and (C) represent MCC tablets, while (B) and (D) represent MCC-CCS (8%) tablets.

The influence of porosity on the moisture sorption properties of tablets was also examined. Results indicate that porosity affects the EMC under low RH levels (30% RH); i.e., tablets with higher porosities exhibit greater moisture uptake compared to their less porous counterparts. For example, at 25°C/30% RH, MCC tablets with 10% porosity

absorbed approximately 2.3%, while those with 29% porosity absorbed around 3.7%. This can be attributed to the larger surface area of the more porous tablets, which facilitates moisture sorption.

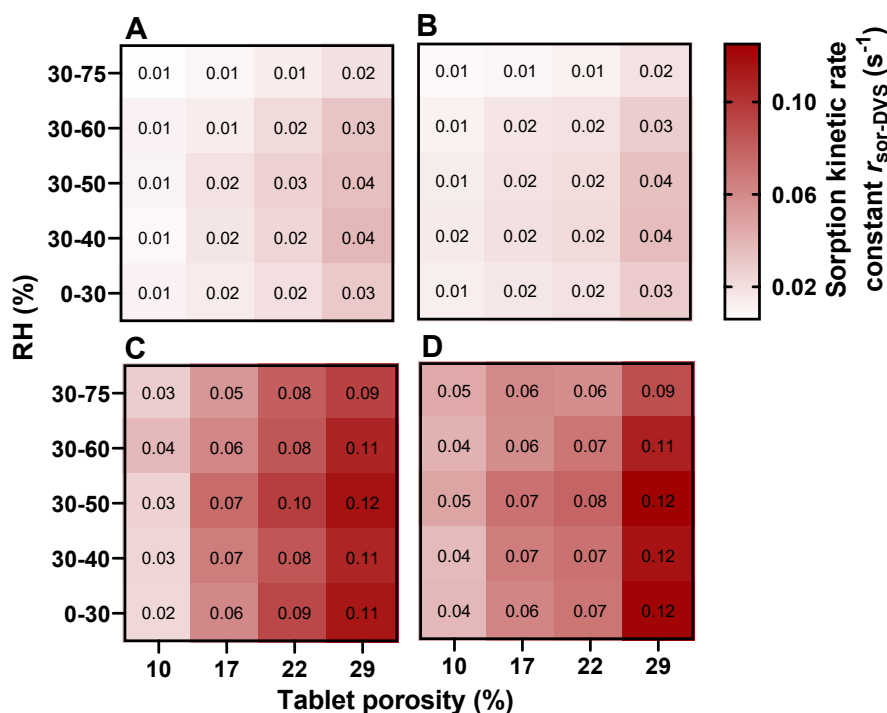


Figure 5.4: Sorption kinetic rate constant of the tested tablets at 25°C (A, B) and 50°C (C, D). (A) and (C) represent MCC tablets, while (B) and (D) represent MCC-CCS (8%) tablets.

As the RH level increased above 30% RH, tablets with varying porosities exhibited similar moisture uptake values. In these conditions, the amount of moisture sorbed was determined by the surrounding RH and the presence of CCS, regardless of tablet porosity, indicating that porosity had minimal influence on moisture uptake. At 50°C, MCC tablets of different porosities showed approximately 3.5% moisture uptake at 75% RH compared

to only 0.7% at 40% RH. On the other hand, MCC-CCS tablets exhibited around 4.1% moisture uptake at 75% RH versus 0.8% at 40% RH.

Although tablet porosity had minimal impact on EMC, it influenced the rate of moisture sorption and the time required to reach equilibrium to a higher extent, especially at high temperatures. Tablets with higher porosities exhibited faster moisture sorption rates than those with lower porosities. For instance, at 50°C/75% RH, MCC tablets with 10% porosity showed a sorption rate constant of 0.03 s^{-1} , while those with 29% porosity exhibited a rate constant of 0.09 s^{-1} . The addition of CCS had a minimal impact on the moisture sorption rate. In most studied conditions, tablets with and without CCS exhibited similar sorption rate constants.

Building upon the previous discussion on the influence of tablet porosity and RH levels on moisture sorption behaviour, Figure 5.5A illustrates the average moisture uptake of tablets across various porosities, plotted against the increment in RH level above 30% RH, serving as a baseline RH. This provides insight into the moisture uptake of tablets over 30% RH mass at various RH levels, regardless of tablet porosity. In Figure 5.5B, the average actual porosities of the tested tablets were plotted against their sorption kinetic rate constants regardless of the RH level. This data was extrapolated to include powder data, assuming a porosity of 100%. This analysis demonstrates that it is possible to predict the sorption rate constant for tablets with different porosities and the same composition.

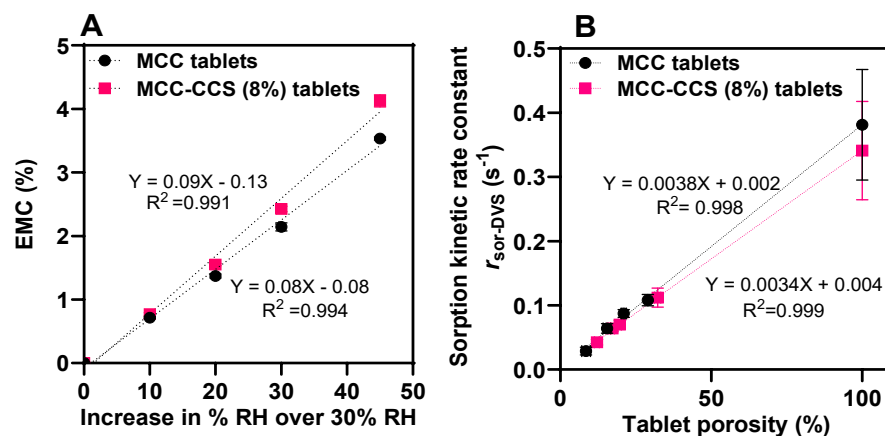


Figure 5.5: The relationship between tablet properties, RH level, and moisture behaviour. (A) The average EMC of tablets over incremental RH levels above 30% RH, (B) A correlation between average tablets' porosities and sorption kinetic rate constants, extrapolated to include powder data. Data points were fitted using linear regression analysis. Some error bars are not visible due to their small size.

Results in Figure 5.2 and Figure 5.3 indicate that powders tend to sorb more moisture than their corresponding tablets, which is more evident at higher RH levels. For example, at 50°C/75% RH, the MCC-CCS powder absorbed 4.7% moisture, compared to 4.2% absorbed by 29% MCC-CCS tablets. This can be attributed to the deformation of the particles during the compaction process, which prevents the particles from reaching their maximum moisture capacity. Furthermore, the DVS stop criterion was based on a minimal mass variation threshold (0.002% change over 10 minutes) rather than a fixed duration. Extending this stabilisation period, for instance, by requiring a 0.002% change over a longer time, such as 1 hour, would likely allow further moisture uptake by tablets. This suggests that, given sufficient time, tablets could absorb moisture levels closer to those of the corresponding powders.

Moreover, the sorption kinetic rate constants of the powders are higher than those of the tablets across all tested porosities (Figure 5.2 and Figure 5.4). For example, at 50°C, the sorption rate constant for MCC powder was 0.28 s^{-1} , whereas for MCC tablets with 29% porosity, it was 0.09 s^{-1} . This arises from the surface areas available for sorption, with powders exhibiting a larger surface area compared to tablets due to their loose nature. This increased surface area facilitates more rapid interaction with moisture molecules, resulting in higher sorption rate constants. In contrast, tablet compaction reduces their surface area and, consequently, slows down the rate of moisture sorption.

To bridge the gap between powder and tablet data and facilitate future predictive modelling, a correlation between the two datasets has been established (Figure 5.6). By making this correlation, it becomes possible to extrapolate the moisture sorption of tablets from the powder data, offering an understanding of the moisture behaviour of tablets based on their composition and RH conditions.

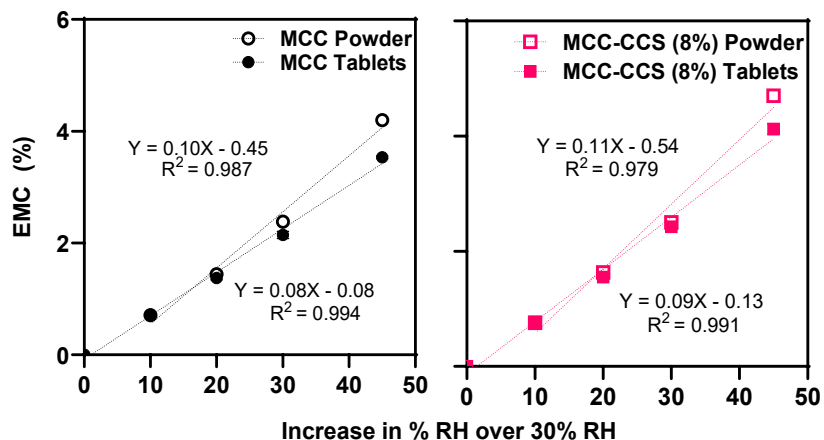


Figure 5.6: Correlation between MCC and MCC-CCS (8%) powder and their corresponding tablets' EMC (%) relative to the mass at the end of 30% RH at 50°C. (0,0) represents the 30% RH baseline EMC. Averaged values of tablets' EMC at each RH level are shown.

5.3.2.1.2 Jars stored tablets

The variations in tablet weights following storage at 50°C/75% RH and during equilibration were monitored and recorded in Figure B.3 in Appendix B. The weight of the tablets immediately after removal from storage reflects the moisture absorbed during the storage period. MCC-CCS formulations exhibited higher moisture uptake compared to pure MCC, with most of the moisture being sorbed within the first day of storage, followed by a gradual increase over time. By the final time point, tablets of each formulation, regardless of porosity, exhibited a comparable change in mass. These observations are consistent with DVS results. Monitoring weight changes after removal from storage was crucial for determining the duration required for tablets to reach their equilibrium moisture levels following moisture desorption. It was observed that tablets experienced a slow, gradual loss of moisture after removal from storage, with residual

moisture remaining even after two months in resting conditions. The time required for moisture loss increased with longer storage durations and higher levels of moisture sorption. For instance, tablets stored for 42 days took longer to reach equilibrium moisture levels under resting conditions at 30% RH compared to those stored for only 1 or 3 days. To ensure optimal moisture desorption, a three-week resting period was necessary for all tablets after removal from storage. The percentage change in tablet weight at the end of the resting period before any subsequent analyses or tests is included in Figure B.4 in Appendix B. Findings showed that tablet moisture content at the time of analysis was below 1.26% of their initial weight before storage. However, with longer storage periods, tablets exhibited increased moisture retention. Furthermore, tablets with lower porosities generally retained more moisture at the time of analysis compared to those with higher porosity, with few exceptions. Moreover, MCC-CCS tablets exhibited a greater weight change relative to MCC tablets of the same porosity, indicating greater moisture sorption, which was consistent across both DVS and jar storage methods.

A clear relationship was observed between tablet porosity and rate constants (Figure 5.7), with tablets exhibiting higher porosity showing higher rate constants. The model's fit varied in accuracy, with the 22% MCC-CCS formulation showing the best correlation, while the 10% MCC formulation displayed the weakest fit. The poor model fitting is partly due to the use of averaged initial weights for all tablets of the same porosity before storage, and the use of averaged data from three different tablets at each time point. Since we did not have a single tablet stored and measured at each time point, this introduced

variability, reducing the accuracy of the fit and making it more difficult for the model to capture the precise behaviour of individual tablets.

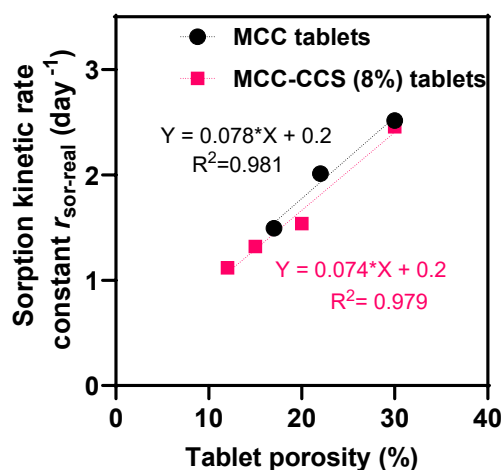


Figure 5.7: Sorption kinetic rate constants of the tested tablets at 50°C/75% RH. The sorption kinetic rate constants were calculated using the kinetic rate constant model (Eq. 3.1). Additional details on the model's predictive performance are provided in Table B.3 in Appendix B. Only data shown where the fitting resulted in an $R^2 > 0.85$. The 10% MCC formulation was excluded from this figure as the fit resulted in an R^2 of 0.72.

For the 10% MCC dataset specifically, a single anomalous averaged value at day-3 produced a slight non-monotonic trend, lowering the regression quality ($R^2 = 0.72$). Importantly, individual tablets did not show a decrease in mass, and when this point was excluded, the fit improved markedly ($R^2 = 0.991$), confirming that the overall sorption behaviour remained consistent with the higher porosities (Figure B.5 in Appendix B). However, this approach was necessary to ensure a consistent and controlled measurement process, as tracking the same tablets over time would have introduced additional variations caused by repeatedly removing and returning samples to storage. Though these

fits are not perfect, the approach used is consistent and based on small changes, which requires careful consideration when interpreting the results.

5.3.2.2 Dimensional changes

While the change in mass of tablets after storage reflects the moisture sorbed during storage, the alteration in tablets' dimensions enhances our understanding of moisture-induced swelling. The changes in tablet volume post-storage were investigated, representing the extent of swelling experienced by tablets under 50°C/75% RH (Figure 5.8). The variations in tablet volumes following storage were monitored and recorded in Figure B.6 in Appendix B.

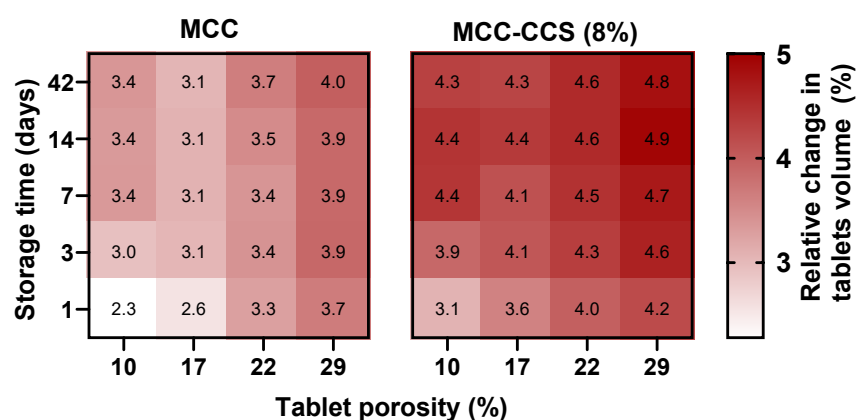


Figure 5.8: The average relative change in tablets' volume (%) after storage at 50°C/75% RH over time relative to the tablets' volume before storage (each point represents an average of 3 different tablets).

Initially, tablets with higher porosities exhibited a more significant volume increase, indicating a direct correlation between porosity and the extent of swelling. For instance, MCC tablets with 29% porosity experienced a volume increase of approximately 3.7%, while those with 10% porosity showed a more modest increase of around 2.3% after the

first day of storage. This agrees with findings from DVS analysis, where higher porosity translates to greater surface area available for moisture absorption. This difference becomes less pronounced with longer storage durations, where the same MCC tablets of 29% porosity experienced a volume increase of 4%, compared to 3.4% for the 10% porosity tablets of the same composition after 42 days of storage under the same conditions. Furthermore, tablets containing CCS showed a more pronounced change in volume compared to pure MCC tablets. For example, tablets with 22% porosity and CCS experienced an average volume increase of 4.6%, whereas pure MCC tablets with the same porosity showed an increase of only 3.7% after 42 days of storage. This indicates that the inclusion of CCS enhances the swelling of the tablets, primarily because it has the capacity to sorb more moisture into the tablet and the higher swelling potential of CCS particles in response to storage moisture, which exceeds that of MCC. The swelling of all tablets was primarily driven by changes in thickness, occurring mainly in the axial direction rather than the radial direction. Berardi et al. (2018) employed image analysis to investigate the kinetics of size expansion in three pure disintegrants upon exposure to water, finding that CCS tablets exhibited significant axial expansion (Berardi et al., 2018).

It should be highlighted that the bulk of volume changes in tablets occurred within the first day of storage. However, all tablets reached volume equilibrium within the first week of storage, indicating a rapid change due to the storage moisture conditions. The swelling and volume expansion of tablets resulted in a decrease in their bulk density. This decrease in bulk density signifies a critical aspect of the tablets' physical changes due to storage.

The average relative changes in the bulk densities of the tablets are illustrated in Figure B.7 in Appendix B.

5.3.2.3 Porosity

Figure 5.9 illustrates the change in tablet porosity following storage at 50°C/75% RH. The after-storage porosity values were estimated at the final time point (42 days) using the particle swelling data previously shown in Chapter 4.

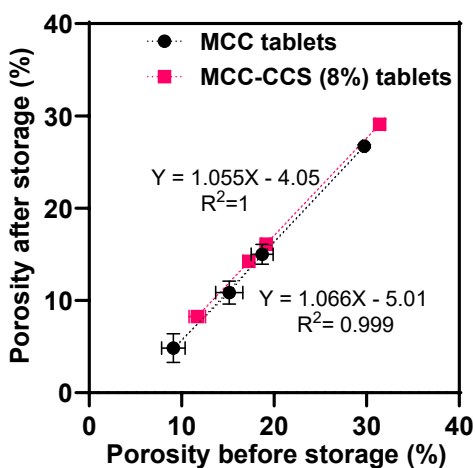


Figure 5.9: Tablets' porosity before and after storage at 50°C/75% RH for 42 days (n = 3, mean $\pm$ SD).

Storing 10% porosity MCC tablets at 50°C/75% RH for 42 days resulted in a decrease in their porosity to 4%, while those of 29% porosity reduced to 26%. The reduction in inter-particle porosity is a result of the irreversible swelling of CCS particles and the partial reversibility of MCC particles within the inter-particle voids and pores induced by the sorbed moisture during storage at 50°C/75% RH. Using the particle swelling data enabled the estimation of the inter-particle porosity after storage. Figure B.8 in Appendix B

represents the absolute decrease in inter-particle porosity resulting from particle swelling. Combining the particle swelling data with the tablet volume data after storage can be used to estimate the inter-particle porosity of the tablets post-storage. This approach provided information about the structural changes induced by moisture sorption and swelling.

The observed reduction in porosity due to the swelling of particles and tablets during storage is an important factor in understanding the performance of IR tablets. Lower porosity can hinder the penetration of water into the tablet matrix, which may negatively affect both disintegration and dissolution rates. As water absorption is critical for the rapid breakdown of these tablets, reduced porosity could lead to slower disintegration, ultimately delaying drug release.

As a result of the decrease in tablet bulk densities due to tablet swelling and the concurrent reduction in the inter-particle porosity due to swelling of particles within the inter-particle voids, a decrease in the true density of particles is expected. It is essential to keep in mind that the true density here refers to the skeletal material, that is, without the closed intraparticle pores. The calculated true density, derived from the estimated porosity and bulk density data (Figure B.9 in Appendix B), shows that the true density of the MCC-CCS formulation decreased more compared to MCC alone, due to the higher swelling capacity of CCS relative to MCC.

5.3.2.4 Tensile strength and bonding capacity

Figure 5.10A illustrates the tensile strengths of MCC and MCC-CCS tablets before and after exposure to storage conditions at 50°C/75% RH. Before storage, MCC tablets exhibited higher tensile strength compared to those containing CCS, consistent with

previous findings (Hersen-Delesalle et al., 2007). The relationship between porosity and tensile strength before storage is evident, with tablets exhibiting higher porosity consistently showing lower tensile strength compared to those with lower porosity. This inverse relationship between porosity and tensile strength has been previously reported and is attributed to the structural characteristics of the tablets, where higher porosity tablets typically have larger void spaces within their matrix, resulting in reduced intermolecular forces and weaker mechanical integrity (Hersen-Delesalle et al., 2007).

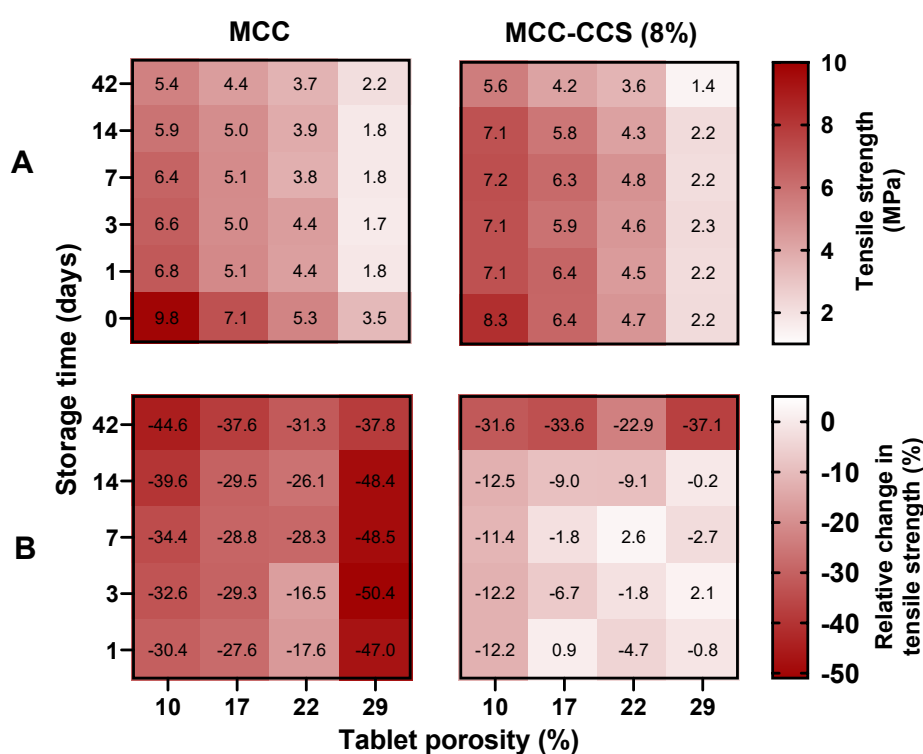


Figure 5.10: Tensile strength analysis of tablets: (A) Average tensile strength of tablets before and after storage at 50°C/75% RH (0-time point represents initial values); (B) Average relative change in tensile strength after storage relative to initial values for MCC and MCC-CCS tablets. (Each point represents an average of 3 different tablets).

Following exposure to storage conditions, changes in the tensile strength of tablets were observed. Initially, within the first day of storage, the tensile strength of all MCC tablets decreased sharply, stabilising over time with no significant further reduction observed (Figure 5.10B). In contrast, most MCC-CCS tablets maintained their tensile strength during the initial days of storage, helping to stabilise the structure despite moisture sorption. However, by day 42 of storage, a decline in the tensile strength of all tablets was observed. This reduction can be attributed to moisture disrupting the inter-molecular bonding within the tablet matrix, which weakens structural integrity. Furthermore, moisture acts as a plasticiser, reducing the rigidity of the tablet components and compromising their mechanical strength.

Figure 5.11 illustrates the relationship between the tensile strength of tablets and their porosities, as described by the Ryshkewitch-Duckworth equation. The strength of tablets is influenced by both the individual strength of the particles and the cumulative strength of the bonds holding them together. The parameter σ_0 can be interpreted in various ways, such as an intrinsic material strength or an indication of the total strength of inter-particulate bonds at the fracture plane. Similarly, the rate constant (b), termed as a bonding capacity factor, reflects the powder's ability to bind under pressure (Pazesh et al., 2019; Persson et al., 2022). Before storage, MCC tablets exhibited a higher tensile strength at zero porosity (17.9 MPa) compared to MCC-CCS tablets (17.5 MPa), indicative of stronger inter-particle bonds in the former. Following 42 days of storage at 50°C/75% RH, both the intrinsic tensile strength and the bonding capacity factor decreased, indicating weaker inter-particle bonding within the tablet structure. However,

despite the reduction in tablet porosity after storage, there was no corresponding increase in tensile strength. The magnitude of the decline was greater for the intrinsic tensile strength than for the bonding capacity factor. Specifically, σ_0 decreased from 17.9 to 6.5 MPa for MCC tablets and from 17.5 to 8.9 MPa for MCC-CCS tablets, while b decreased from 5.5 to 4.1 for MCC tablets and from 6.4 to 5.9 for MCC-CCS tablets. The consistently smaller reduction observed for MCC-CCS tablets suggests that incorporation of CCS attenuated the extent of storage-induced tensile weakening relative to MCC-only tablets. These differences are interpreted in terms of relative magnitude and consistency of change rather than statistical significance.

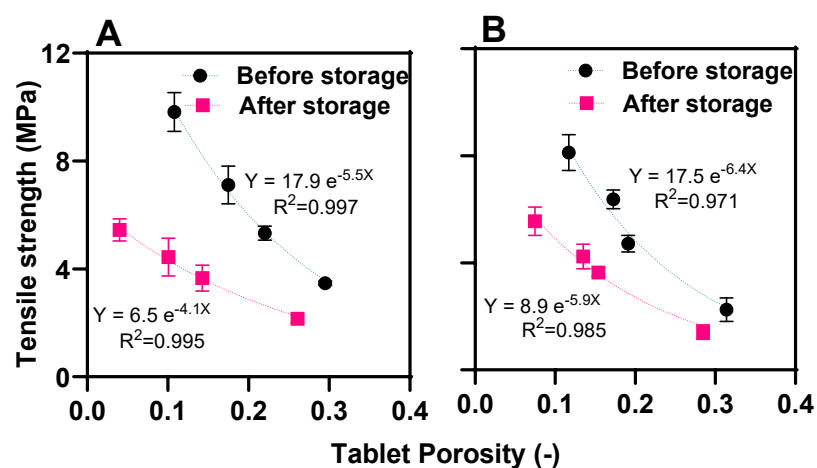


Figure 5.11: The relationship between (A) MCC and (B) MCC-CCS (8%) tablets tensile strength and porosity, before and after storage at 50°C/75% RH for 42 days. The line represents a fit to the Ryshkewitch-Duckworth model (Eq. 3.7) ($n = 3$, mean $\pm$ SD).

5.3.2.5 Terahertz spectroscopy

In this study, terahertz spectroscopy emerges as a valuable tool for understanding the internal structure of tablets. One of the significant advantages of terahertz spectroscopy

is its non-destructive nature, which allows for repeated analysis of the same tablets before and after storage to monitor changes in the refractive index and loss coefficient. Typically, the porosity determined by THz-TDS captures both intraparticle and interparticle pores, including open and closed pores, if the latter exist (Markl et al., 2017b). Before storage, a significant correlation was observed between the porosity of the tablets and their refractive index (Figure B.10A in Appendix B). This correlation suggests that tablets with higher porosity tend to have lower refractive index values, a relationship that has been previously reported in the literature (Bawuah et al., 2020, 2014; Markl et al., 2017a). This refractive index-porosity relationship can thus be used to calculate the porosity of tablets before storage from terahertz measurements. However, this approach may not be applicable for calculating porosity after storage if the true density of the particles changes due to swelling, as previously discussed.

When the formulation of a tablet remains constant, any variations in n_{eff} are due to changes in the intra- and/or inter-particle porosity or density of the particles. After storage, shifts in refractive index serve as indicators of internal structural alterations in tablets resulting from moisture sorption or desorption. As presented in Figure 5.12, there is a slight decrease in refractive index across all tablets during storage, with the majority of the change occurring within the first day of storage. The reduction in the refractive index after storage suggests an increase in overall porosity or a decrease in true density. However, as discussed previously, the interparticle porosity decreased due to particle swelling, indicating that the true density of the material has decreased. Figure B.10B in Appendix B illustrates the relationship between the refractive index of tablets and their

porosity after storage, derived from the swelling data of particles and tablets previously presented in Figure 5.1. The intrinsic n_{eff} of the tablets decreased after storage, dropping from 1.87 to 1.82 for MCC tablets and from 1.89 to 1.83 for MCC-CCS tablets. This decline in intrinsic n_{eff} reflects a reduction in the true density of the particles, a consequence of their swelling during storage.

A correlation has also been made between n_{eff} and bulk density of tablets (Figure B.10C in Appendix B), which can be used to estimate the bulk density of tablets after storage from their n_{eff} values. The results of bulk density estimation align with those calculated from tablet dimensions after storage (Figure B.10D in Appendix B).

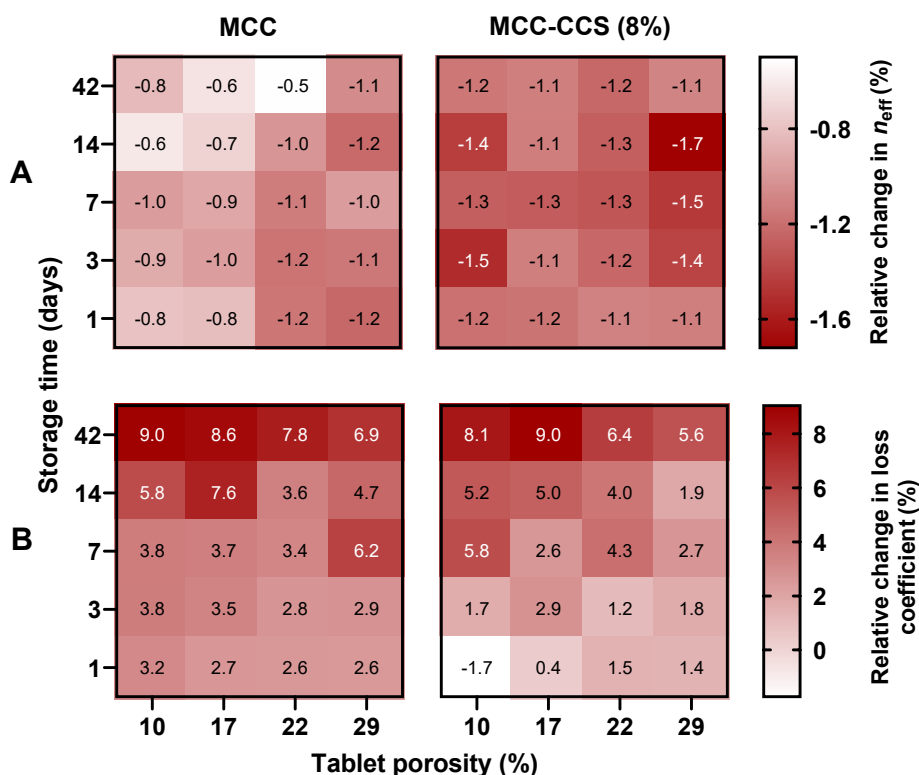


Figure 5.12: The relative change in (A) refractive index and (B) loss coefficient of tablets after storage at 50°C/75% RH across different time points. (Each point represents an average of 3 different tablets).

On the other hand, a higher and more significant increase in loss coefficient was observed with storage time, indicating a higher extent of absorption and scattering by the materials when exposed to terahertz waves. For instance, the loss coefficient for 10% porosity MCC tablets increased by 9% after 42 days of storage at 50°C/75% RH, compared to 3.2% after the first day of storage. The loss coefficient is sensitive to the presence of void spaces and moisture content within the tablet, reflecting the interactions between water molecules and terahertz waves. Higher moisture content can lead to increased absorption and, consequently, a higher loss coefficient. The observed increase in the loss coefficient for

all tablets after storage can be attributed to the growth of domain sizes within the tablets, resulting from the swelling of particles and, to some extent, the residual moisture content in the tablets.

5.4 Discussion

5.4.1 Bridging the gap between DVS and real-storage analysis

Due to the method used on DVS, where the change in mass (%) was assessed relative to the mass of tablets at 30% RH (an equilibrium condition of the tablets to rest before and after removal from storage), it becomes possible to compare the results between DVS and the jars method under the same storage conditions. The comparison between the results obtained from the DVS and the traditional storage jar method can be made in terms of the change in mass (%) and the sorption kinetic rate constant. Tablets subjected to the jar method experienced comparatively less weight gain, indicative of lower moisture sorption, in contrast to those analysed using DVS (Figure B.11 in Appendix B). This difference persisted even when assessing tablets at the final time point of storage (42 days). This is attributed to the enclosed system within the DVS and the continuous flux of partially humidified nitrogen gas. This continuous flux promoted equilibrium attainment beyond what was achievable with the jars method, where such driving forces were absent. Additionally, the weight measurements obtained from DVS were recorded precisely at the equilibrium point within the sample compartment, whereas for the jar method, tablets had to be removed from their jars for weighing. This process led to a rapid loss of vapour, particularly the free unbound water molecules, resulting in variations in the measurement of mass gain at 75% RH compared to DVS. Figure B.12 in Appendix B

provides two examples of moisture loss observed after removing tablets from the DVS. These results highlight the rapid vapour loss that occurs during the measurement process, confirming that part of the discrepancy between the jar and DVS methods can be attributed to this moisture loss. Consequently, this loss also affects the calculation of the moisture sorption rate constant by altering the $M_{\max}$ value in the model. Building on the preceding analyses, DVS provides a controlled and precise method for measuring moisture sorption, making it a reliable reference for understanding how tablets respond to specific humidity and temperature conditions. While the jar method more closely reflects real-world storage, inconsistencies such as handling and fluctuations can introduce variability, making data interpretation more challenging.

5.4.1.1 Length-scale assessment: establishing a link between powder and tablet sorption in DVS

To bridge the gap between DVS and real storage conditions, as well as powder and tablet moisture behaviour, a length-scale assessment was conducted. This involved measuring moisture sorption for both powder and tablets at different porosities using DVS. The goal was to establish relationships between storage conditions and moisture content, as well as between sorption rate constants and tablet porosity (Figure 5.5 and Figure 5.6), allowing for a more structured transition from DVS measurements to real storage scenarios. The results showed that powder and tablet DVS data followed similar trends, with EMC being dependent on RH, while the sorption rate was primarily influenced by tablet porosity rather than humidity. In terms of EMC, both powder and tablets exhibited comparable EMC, though deviations were observed at higher RH levels. However, the

sorption rate constant was higher for powder due to its larger surface area. Since the rate constant varied with tablet porosity, some tablet data were required to establish this relationship before extending predictions to other porosities. Once this correlation was established, powder DVS data provided a reliable estimate of tablet moisture uptake, with only minor overestimations at high RH.

5.4.1.2 Time-scale assessment: establishing a link between DVS data and real storage

Tablets were subjected to real storage conditions using the jars method. Moisture content was measured at different time points (Figure B.3 in Appendix B), and the sorption rate constant was determined using the same model described previously (Eq. 3.1; Figure 5.7). This step enabled direct comparison of how moisture uptake progresses over time in real storage compared to controlled DVS conditions, where equilibrium is reached more rapidly.

To quantify the relationship between DVS and real storage conditions, a scaling factor was determined by comparing the EMC and sorption rate constants obtained using the two methods. While some errors exist, they are not significant enough to preclude the potential prediction of EMC in real storage conditions based on DVS data, using a consistent scaling factor.

Table 5.2 provides the calculated scaling factors derived for both moisture uptake and sorption rate constants. For all tablets, except for MCC 10%, which showed a poor model fit (Eq. 3.1), the scaling factors are close to each other. This consistency indicates that the kinetics of moisture uptake in real storage occur at a consistently scaled rate compared to

those observed in DVS. The uniform scaling factors across tablets suggest that real storage rate constants can be predicted from DVS data, which is crucial for predicting long-term behaviour based on short-term experimental results.

Table 5.2: Calculated scaling factors for (A) moisture uptake and (B) sorption kinetic rate constants, bridging the gap between DVS observations and real storage at 50°C/75% RH.

Formulation and tablet Porosity (%)	EMC scaling factor (EMC_{real}/EMC_{DVS})				r_{sor} scaling factor $10^{-4} \times (r_{sor-real}/r_{sor-DVS})$			
	10%	17%	22%	29%	10%	17%	22%	29%
MCC	0.8	0.82	0.86	0.81	0.82	3.17	2.89	3.1
MCC-CCS	0.76	0.78	0.75	0.8	2.81	2.5	2.98	3.23

The scaling factor for the kinetic rate constant has also been applied to calculate the moisture sorption rate of MCC and MCC-CCS powders at 50°C/75% RH, reflecting real storage scenarios in jars. The relationship between tablet porosity and rate constants, including powder, is shown in Figure B.13 in Appendix B.

Figure 5.13 outlines the workflow for linking DVS analysis with real storage conditions to predict the moisture sorption behaviour of tablets under real storage based on DVS data. This approach was used to predict the moisture sorption dynamics of MCC and MCC-CCS tablets at different porosities using two modelling approaches: one based on a single powder DVS measurement at the same storage condition and another derived from tablet DVS data (Figure 5.6). The results, combined with the averaged scaling factor, were applied to estimate the EMC and rate constant of tablets under real storage conditions. Figure 5.14 illustrates the moisture-induced mass increase for MCC and MCC-CCS (8%) tablets, comparing predictions from DVS with experimental results. Additional details on the model's predictive performance are provided in Table B.4 in

Appendix B. The findings confirm that while DVS powder data can predict tablet moisture content at a given RH, the model fit improved when using tablet-based data compared to powder data.

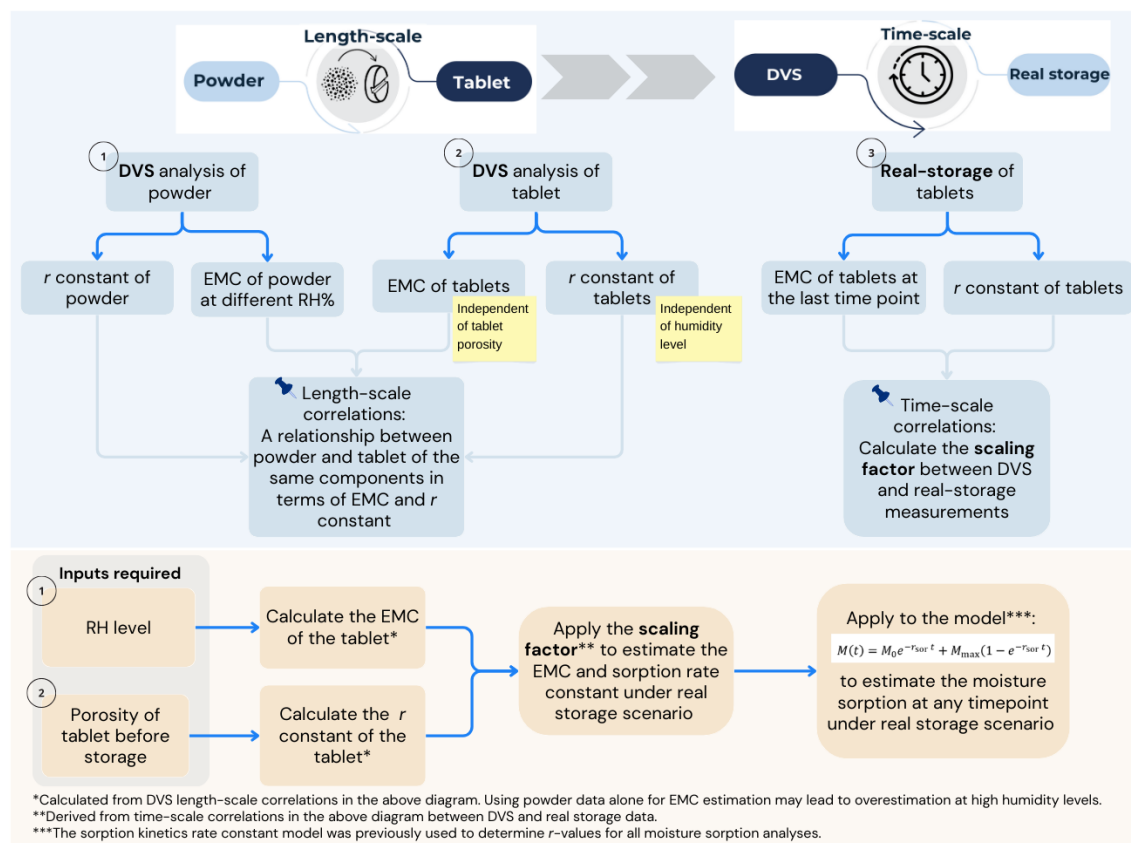


Figure 5.13: A framework for predicting moisture sorption in tablets under real storage scenarios. The upper section illustrates the length-scale and time-scale correlations between powder and tablet DVS data and the real-storage data, establishing the scaling factors. The lower section demonstrates how these correlations can be applied to estimate tablet moisture sorption in real storage scenarios.

Variability in predictions from powder data reflects an overestimation that can be attributed to the observed differences in EMC between powder and tablets at high humidity levels. As seen from the DVS relationship (Figure 5.6), EMC values deviate at

elevated RH levels, leading to an overestimation of moisture content in the model. Additionally, the initial mass used for calculations was determined by averaging the weights of all tablets of the same porosity before storage. This averaged value was then used as the initial reference point for all subsequent time points; however, this potentially introduced some variability as small discrepancies in initial mass influence the calculated moisture uptake trends.

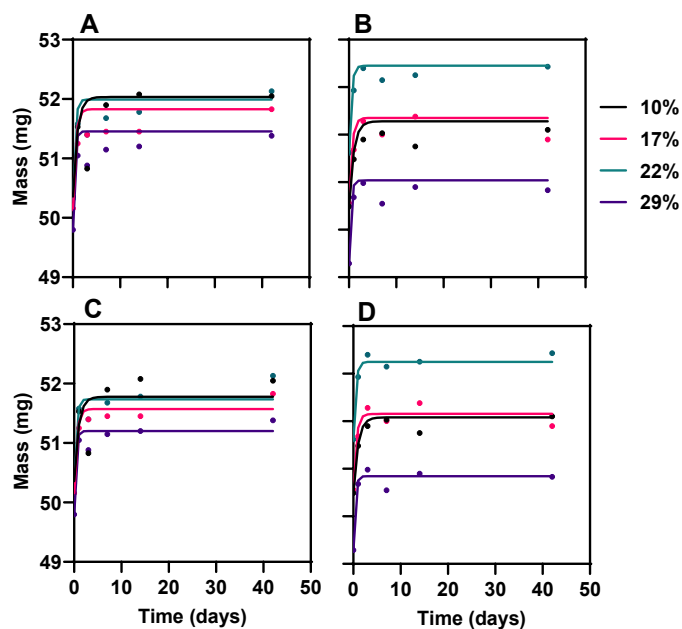


Figure 5.14: Mass increase for (A and C) MCC and (B and D) MCC-CCS (8%) tablets at different porosities. Model predictions (lines) based on a single DVS powder measurement (A and B), and based on tablets' DVS measurements (C and D), compared to jars-storage experimental data (points).

However, while the predictive framework in Figure 5.13 effectively captures moisture kinetics and equilibrium behaviour, it does not explicitly account for mechanical damage that can develop during prolonged storage. Moisture-induced swelling and subsequent

redistribution or equilibration can generate internal stresses within the tablet matrix, leading to mechanical relaxation, crack formation, or partial loss of inter-particle contact over time. These effects highlight important limitations of in, on, and at-line testing approaches when used to predict long-term tablet performance. Measurements acquired during processing or immediately after manufacture reflect the instantaneous physical state of the dosage form and may not capture delayed mechanical instabilities that develop after sustained exposure to humidity. As a result, tablets that appear stable based on early moisture uptake, porosity, or tensile strength measurements may still undergo progressive structural degradation during storage that is not evident from short-term or in-line data. Such mechanically driven changes are particularly relevant for disintegration performance. Crack formation can alter liquid penetration pathways and stress distribution during wetting, leading to inconsistent tablet breakup. Consequently, although the DVS-based framework provides robust prediction of moisture uptake, its predictive power for long-term functional performance must be interpreted in light of time-dependent mechanical relaxation processes that fall outside the scope of moisture sorption scaling alone.

5.5 Conclusion

This chapter established a link between the physical stability of (MCC and CCS) powder and tablet by investigating moisture sorption across different length and time scales. Using DVS, the effects of tablet porosity and swelling excipients (MCC and CCS) on moisture uptake were evaluated to understand how these factors influence tablet stability

during storage. Correlations were established between DVS data and real-storage data, as well as between powder and tablet moisture sorption behaviour.

The study also investigated the progression of structural physical changes in tablets under extreme storage conditions (50°C/75% RH) over time, providing insights into how environmental factors, such as moisture, affect tablet integrity in formulations with swelling excipients and varying porosity levels. These structural changes include reductions in tensile strength, porosity, and bulk density, occurring primarily within the first day of storage. The rapid onset of these changes indicates that early storage periods are critical for capturing physical instability during accelerated stability testing.

5.6 Future implications

The framework established in this chapter demonstrates that moisture sorption behaviour at the powder scale can be translated to tablet-level response and real-storage performance. The ability to scale DVS-derived kinetics to realistic storage conditions offers a practical route to early prediction of tablet physical stability using small sample quantities and short experimental times. This has clear implications for formulation screening, where rapid ranking of formulations based on moisture sensitivity and porosity-driven stability could be implemented early in development.

The observation that structural changes occur within the first day of storage suggests that conventional accelerated stability protocols may overlook critical early-stage instabilities. Future stability strategies could therefore benefit from incorporating short-term time points supported by DVS-guided predictions, enabling earlier identification of high-risk formulations.

While the present analysis focused on MCC and MCC-CCS systems under a single storage condition, the established scaling approach provides a basis for expansion to broader formulation spaces. Extending the framework to additional excipients, porosity ranges, and environmental conditions will be necessary to assess its generality and to refine the scaling factor between DVS and real-storage behaviour. Integration of formulation composition, porosity, and moisture uptake kinetics into unified predictive models represents a key opportunity for advancing stability assessment practices.

Overall, this chapter positions DVS as a tool not only for material characterisation but also for quantitative prediction of tablet moisture uptake behaviour under realistic storage conditions. Adoption of such particle- and tablet-informed scaling approaches has the potential to reduce experimental cost, accelerate development timelines, and support more robust formulation design in pharmaceutical development.

6.From simplicity to complexity: how excipients shape stability and disintegration of IR tablets

Chapter summary

This chapter examines the role of excipients in the physical stability of IR tablets stored under accelerated conditions (50°C/75% RH). A formulation staircase design with MCC, CCS, MgSt, and lactose across varying porosities reveals two pathways of change: rapid, moisture-driven weakening of tensile strength, and a slower, progressive increase in disintegration linked to wetting and swelling dynamics. Scaled DVS data reliably predict moisture uptake and loss of tensile strength, supporting its use as a tool for predicting long-term stability.

6.1 Introduction

Disintegration is a complex process involving several mechanisms, including the penetration of the dissolution medium into the tablet's porous structure, swelling (uni- and omni-directional), shape recovery, and dissolution of excipient particles (Desai et al., 2016; Markl and Zeitler, 2017; Quodbach and Kleinebudde, 2016). The impact of the tablet formulation on its disintegration process has been widely explored previously (Berardi et al., 2021; Desai et al., 2016; Maclean et al., 2021; Quodbach and Kleinebudde, 2016), with disintegrants being a primary contributor to breaking apart the tablet through swelling and shape recovery. However, other excipients, such as fillers, also influence this process. Soluble fillers, in particular, introduce additional complexity, as factors such as solubility, hydrophilicity, wettability, pore size, and swelling characteristics can influence disintegration efficiency (Berardi et al., 2021; Maclean et al., 2021; Janssen et al., 2022). These fillers dissolve upon liquid penetration and may compete with disintegrants for the available water, thereby reducing disintegration efficiency (Berardi et al., 2018; Johnson et al., 1991). Insoluble fillers, in contrast, require less liquid to wet fully, leaving more water available for disintegrants, thereby enhancing the performance of the disintegrants (Ekmekciyan et al., 2018). In addition to fillers, lubricants also affect disintegration by influencing tablet wettability and mechanical properties. Hydrophobic lubricants, such as MgSt, can affect disintegration through direct impacts on wettability and indirect effects on tablet tensile strength. While fine-grade MgSt has been shown to form softer tablets and improve disintegration in certain formulations, such as paracetamol tablets (Zarmpi et al., 2020), its general effect is to delay disintegration due

to its hydrophobic nature across both brittle and plastic tablet matrices (Paul and Sun, 2018).

Numerous studies have examined the disintegration behaviour of freshly manufactured tablets, with limited studies investigating how storage conditions influence this process to ensure tablets retain their disintegration performance until the time of administration. Storage can alter the contribution of each disintegration mechanism to overall tablet performance by inducing changes in tablet microstructure, such as particle swelling that impacts wettability and swelling capacity, as well as surface characteristics, including surface energy, which influences wettability and particle dissolution (Markl et al., 2021).

Previous research on tablet disintegration has primarily focused on the combined effects of complex formulations, examining how excipients such as disintegrants, fillers, and lubricants interact. Each of these components has unique properties that can make it difficult to pinpoint its individual roles in the disintegration process. The current United States Pharmacopoeia (USP) standard for dissolution and disintegration tests evaluates the tablet as a single unit, offering limited insight into how each excipient contributes to the overall performance. What makes this even more challenging is the diverse range of disintegrating matrices, reflecting the nearly endless possibilities for combining different drugs and excipients that behave differently, especially after storage. This highlights the importance of taking a more detailed approach to understanding how excipient interactions change over time. Additionally, mechanistic studies, such as those investigating liquid uptake, swelling, and force development in powder mixtures and tablets, could provide the kind of mechanistic understanding that traditional disintegration

tests cannot provide. In the previous chapter, simplified systems of pure MCC and MCC-CCS (8%) tablets were examined under accelerated conditions (50°C/75% RH) to track the progression of structural and physical changes over time and to identify the individual roles of each component in stability outcomes (Chapter 5). That chapter also introduced a predictive framework linking DVS measurements with real-storage behaviour through scaling factors for EMC and sorption rate constants. In addition to bridging short-term DVS experiments with long-term storage outcomes (time scale), relationships were also established between powder and tablet sorption behaviour (length scale).

This chapter aims to extend this approach by systematically investigating the impact of individual excipients on the stability and disintegration behaviour of more complex tablet formulations. Using a sequential design, excipients are progressively added to an MCC-based formulation to evaluate their specific contributions across varying porosities. Structural changes during storage at 50°C/75% RH are monitored by assessing weight, dimensions, tensile strength, and disintegration time, alongside surface liquid absorption and swelling kinetics. In addition to characterising these mechanistic changes, the study evaluates whether the predictive framework developed previously remains valid in multi-component formulations, examining the extent to which DVS-derived data can be used to estimate tablet moisture sorption behaviour under real-storage conditions. The inclusion of lactose and MgSt in this chapter is intended not only to increase formulation complexity, but also to challenge the applicability of the proposed framework beyond purely swellable excipient systems.

6.2 Materials and Methods

6.2.1 Materials

All materials used in this study are described in 3.1.

6.2.2 Raw materials characterisation

6.2.2.1 Moisture sorption analysis

Moisture sorption isotherms for powder blends were obtained as described in Section 3.2.1.1. The measurements were carried out at 50°C/(30-75% RH), as shown in Figure 3.1.

6.2.2.2 Sorption kinetic rate constant model

The model used to calculate the moisture sorption kinetic rate constant is described in Section 3.2.1.2.

6.2.2.3 True density

True density measurements of raw materials needed to calculate the porosity were conducted as described in Section 3.2.1.3. and are presented in Table C.1 in Appendix A.

6.2.3 Tablet manufacturing

Full details of the tablet manufacturing process are provided in Section 3.2.2. The formulations were developed stepwise, beginning with tablets composed solely of MCC. Subsequently, (3% w/w) CCS was incorporated to produce MCC-CCS tablets, followed by the addition of (1% w/w) MgSt to yield MCC-CCS-MgSt tablets. Finally, lactose (48% w/w) was introduced alongside MCC (48% w/w), CCS, and MgSt to create the MCC-

CCS-MgSt-Lac formulation (Table 6.1). Powder blends were prepared following the procedure outlined in Section 3.2.2.

Table 6.1: Compositions and abbreviations of the studied formulations.

Abbreviation	Components (% w/w)			
	MCC	CCS	MgSt	Lac
MCC	100	-	-	-
MCC-CCS	97	3	-	-
MCC-CCS-MgSt	96	3	1	-
MCC-CCS-MgSt-Lac	48	3	1	48

6.2.4 Tablet storage

Tablets were stored at 50°C/75% RH as described in Section 3.2.3, which details the storage setup and time points.

6.2.5 Tablet characterisation

Each tablet was characterised before and after storage, allowing the same tablet to be monitored throughout the study and ultimately retained for sessile drop measurements. For other destructive tests, including tensile strength and disintegration time, separate tablets were used. To ensure reproducibility, three freshly prepared tablets were tested at each time point.

6.2.5.1 Moisture sorption and kinetic rate constants

Tablet moisture sorption analysis to measure the EMC and the moisture kinetics rate constant is described in Section 3.2.4.1.

6.2.5.2 Weight, dimensions, and tensile strength

The weight, dimensions and tensile strength before storage were reported as described in Section 3.2.4.2.

The relationship between tablet porosity (f) and tensile strength was examined using the Ryshkewitch-Duckworth equation as described in Section 3.2.4.2.

Kinetic analysis of tensile strength during storage was performed using the rate constant model (Eq. 6.1). For each formulation and porosity, the rate constant was derived (r_{TS}), and model performance was assessed by R^2 and RMSE.

$$TS(t) = TS_0 e^{-r_{TS} t} + TS_{\infty} (1 - e^{-r_{TS} t}) \quad \text{Eq. 6.1}$$

$TS(t)$ denotes the tensile strength at time (t), TS_0 is the initial tensile strength as $t = 0$, r_{TS} represents the kinetic rate constant for tensile strength change and TS_{∞} corresponds to the tensile strength after long storage (the plateau value).

A supplementary table (Table C.2) is provided in Appendix C, showing the mean and standard deviation for the weights and volume measurements of tablets in the study at each storage time point.

6.2.5.3 Porosity

Tablet porosity before storage was calculated as described in Section 3.2.2.

6.2.5.4 Disintegration time

Tablet disintegration time was determined using a Charles Ischi AG disintegration bath (ED v.2. Zuchwil, Switzerland). The test was conducted in 800 mL of distilled water

maintained at 37°C. Disintegration time, recorded in seconds, was measured for three tablets of each formulation at each time point. The endpoint was defined as the complete disintegration of the tablet with no visible fragments remaining on the mesh screen.

6.2.5.5 Sessile drop method

The sessile drop method is based on placing a liquid droplet on a solid surface and analysing the droplet shape as governed by the balance of interfacial tensions at the solid-liquid-vapour contact line. In its conventional application, the method is used to determine the static or dynamic contact angle, which is a measure of surface wettability. Under ideal conditions, the contact angle is defined by Young's equation and is obtained once interfacial equilibrium is reached (Drelich, 2013). Accordingly, classical sessile drop experiments typically assume a non-porous, rigid substrate and focus on a single droplet profile at equilibrium or over a short time interval where liquid penetration into the solid is negligible. For porous and hygroscopic materials such as pharmaceutical tablets, these assumptions no longer hold. Liquid penetration into the pore network and surface swelling occur immediately after droplet deposition, preventing establishment of a true equilibrium contact angle. Consequently, time-dependent changes in droplet shape and footprint primarily reflect liquid absorption and surface deformation rather than intrinsic wettability alone (Quéré, 2008).

To analyse the surface liquid absorption and swelling kinetics of tablets, measurements were made using a drop shape analyser (Krüss DSA30, Krüss GmbH, Hamburg, Germany). Video recordings were captured at a frame rate of 50 frames per second while a single droplet of MilliQ® Ultra-pure water was dispensed onto the tablet surface.

Python 3.10 (Python Software Foundation, Virginia, USA) was used to analyse the video files to separate the droplet from the tablet surface at each frame. Details on the processing of sessile drop measurements can be found in the work of Markl et al. (2021). In summary, the analysis of liquid absorption and swelling behaviour involves determining characteristic parameters from the measured surface area (S_t) of the droplet over time. The liquid absorption ratio ($y(t)$) is calculated relative to the initial droplet size (S_0) at $t=0$ (Eq. 6.2). A power law equation (Eq. 6.3) is utilised to extract liquid absorption parameters, with k and m as fitting parameters determining the rate of liquid absorption and linearity of the process, respectively.

$$y(t) = \frac{S_t - S_0}{S_0} \quad \text{Eq. 6.2}$$

$$y(t) = kt^m \quad \text{Eq. 6.3}$$

Values of m close to 0.5 are characteristic of Darcy-type flow, which is driven by a capillary pressure gradient that causes liquid to flow from regions of low to high concentration. In contrast, values approaching 1 correspond to case II transport, where penetration is dominated by swelling processes driven by an activity gradient. Here, solvent ingress is restricted by factors such as increased tortuosity, hydrogel formation, reduced porosity, or pronounced swelling of the excipient matrix. Intermediate values are generally associated with anomalous transport, reflecting a mixed contribution from both mechanisms.

The swelling (s_t) as a function of time is described by the absolute change in surface area:

$$s(t) = S_t - S_{t,0} \quad \text{Eq. 6.4}$$

where $S_{t,0}$ represents the initiation of swelling. After determining $S_{t,0}$, a modified Schott model was used to describe the swelling behaviour (Schott, 1992). The initial non-uniform swelling, influenced by liquid absorption, is characterised by a delay, t_r , after which it follows the Schott model. The parameters of the Schott model, A and S_∞ , represent the reciprocal of the initial swelling rate and the swelling at infinite time, respectively (Eq. 6.5). This test was conducted for three repeats of the tablets' porosity at each time point during the stability testing.

$$s(t) = \frac{t - t_r}{A + \frac{(t - t_r)}{S_\infty}} \quad \text{Eq. 6.5}$$

6.3 Results

6.3.1 Effect of excipient on tablet characteristics before storage

6.3.1.1 Tensile strength

Figure 6.1 illustrates the relationship between tablet porosity and tensile strength for various formulations. As porosity increases, tensile strength consistently decreases across all formulations. With increasing porosity, the contact points between particles are reduced, thereby weakening inter-particle bonds and resulting in a less cohesive and compact structure (Hersen-Delesalle et al., 2007). This behaviour aligns with the Ryshkewitch-Duckworth equation, which describes the exponential decay of tensile

strength (σ_t) with increasing porosity. Within this model, two key parameters are used to characterise compactibility: σ_o , the extrapolated tensile strength at zero porosity, which reflects the intrinsic bonding potential of the powder; and b , the bonding capacity factor, which indicates how rapidly strength declines as porosity increases.

Among the formulations, tablets composed solely of MCC consistently demonstrated the highest tensile strengths at each porosity level, as well as the highest σ_o value. This highlights MCC's strong compaction properties and intrinsic ability to form strong inter-particle bonds (Thoorens et al., 2014). The addition of excipients, specifically MgSt and lactose, results in a decrease in tensile strength. Introducing MgSt into MCC-based tablets reduces tensile strength, lowers σ_o and increases b , signifying both a reduced bonding potential and greater sensitivity to porosity. This reduction occurs because MgSt, as a lubricant, covers particle surfaces, limiting effective bonding and reducing the overall cohesive strength of the tablet structure (Paul and Sun, 2018). The inclusion of lactose alongside MgSt further lowers tensile strength, resulting in the weakest tablets among all formulations tested at equivalent porosities. Lactose is known to be brittle and lacks the inherent bonding strength of MCC (Arida and Al-Tabakha, 2008; Dun et al., 2020); its presence disrupts the cohesive network of MCC, compounding the weakening effect introduced by MgSt. Consequently, tablets containing both MgSt and lactose exhibit the lowest tensile strengths, the lowest σ_o and the steepest b , clearly illustrating the additive detrimental impact of these excipients on tablet mechanical strength and the most pronounced loss of tensile strength with increasing porosity.

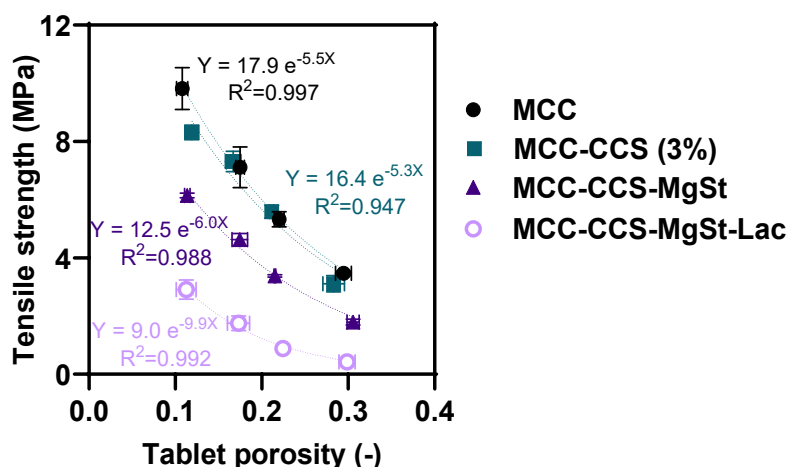


Figure 6.1: The relationship between tablet tensile strength and porosity. The line represents a fit to the Ryshkewitch-Duckworth model (Eq. 3.7) ($n = 3$, mean $\pm$ SD).

6.3.1.2 Disintegration time, liquid absorption, and swelling kinetics

Figure 6.2 illustrates how tablet porosity and formulation composition affect disintegration time and the key parameters describing liquid uptake and swelling, as determined from sessile drop measurements. Together, the six panels provide a mechanistic understanding of how excipient selection and pore structure interact to govern the performance of IR tablets. Figure 6.2A shows that all MCC-CCS tablets consistently showed rapid disintegration across all porosities, with times remaining below 60 seconds even at the lowest tested porosity. For example, at approximately 10% porosity, MCC-CCS tablets disintegrated in about 45 seconds. In contrast, the addition of MgSt (MCC-CCS-MgSt) delayed tablet disintegration at low porosities compared to formulations without MgSt, reaching times exceeding 70 seconds at around 10% porosity. This pronounced delay demonstrates MgSt's hydrophobic effect, which effectively restricts water penetration at lower porosity levels. However, this hindrance was reduced

at higher porosities (17-29%), where disintegration times were lower than those of the MCC-CCS formulation, indicating that increased porosity partially offsets the lubricant's negative impact by providing alternative water-access pathways. Additionally, MgSt is known to reduce tablet tensile strength by weakening inter-particle bonds (Figure 6.1).

Since tensile strength directly influences disintegration behaviour, the MgSt-induced weakening at higher porosity accelerates tablet breakup once water penetration occurs. These observations align with the findings of Lee et al. (2025), who demonstrated that MgSt prolongs hydration and disintegration due to its hydrophobic film, but simultaneously weakens interparticulate bonding (Lee et al., 2025). In contrast, CCS consistently accelerates disintegration by promoting swelling-driven rupture of the matrix. The addition of lactose to the formulations improved disintegration time. This faster disintegration can be attributed to lactose's water solubility. Although MgSt initially slows water entry due to its hydrophobic nature, the eventual ingress of water dissolves lactose rapidly, the existing pores enlarge, and additional pores gradually form, facilitating deeper liquid ingress and quicker structural breakdown.

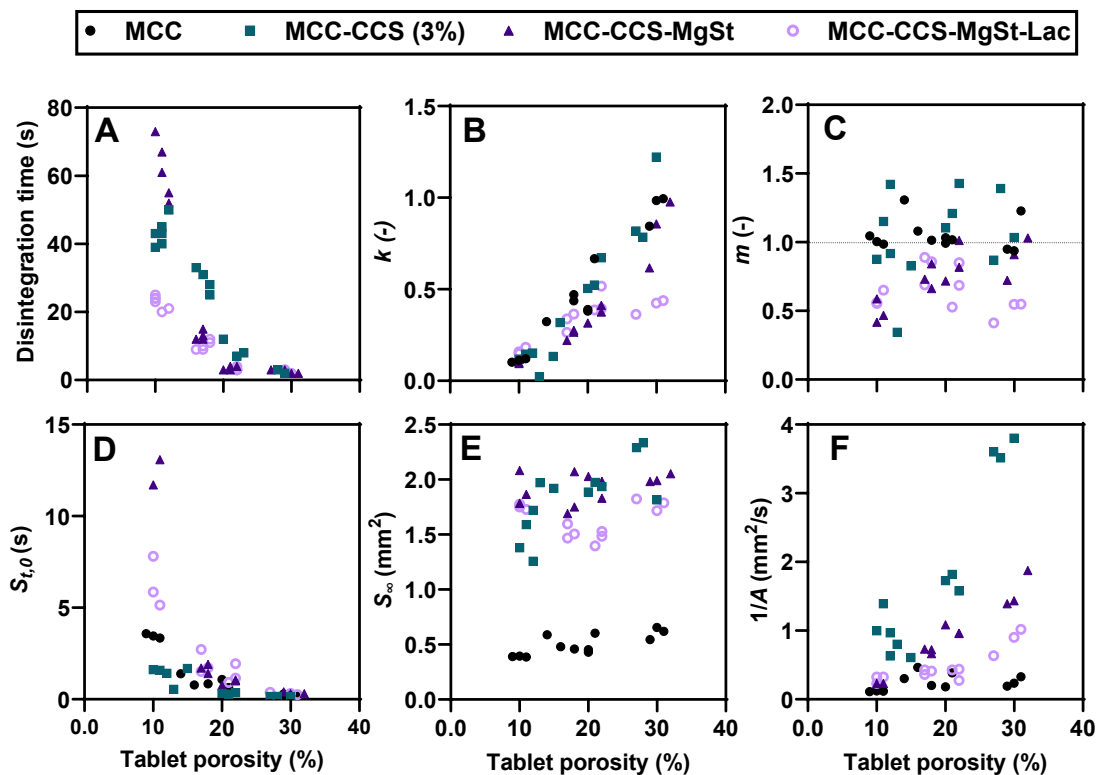


Figure 6.2: Effect of porosity and formulation composition on tablet disintegration and liquid uptake/swelling behaviour. (A) Disintegration time; (B) liquid absorption rate constant (k); (C) linearity of liquid absorption (m); (D) swelling onset time ($S_{t,0}$); (E) maximum swelling area (S_{∞}); and (F) initial swelling rate ($1/A$), as functions of tablet porosity. The disintegration time of pure MCC tablets was not measured.

These trends are further explained by looking at the liquid absorption rate (k , Figure 6.2B) and the uptake mechanism (m , Figure 6.2C). Across all formulations, increasing porosity consistently led to higher k values as the open structure facilitates water ingress. Pure MCC and MCC-CCS tablets exhibited higher k values at all porosities, indicating their superior ability to absorb water rapidly. The hydrophobic MgSt coating substantially reduced the water uptake rate compared to MCC-CCS tablets, which aligns with the delayed disintegration noted earlier. However, lactose inclusion showed a more complex

trend, initially increasing the rate of liquid absorption relative to MCC-CCS-MgSt formulations at lower-to-intermediate porosities (10-22%), indicating lactose's role in enhancing early-stage water uptake, possibly due to its dissolution and the resultant pore enlargement. Yet at higher porosities (29%), lactose-containing tablets showed decreased k values, suggesting that the dissolved lactose may form a saturated solution layer around the tablet surface and fill the pores, which act as a barrier and hinder further liquid penetration into the tablet core (Berardi et al., 2018; Janssen et al., 2022; Johnson et al., 1991).

The kinetic exponent (m , Figure 6.2C) further illustrates these transport mechanisms. For pure MCC and MCC-CCS tablets, m remained consistently close to or slightly above 1, a characteristic of a linear, case II transport, where solvent penetration is governed by an activity gradient associated with matrix swelling. This indicates that porosity had no significant effect on the uptake mechanism for these systems. In contrast to this observation, Yassin et al. (2015) reported a strong dependence on porosity for MCC-based tablets, where at very low porosity (5%) liquid ingress was severely hindered by the limited pore network, and the relative contribution of swelling became dominant, giving rise to strong case II behaviour. It should be noted, however, that the present study evaluates wetting behaviour at the tablet surface using sessile drop measurements, whereas Yassin et al. (2015) examined liquid uptake across the entire tablet. The hydrodynamic conditions in their setup, therefore, differ substantially from those in the current method, which may explain the observed discrepancy in porosity dependence. At intermediate porosity (15%), the greater pore volume facilitated rapid capillary transport,

consistent with Darcy flow, while at very high porosity (40%), swelling became so pronounced that it once again affected the liquid penetration kinetics, leading to a mixed case II and Darcy contribution. The addition of CCS in their study also promoted rapid swelling and case II behaviour (Yassin et al., 2015). In contrast, tablets with MgSt showed m values between approximately 0.6 and 0.8 at lower porosities (10-22%), indicating a mixed mechanism where Darcy-type capillary flow plays a significant role due to the lubricant's hydrophobic barrier that suppresses wicking. At higher porosities (>22%), m values for MgSt formulations approached approximately 0.9, indicating a gradual shift towards case II transport when pores became more accessible. Tablets with lactose did not exhibit a clear trend in porosity, with m values scattered between 0.7 and 0.9, indicating a combined contribution of Darcy flow and case II transport.

Swelling dynamics were closely aligned with these absorption mechanisms. The swelling onset time ($S_{t,0}$, Figure 6.2D) was the shortest in MCC-CCS tablets at all porosities; at approximately 29% porosity, swelling began almost instantly (within 1 second). For MgSt tablets, the onset of swelling was substantially delayed, especially at lower porosities (12 seconds at 10% porosity). Lactose tablets exhibited intermediate swelling onset, confirming that lactose promotes earlier wetting compared to MgSt-alone formulations, but does not match the efficiency of CCS alone. Several studies have reported that the dissolution of soluble ingredients can influence the extent and rate of liquid penetration, thereby affecting the swelling of disintegrants passively. However, soluble components may act as a double-edged sword. While their dissolution enhances initial wetting, they can also retard disintegration by consuming water molecules that

would otherwise be available to activate the disintegrant (Berardi et al., 2021; Ekmekciyan et al., 2018; Gordon and Chowhan, 1987).

Further supporting these trends, the maximum swelling area (S_{∞} , Figure 6.2E) and initial swelling rate ($1/A$, Figure 6.2F) illustrate how strongly formulation and porosity shape swelling extent and kinetics. Pure MCC tablets exhibited the lowest swelling extent and initial swelling rate across all porosities. The limited swelling observed for these tablets is entirely due to the intrinsic swelling capability of MCC, which remains modest without the addition of CCS. In contrast, formulations containing CCS demonstrated greater swelling extents. Since these formulations contained identical amounts of CCS, their swelling areas were generally comparable and showed minimal sensitivity to changes in tablet porosity, except with the MCC-CCS tablets, where porosity had an impact on the extent of swelling. However, differences emerged in the initial swelling rates among these CCS-containing formulations. MCC-CCS tablets consistently showed the highest initial swelling rates, emphasising CCS's dual role in rapidly absorbing water and driving immediate expansion. The presence of MgSt reduced initial swelling rates compared to MCC-CCS formulations, an effect observed clearly across all porosities. This reduction can be attributed to MgSt's hydrophobic coating, which initially delays water ingress. Tablets incorporating lactose exhibited even lower initial swelling rates across most porosities. This further reduction is primarily due to lactose's limited contribution to swelling, being water-soluble but non-swelling, lactose promotes initial water ingress but does not contribute directly to the tablet's expansion. Moreover, these lactose-containing tablets possess approximately half the MCC content compared to other formulations,

further restricting their overall swelling potential. Thus, despite aiding early liquid uptake, lactose limits the overall swelling response, resulting in the slowest swelling rates among the CCS-containing formulations.

6.3.2 Effect of excipient on tablet characteristics after storage

6.3.2.1 Moisture sorption

The extent and kinetics of moisture sorption varied with tablet composition and porosity. To capture these effects, results are presented from both DVS and jar storage.

6.3.2.1.1 DVS analysed tablets

Results from DVS analysis (Figure 6.3) distinguish between two aspects of sorption: the EMC and the kinetics of moisture uptake. In agreement with previous findings, EMC did not vary with porosity. This suggests that the water content at equilibrium is primarily determined by the excipient's hygroscopicity rather than by the tablet's microstructure. Across formulations, the inclusion of CCS resulted in a higher EMC, consistent with its strong affinity for water. In contrast, the partial replacement of MCC with lactose reduced EMC due to lactose's lower hygroscopicity. The addition of MgSt, however, did not affect EMC, reflecting its limited contribution to the equilibrium sorption capacity of the formulation. Thus, although excipient composition governs the extent of sorption, porosity does not appear to influence the equilibrium state. The corresponding EMC values for the powder blends are provided in Table C.3 in Appendix C.

In contrast, the sorption rate constant exhibited a strong dependence on porosity across all formulations (Figure 6.3). A clear linear relationship was observed between porosity

and r_{sor} , with powders (represented by 100% porosity) consistently showing the fastest kinetics. This behaviour indicates that microstructural factors primarily control the time scale of moisture uptake. Higher porosity provides greater pore connectivity and accessible surface area, allowing vapour to diffuse more rapidly into the compact.

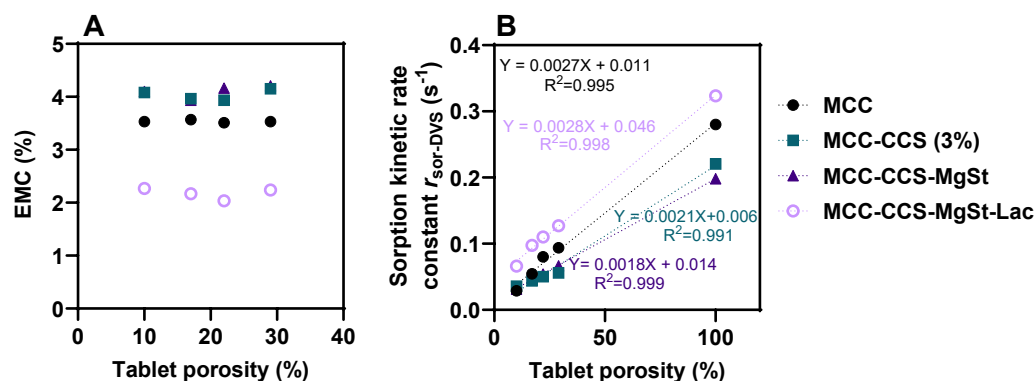


Figure 6.3: DVS analysis of tablets and powders at 50°C and 30-75% RH. (A) Equilibrium moisture content as a function of porosity. (B) The relationship between tablet porosity and the sorption rate constant, extended to 100% porosity to represent the powder state, and calculated using the kinetic rate constant model. Additional details on the model's predictive performance are provided in Table C.4 in Appendix C.

Introducing CCS reduced the moisture sorption rate compared to MCC alone. This behaviour suggests that while CCS contributes to higher EMC, it results in slower moisture sorption. This outcome can be attributed to the higher hygroscopicity of CCS, where excipients with a greater capacity for moisture uptake tend to reach equilibrium more slowly, as previously reported (Heidemann and Jarosz, 1991). By contrast, MCC, with lower hygroscopicity, required less total moisture to equilibrate and therefore displayed a relatively faster rate. The inclusion of MgSt across the different tablet porosities showed behaviour largely overlapping with MCC-CCS. However, when

examined in powder form, the MgSt-containing blend exhibited a lower rate constant than MCC-CCS. However, its effect is masked once the material is compacted into tablets. Replacing part of the MCC with lactose gave the fastest uptake across the porosity range and the highest powder limit. As a non-hygroscopic excipient, lactose requires only a small amount of moisture to reach equilibrium. With fewer binding sites to saturate, the system equilibrates more quickly, leading to higher observed rates.

In terms of porosity dependence, the lactose-containing formulation showed the strongest response, with a fitted slope of 0.0028. Sorption rates nearly doubled between 10% and 29% porosity, and the extrapolated powder value was more than five times higher than that of the lowest-porosity tablet, confirming an intrinsically rapid uptake. On the other hand, the MgSt-containing blend exhibited the lowest slope at 0.0018, indicating that porosity exerted the weakest influence on its sorption dynamics.

6.3.2.1.2 Jars stored tablets

Figure 6.4 shows the changes in tablet mass during storage at 50°C/75% RH as a function of porosity and formulation. All formulations gained mass, reflecting moisture uptake, and the extent of this uptake increased consistently with porosity. For example, MCC-CCS tablets with an initial porosity of 29% gained approximately 3.1% in mass, compared with 2.7% for tablets with a 10% porosity, highlighting the role of pore structure in facilitating moisture ingress under humid conditions.

Formulation effects followed the same hierarchy observed in the DVS experiments. The inclusion of CCS increased mass gain relative to MCC tablets, in line with its higher moisture affinity. Incorporating MgSt reduced uptake across the porosity range,

suggesting that its hydrophobic surface layer restricts ingress; however, this effect was more pronounced with the tablets stored in jars compared to the DVS-analysed tablets. The largest reduction was observed when lactose was introduced alongside MgSt, with mass gains lower than the other formulations. At 17% and 22% porosity, these tablets showed roughly half the mass increase of the MgSt-containing system, consistent with lactose's low hygroscopicity and its dilution of the overall MCC content.

Temporal analysis of Figure 6.4 also reveals that most mass gain occurred within the first 24 hours of storage, followed by only minor changes up to day 42. This indicates that moisture uptake is a relatively rapid process, largely driven by initial exposure. The early uptake likely saturates accessible pores and interacts with hydrophilic sites, after which the system approaches equilibrium.

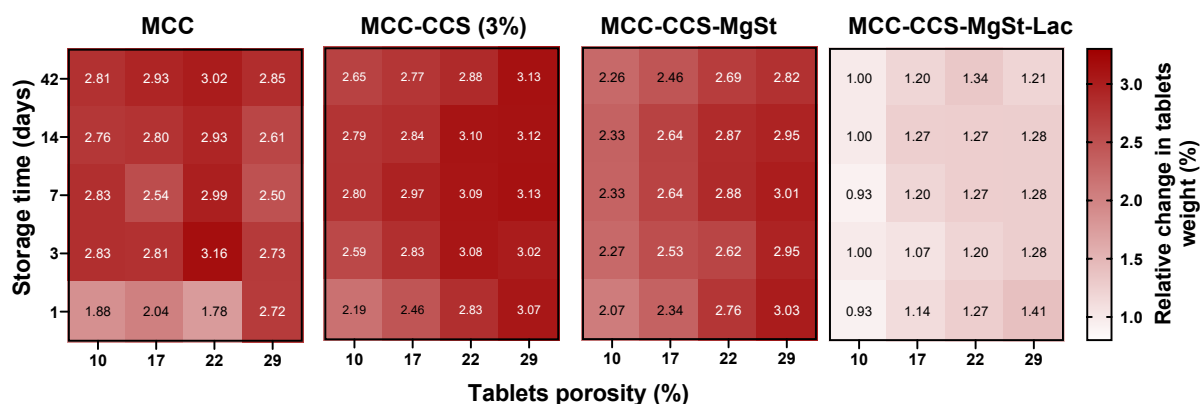


Figure 6.4: The average relative change in tablet weight (%) after storage at 50°C/75% RH over time relative to the tablets' mass before storage (each point represents an average of 3 different tablets).

The rate constants derived from the jar stored tablets showed a consistent linear increase with porosity for all formulations (Figure 6.5). The MgSt blend showed the weakest

porosity dependence. The high R^2 demonstrate that porosity predominantly governs the kinetics of moisture ingress under storage conditions.

When compared with the DVS analysed tablets, the overall hierarchy of formulations was maintained, and the dependence of sorption rate constants on porosity was similarly linear. However, the absolute rate constants were lower in jars than in DVS, reflecting the slower equilibration that occurs under real storage, where vapour flow and exchange are less efficient than in the DVS system.

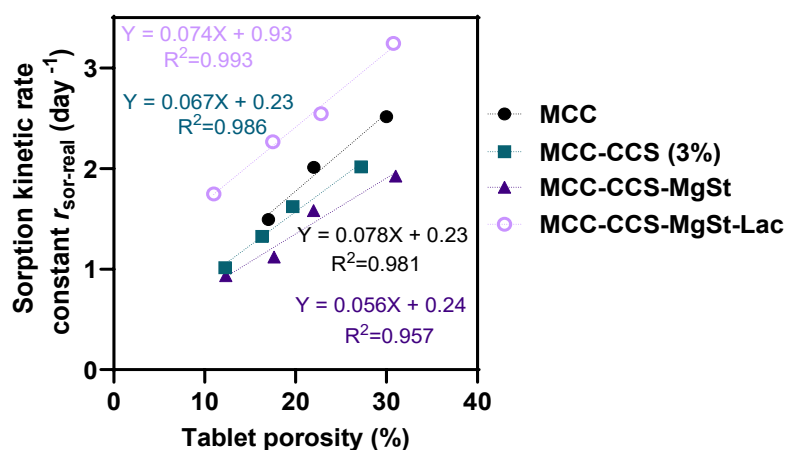


Figure 6.5: Sorption kinetic rate constants of jar-stored tablets stored at 50°C/75% RH, calculated using the kinetic rate constant model. Details of the model performance are provided in Table C.5 in Appendix C. Data are reported only where the fit achieved $R^2 > 0.85$.

6.3.2.2 Tablet volume

Figure 6.6 presents a heatmap showing the relative volume increase of tablets over time after storage at 50°C/75% RH. All tablets experienced measurable swelling after storage, corresponding with their moisture uptake profiles. Tablets with higher initial porosity

consistently displayed greater volumetric expansion, supporting the notion that increased porosity facilitates greater moisture ingress and subsequent swelling.

MCC tablets showed significant swelling, particularly at higher porosities (29%), which aligns with MCC's known swelling capability due to extensive hydrogen bonding with water. The incorporation of CCS further enhanced swelling across all porosities, consistent with CCS's high water absorption potential and swelling capacity (Soundaranathan et al., 2020). Conversely, the addition of MgSt markedly reduced swelling compared to MCC-CCS tablets, attributable to MgSt's hydrophobic character, which impairs water ingress by forming a lubricating film over particle surfaces, thereby reducing the moisture-driven expansion of the matrix.

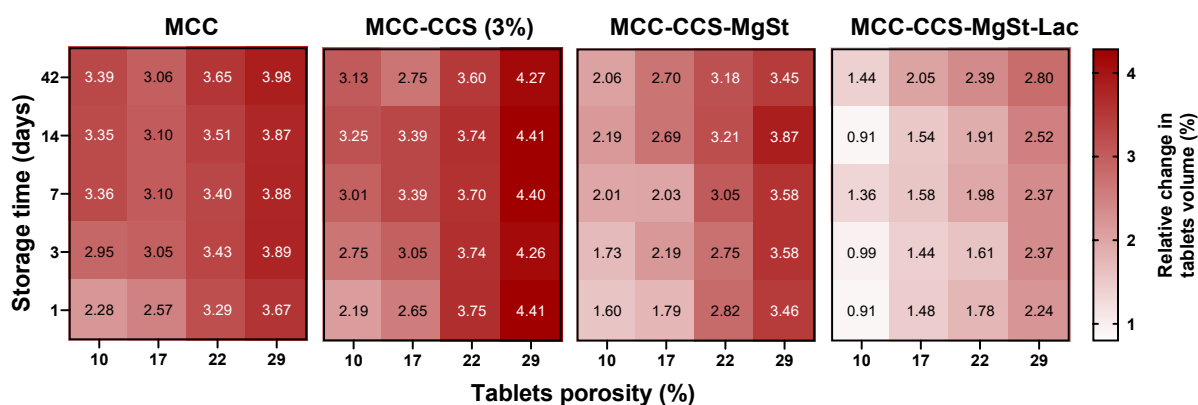


Figure 6.6: The average relative change in tablets' volume (%) after storage at 50°C/75% RH over time relative to the tablets' volume before storage (each point represents an average of 3 different tablets).

Further reduction in swelling was observed upon the addition of lactose in the MCC-CCS-MgSt-Lac formulation. Volume increases remained consistently low, ranging between 0.94% and 2.8%, even at the highest porosity level. Lactose, being a crystalline

and non-hygroscopic excipient, does not readily interact with moisture. Moreover, replacing a large proportion of MCC with lactose dilutes the overall swelling potential of the matrix, as MCC is the primary swelling driver in the original formulation (Markl et al., 2017c; Yassin et al., 2015). Temporal analysis shows that most volume expansion occurred within the first day of storage. For example, in the MCC-CCS system, the majority of swelling was already evident by day 1, after which the change plateaued. This rapid initial expansion suggests that the system reaches moisture equilibrium relatively quickly under the severe storage condition of 50°C/75% RH. For more hydrophobic formulations (e.g., MgSt-containing), the swelling curve remained flatter and delayed, indicating slower moisture access and lower final expansion.

6.3.2.3 Tensile strength

Figure 6.7 presents both the absolute tensile strength values (top panels) and the corresponding percentage changes relative to the initial pre-storage values (bottom heatmaps) for tablets stored at 50°C/75% RH. The data illustrate a clear pattern of rapid mechanical degradation across all formulations, predominantly within the first day of exposure, followed by minimal additional change over the remainder of the 42-day storage period. Starting with MCC-only tablets, the highest tensile strength values were recorded at time zero, particularly for the 10% porosity group (9 MPa). Following storage, the strength dropped sharply within the first day and gradually stabilised, with final values around 5 MPa for low porosity tablets. The relative strength reduction for MCC ranged between 18% and 48%, depending on porosity (Figure 6.7, bottom left panel). These

reductions reflect water-mediated disruption of the extensive hydrogen bonding network typical of MCC-rich compacts.

When CCS was added, a moderate decrease in both initial tensile strength and the magnitude of strength loss upon storage was observed. Particles that can swell upon moisture uptake generate internal stresses within the compact, pushing neighbouring particles apart and interrupting inter-particle bonding, which leads to a reduction in tensile strength.

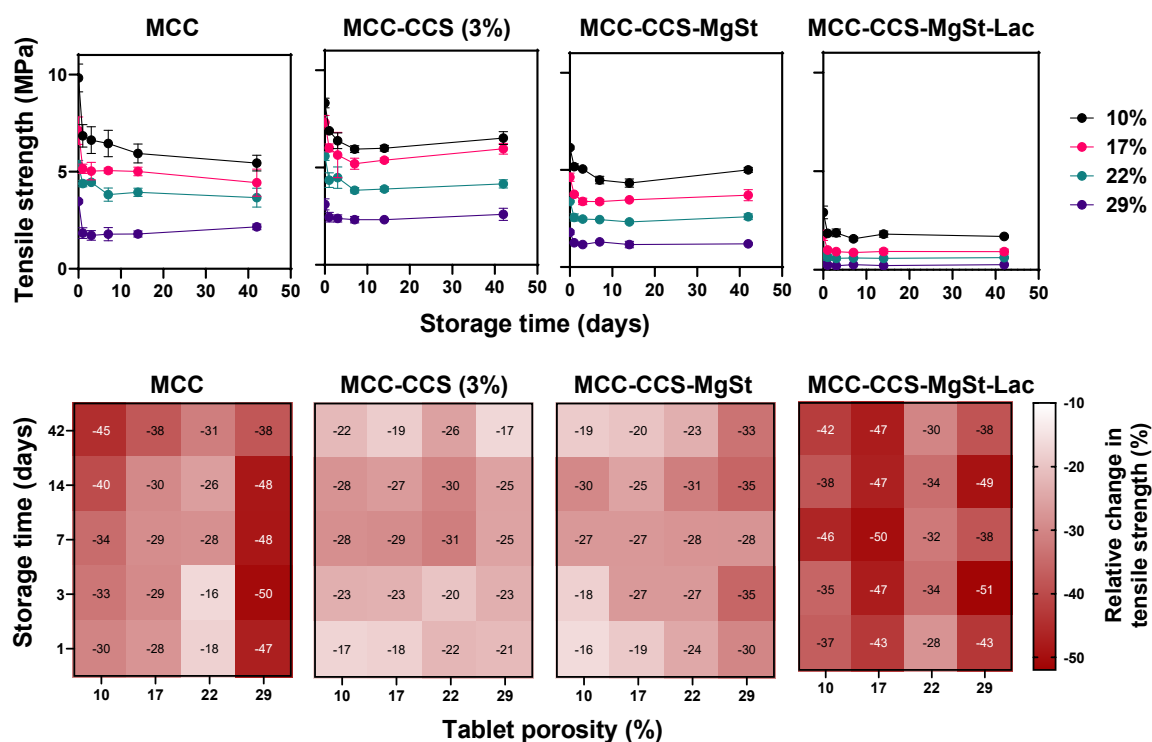


Figure 6.7: Effect of storage time on tensile strength of tablets. Top panel: Tensile strength values over 42 days of storage at 50°C/75% RH ($n = 3$, mean $\pm$ SD). Bottom panel: The percentage change in tensile strength relative to before storage values for the same formulations across porosity levels.

The heatmap shows a lower drop in strength, particularly for lower porosities. This suggests that CCS, while hygroscopic, can provide a degree of structural buffering during moisture uptake. In contrast, the incorporation of 1% of MgSt reduced the initial tensile strength at all porosities, and storage induced further declines. The heatmap for MCC-CCS-MgSt shows losses ranging from 19% to 33% after 42 days, with higher porosity tablets being the most affected. Several studies have reported that moisture can influence the solid-state properties of MgSt, particularly its crystallinity and hydration state (Calahan et al., 2021; Rajala and Laine, 1995; Swaminathan and Kildsig, 2001). These hydration states influence the functional properties of tablets, including hardness, disintegration, dissolution, and surface free energy (Yamamoto et al., 2017). Other studies have demonstrated that the crystal form, water content, and surface properties of MgSt undergo changes under storage conditions in both bulk and tablet forms, with implications for lubrication and dissolution (Calahan, 2020).

The most dramatic effect was seen in tablets containing both MgSt and lactose. These tablets initially exhibited the lowest tensile strengths (mostly below 3 MPa) and showed the largest relative strength losses across all porosities, ranging from 30% to 47% by day 42. The effect of storage on the tensile strength of lactose tablets has shown varied outcomes across different studies. Riepma et al. (1992) reported a rapid decline in the crushing strength of lactose tablets within minutes of exposure to ambient humidity, which they attributed to dissolution at particle contact points and associated relaxation. Interestingly, they also observed that this loss could be partially reversed through post-storage drying, presumably due to recrystallisation and formation of new solid bridges.

In contrast, Shi et al. (2025) found that storage led to increased tensile strength in most lactose tablets, attributed to solid bridge formation or densification, except in spray-dried lactose. These differences highlight the role of lactose type, particle morphology, and storage conditions in modulating the mechanical response to moisture exposure.

Porosity exerted a consistent influence across all formulations. Lower porosity tablets maintained higher tensile strength values post-storage, while higher porosity ones were more prone to drastic weakening. This trend is attributed to the reduced number of particle contact points in high-porosity compacts, which diminishes the number of interparticle bonding sites and allows for more rapid moisture ingress and swelling-induced mechanical failure. The kinetic profiles in the upper plots of Figure 6.7 show that most tensile strength loss occurred within the first day of storage. This is visible in the steep drop between day 0 and day 1, followed by minimal change thereafter. This rapid equilibration indicates that the structural rearrangements, including bond weakening, swelling, and possible recrystallisation, occur quickly once the tablets are placed in high-humidity conditions.

To understand the kinetics of tensile strength loss during storage, Figure 6.8 plots the fitted rate constant (r_{TS}) against tablet porosity at 50°C/75% RH. Overall, r_{TS} increased with porosity, indicating that more open tablets lose tensile strength more rapidly. The magnitude of this dependence varied by formulation, with MCC-CCS exhibiting a clear positive trend, whereas pure MCC showed a weak, poorly correlated dependence. These observations suggest that the microstructure sets the timescale of weakening, while composition modulates its magnitude.

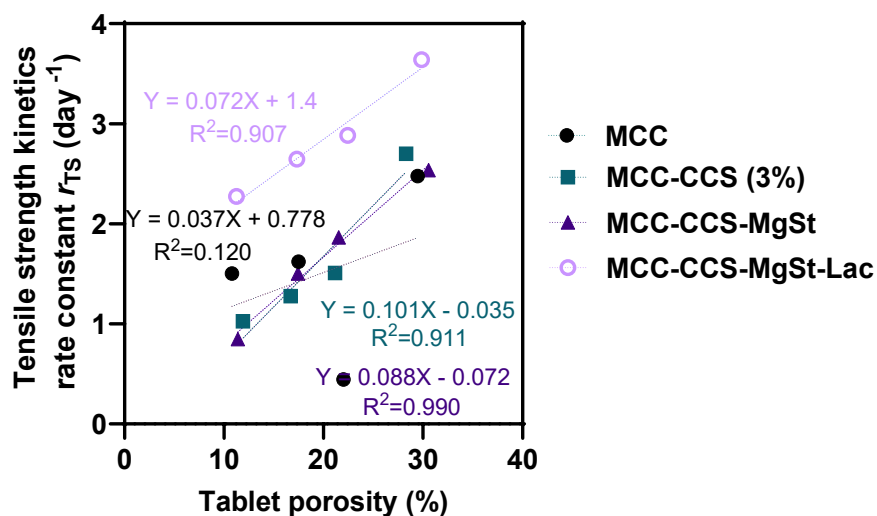


Figure 6.8: Kinetic rate constants for tensile strength loss in tablets stored at 50°C/75% RH, estimated using the model applied to tensile strength data (Eq. 6.1). Model fit statistics are summarised in Table C.6 in Appendix C.

6.3.2.4 Disintegration time

Figure 6.9 presents the evolution of disintegration time for three formulations (MCC-CCS, MCC-CCS-MgSt, and MCC-CCS-MgSt-Lac) after storage at 50°C/75% RH. The data clearly show that the impact of storage on disintegration kinetics is highly formulation and time-dependent, with a more delayed response compared to moisture uptake or mechanical weakening.

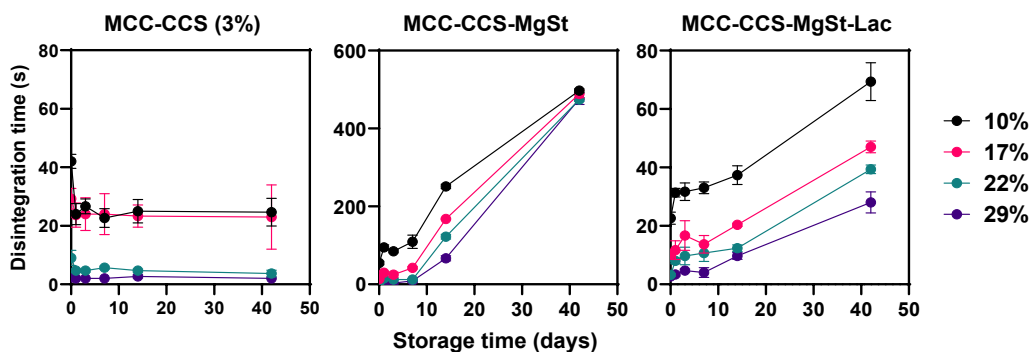


Figure 6.9: The disintegration time of tablets of different formulations after storage at 50°C/75% RH over time (n = 3, mean $\pm$ SD).

For MCC-CCS tablets, disintegration times remained largely stable after an initial decline, which reflects the formulation's resilience and the capacity of CCS to retain its swelling and water uptake efficiency under humid conditions. In contrast, MCC-CCS-MgSt tablets exhibited a striking increase in disintegration time over the storage period, particularly evident after day 14. For example, at 10% porosity, the disintegration time increased from approximately 40 s on day 1 to nearly 500 s by day 42. All porosity levels followed a similar upward trend. This delayed but progressive response suggests a moisture-driven consolidation of the MgSt film around particles, likely forming a more continuous and hydrophobic barrier that restricts water penetration and the activation of CCS swelling. The addition of lactose into the MgSt-containing formulation mitigated, but did not eliminate, the disintegration delay. The disintegration time of Lac-containing tablets increased over time across all porosities, but to a lesser extent than MCC-CCS-MgSt formulations. At day 42, 10% porosity tablets disintegrated in 70 s, compared to 500 s in the MgSt formulation without lactose. The inclusion of lactose likely interrupts the continuity of the MgSt film or dilutes its hydrophobic effect. Riepma et al. (1992)

demonstrated that moisture uptake in lactose tablets resulted in a reduced BET surface area, indicative of pore blockage, and was directly linked to moisture-induced recrystallisation within the tablet matrix (Riepma et al., 1992). This mechanism was later reinforced by Shi et al. (2025), who reported that the disintegration time of lactose-based tablets significantly increased after storage under high RH conditions. The authors attributed this delay to the dissolution of lactose particles at the tablet surface, which, upon absorbing moisture, formed a concentrated solution that subsequently recrystallised and partially blocked the tablet pores (Shi et al., 2025).

Although all formulations remained within the USP disintegration limit of 30 minutes for uncoated tablets (USP, 2011), the relative increase in disintegration time, particularly in MgSt-containing formulations, was substantial. This is particularly concerning, considering the tablets were only 5 mm in diameter. According to the FDA draft guidance for BCS class I and III drugs, disintegration may be used as a surrogate for dissolution when $\geq 80\%$ of the drug dissolves within 15 minutes, in which case, complete disintegration within 5 minutes in 0.01 M HCl is expected (Silva et al., 2018). Based on this stricter criterion, the stored MgSt-containing tablets would likely fail, especially if scaled up to larger tablet sizes.

Across all formulations, porosity consistently influenced the disintegration time. Lower porosity tablets exhibited the most pronounced delays after storage, particularly in MgSt and lactose-containing systems. The progression of disintegration delay occurred over weeks rather than hours. This temporal pattern contrasts with moisture-induced dimensional and mechanical changes, which reached equilibrium early, mostly by day 1.

Instead, the delayed disintegration response suggests longer-term microstructural and surface properties changes within the tablet, especially where hydrophobic materials are involved.

6.3.2.5 Liquid uptake and swelling kinetics

To further understand the progressive delay in disintegration observed for certain formulations after storage at 50°C/75% RH, sessile drop analysis was used to investigate the liquid absorption dynamics and swelling response. The parameters extracted provide mechanistic insight into how storage modifies tablet surface wetting and internal expansion capacity (Figure 6.10).

In the MCC-CCS formulation, all sessile drop parameters remained relatively stable throughout storage. k showed no significant drop; the swelling onset time remained short (typically under 3 seconds), and the initial swelling rate remained high. The liquid uptake mechanism exponent remained near 1, indicating that case II transport was maintained. These stable kinetics closely matched the consistent and rapid disintegration behaviour observed over the entire storage period. Although the literature often proposes a loss of disintegrant efficiency due to premature swelling as an explanation for storage-induced delays in disintegration, such a mechanism was not evident in the present study. The MCC-CCS tablets retained their robust disintegration performance after storage, suggesting that the observed structural changes (swelling and reduction in tensile strength) did not compromise the activation of CCS within the compact.

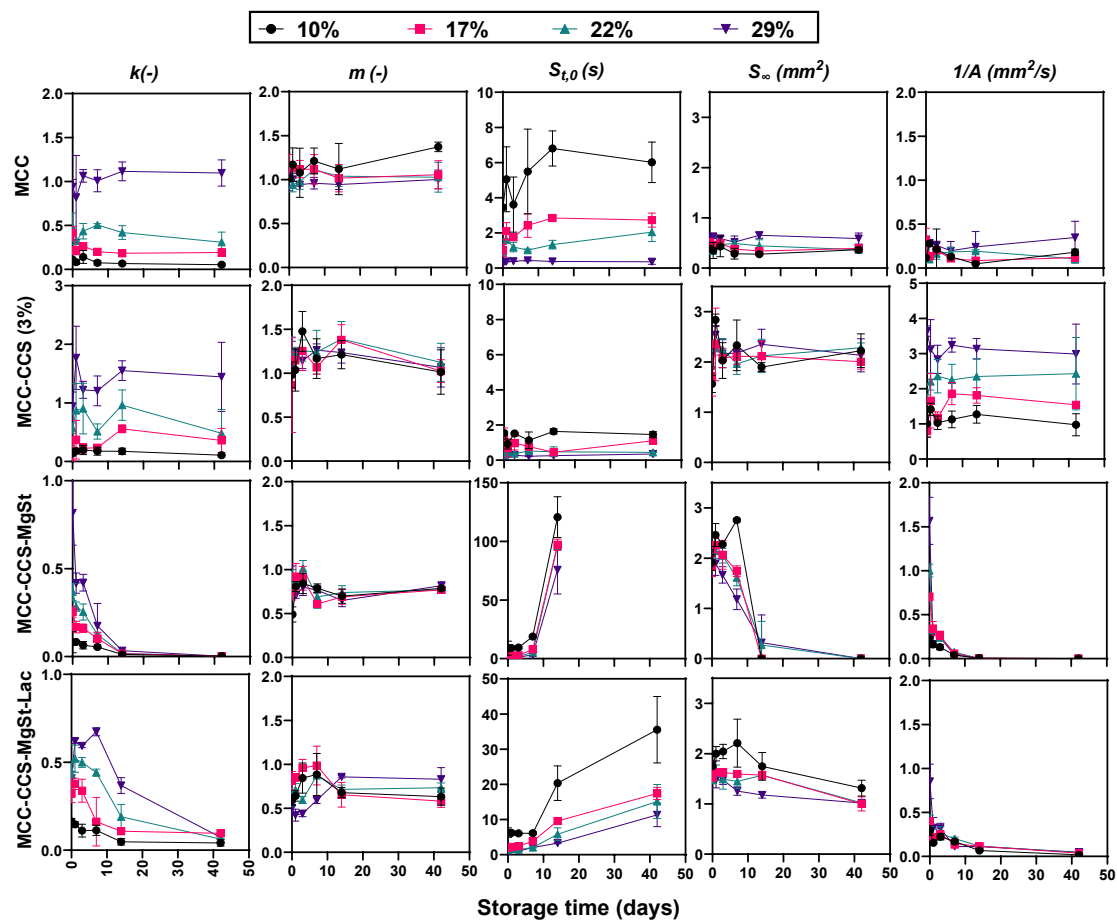


Figure 6.10: Characteristic parameters of the liquid absorption and swelling profiles extracted from the sessile drop profiles using (Eq. 6.3 and Eq. 6.5) after storage at 50°C/75% RH over time ($n = 3$, mean $\pm$ SD).

In contrast, tablets containing MgSt showed progressive changes across all measured parameters. k decreased sharply with time, particularly in low-porosity tablets, suggesting reduced surface wettability and slower capillary flow. At day 42, tablets with 10% porosity exhibited less than 25% of their initial k value. The onset time of swelling increased considerably, and in some cases, no swelling was detected within the 10-minute observation window, indicating near-complete inhibition of swelling initiation. Concurrently, m shifted upward toward 0.8, reflecting a change from Darcy-type flow to

anomalous transport (a mix of case II and Darcy transport mechanisms). As the matrix becomes more hydrophobic due to moisture exposure, liquid uptake may become more dependent on swelling of the matrix or structural rearrangement, rather than free capillary flow. Both the initial swelling rate and final swelling extent declined over time. These observations suggest that storage caused progressive changes in MgSt at particle interfaces, resulting in the formation of a more hydrophobic surface that restricted water ingress and delayed the activation of swelling. These changes align with the disintegration data, which showed a continuous increase in disintegration time, reaching over 500 seconds by day 42. While no study has directly explained why the wettability of MgSt-containing tablets decreases after storage, model investigations of MgSt multilayers show that stearate chains can reorganise under thermal stress (Rapp et al., 1995). In addition, Koivisto et al. (2004) demonstrated that prolonged exposure of MgSt to high humidity altered pore characteristics and introduced irreversibly adsorbed (partly chemisorbed) water, even without a clear change in hydration state. Such exposure may also induce subtle transformations between different crystal and hydrate forms of MgSt, as reported in previous work linking its solid-state structure to functional performance (Calahan, 2020; Rajala and Laine, 1995; Swaminathan and Kildsig, 2001; Yamamoto et al., 2017). Together, these findings support the interpretation that storage conditions can promote structural and interfacial reorganisation of MgSt in tablets. However, the marked hydrophobic surface formation and near-complete inhibition of liquid penetration observed here suggest a more extensive restructuring, most consistent with lubricant redistribution to the tablet surface. Similar phenomena have been reported in polymer

systems subjected to humid and thermal stress, where stearate lubricants accumulate at the surface, resulting in increased hydrophobicity and reduced wetting (Bak et al., 2021). Although the polymer matrix differs from pharmaceutical compacts, this phenomenon provides a mechanistic explanation for the extreme wetting failure seen here, which cannot be fully explained by chain reorientation or hydrate-related changes alone.

The addition of lactose partially offset some of the negative effects associated with MgSt. At early time points, an increase in k was observed, likely due to increased porosity introduced by lactose dissolution. However, over time, k again declined, accompanied by longer $S_{t,0}$, reduced $1/A$, and lower S_{∞} . These effects were more moderate than in the MCC-CCS-MgSt formulation and corresponded with a less sharp rise in disintegration time, which reached about 70-80 seconds by day 42. The lactose may have initially improved wettability, but with extended exposure to humidity, it likely formed a concentrated solution that subsequently underwent recrystallisation, which contributed to densification of the structure and limited the mobility of the expanding matrix.

Porosity played a clear role at early time points. In the MCC and MCC-CCS formulations, higher porosity was associated with increased k and $1/A$, faster swelling onset, and greater swelling extent, all of which translated into faster disintegration, indicating good correlation between wetting and swelling behaviour. However, in the MgSt-containing formulations, the effect of porosity diminished over time. By day 42, there was little variation between porosity levels in the values of k , $S_{t,0}$, and $1/A$. This suggests that the formation of a continuous hydrophobic film effectively masked the internal geometric differences, making porosity a less influential factor for water uptake and swelling. In

this case, surface chemistry and barrier formation become dominant factors, overshadowing the advantages of higher porosity. As a result, tablets with 10% porosity performed similarly to those with 29% porosity in these formulations. Images of some sessile drop measurements are shown in Figure C.1 in Appendix C.

6.4 Discussion

6.4.1 Bridging DVS and real storage in multi-component formulations to predict long-term moisture uptake

To enable prediction of storage behaviour from DVS data, scaling factors were introduced to account for the systematic differences observed between the two methods (Table 6.2). This adjustment translates DVS measurements, conducted in a closed and highly controlled environment, into the slower and more variable uptake seen in jar storage. By comparing both the EMC and sorption rate constants obtained from DVS and real storage, formulation-specific scaling factors were calculated to provide predictive links across methods.

Across all formulations, scaling factors were lower than unity, reflecting the consistent observation that jar-stored tablets retained less water and exhibited slower uptake compared to their DVS counterparts. This difference arises from the intrinsic contrasts between the two techniques. In DVS, samples are measured in a sealed humidity-controlled chamber under a continuous flow of humidified gas, which accelerates sorption and leads to faster uptake. In contrast, jar storage relies on a static atmosphere and requires removal of tablets for weighing, during which brief exposure to ambient air

results in moisture loss. Together, these factors lower the apparent uptake and slow the measured kinetics in jars relative to DVS.

Table 6.2: Scaling factors for EMC and sorption rate constant at 50°C/75% RH, showing the correction required to translate DVS data to real storage across formulations and porosities.

Formulation and tablet Porosity (%)	EMC scaling factor (EMC_{real}/EMC_{DVS})				r_{sor} scaling factor $10^{-4} \times (r_{sor-real}/r_{sor-DVS})$			
	10%	17%	22%	29%	10%	17%	22%	29%
MCC	0.8	0.82	0.86	0.81	0.82	3.17	2.89	3.1
MCC-CCS	0.65	0.69	0.72	0.74	3.27	3.5	3.73	4.16
MCC-CCS-MgSt	0.58	0.6	0.66	0.66	3.44	2.72	3.38	3.35
MCC-CCS-MgSt-Lac	0.44	0.55	0.69	0.54	3.06	2.69	2.67	3.10

EMC scaling factors varied across formulations and appeared to show some dependence on porosity. This variation does not reflect intrinsic changes in equilibrium sorption, since DVS measurements consistently demonstrated that EMC is determined by excipient hygroscopicity and the RH level. Instead, these variations likely arise from artefacts associated with jar method weighing. During weighing, tablets are briefly exposed to ambient conditions, allowing moisture loss that is not captured. The extent of this desorption can vary between formulations and may also depend on porosity, which affects how readily moisture escapes during handling. Such effects alter the apparent EMC measured in jars and, in turn, impact the calculated scaling factor. For lactose-containing tablets, additional variability was introduced by physical changes after storage, where tablets became brittle and lost fragments at the edges, leading to an underestimation of weight gain in the jar method and, consequently, lower scaling values.

By contrast, when analysing the rate constant scaling, the differences across formulations and porosities were relatively minor. Using a single r_{sor} -scaling factor, derived from

MCC formulation, was sufficient to predict moisture uptake kinetics across all systems with high accuracy (Table C.7 in Appendix C), indicating that the offset between DVS and jar measurements for sorption rate constant is largely method-related and independent of formulation or porosity. This supports the interpretation that the kinetic discrepancy arises primarily from the continuous flow of humidified gas in DVS, which accelerates sorption, compared with the static atmosphere in jar storage, rather than from material-specific behaviour.

This suggests a hybrid scaling strategy. A single r_{sor} -scaling factor can be applied universally across formulations and porosities, since the kinetic offset is method-driven and not composition-specific. In contrast, EMC scaling should be retained at the formulation level to account for handling-related moisture loss and, in some cases, physical instabilities such as brittleness.

The predictive performance of the framework is demonstrated in Figure 6.11, where tablet-based DVS data scaled to storage using a single average scaling factor for each formulation (Table 6.2) shows strong agreement with experimental results across all porosities, with high R^2 values (Table C.8 in Appendix C). Powder-based DVS data could also be used for prediction; however, this approach consistently overestimated EMC, likely due to the greater moisture content measured in powders compared to tablets. Nevertheless, powder-based predictions (Figure C.2 and Table C.8 in Appendix C) also captured overall trends but showed reduced accuracy, particularly for formulations with lower porosity.

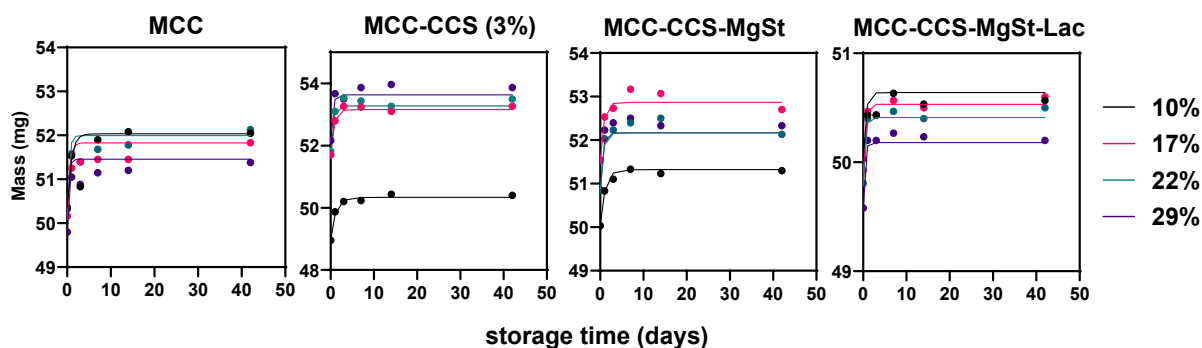


Figure 6.11: Predicted (lines) and experimental (points) moisture uptake of tablets at 50°C/75% RH using tablet-based DVS-derived scaling.

6.4.2 Linking moisture uptake with mechanical and functional changes

The relationship between moisture uptake and storage-induced changes in tablet properties was not uniform across the parameters investigated. Some properties, such as tensile strength and volume expansion, showed rapid changes that closely paralleled the extent of water sorption. In contrast, others, such as disintegration, continued to drift over time even after gravimetric mass had stabilised. This suggests that the impact of humidity is not governed by a single process, but rather by at least two distinct modes of response. Based on these observations, the storage behaviour of IR tablets can be described in terms of an early exposure-driven pathway, directly linked to moisture uptake kinetics, and a prolonged exposure-driven pathway, where functional changes emerge through slower structural processes over time.

6.4.2.1 Early exposure-driven weakening of tensile strength: Kinetic coupling between moisture uptake and tensile strength loss

Figure 6.12 compares the tensile strength rate constant with the sorption rate constant for all formulations. For the three blends (MCC-CCS, MCC-CCS-MgSt, and MCC-CCS-MgSt-Lac), the fitted lines have a close-to-unity slope with small intercepts and a high R^2 . This suggests that the timescale of mechanical weakening closely aligns with the timescale of moisture uptake. Slopes slightly greater than one are consistent with a modest early acceleration in loss of strength relative to bulk mass gain. In contrast, MCC shows a weaker kinetic coupling and greater variability.

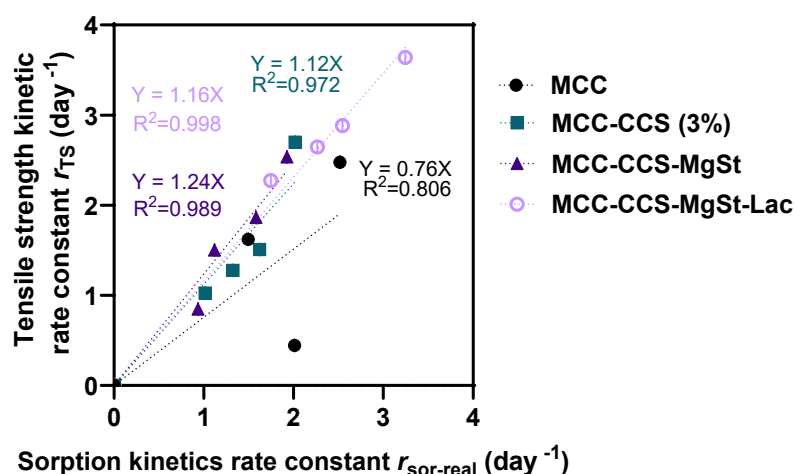


Figure 6.12: Kinetic coupling of moisture uptake and tensile strength loss after storage at 50°C/75% RH.

Although porosity is not explicit in Figure 6.12, the within-formulation scatter is consistent with the porosity dependence of r_{TS} shown in Figure 6.8, where more porous tablets weaken faster, raising both rates but preserving the near-linear mapping between

$r_{\text{sor-real}}$ and r_{TS} . The differences in slopes among the formulations imply that composition, not only microstructure, governs the degree of kinetic coupling.

With this coupling established, DVS sorption rates scaled to storage can be used to predict the timescale of tensile-strength loss. First, sorption rate constants were extracted from DVS data (Figure 6.3B) and translated to real-storage values using the previously established, formulation-specific scaling factor (Table 6.2). The tensile strength model (Eq. 6.1) was then run under two choices for r_{TS} : (i) the fitted linear mapping from Figure 6.12 between r_{TS} and $r_{\text{sor-real}}$ with the slopes slightly >1 with small intercepts, and (ii) a simple 1:1 assumption, $r_{\text{TS}} = r_{\text{sor-real}}$. Both strategies reproduced the experimental tensile strength curves over 0-42 days with high R^2 (Table C.9 in Appendix C), capturing the early decline and the approach to the long-term plateau, and this supports the interpretation that tensile strength loss is exposure-driven and governed by the sorption timescale.

6.4.2.2 Prolonged exposure-driven change in disintegration

In contrast, disintegration time showed a markedly different pattern (Figure 6.13). Moisture uptake plateaued by day 1-3 for all systems, but disintegration continued to increase steadily over 42 days. This decoupling demonstrates a prolonged exposure-driven pathway in which early exposure acts as the trigger, but functional behaviour evolves through slower microstructural processes that persist at near-constant moisture uptake.

Prior terahertz-TDS observations support this interpretation (Figure 5.12), revealing progressive changes in the loss coefficient in MCC and MCC-CCS formulations, despite stable gravimetric mass, which is consistent with microstructural evolution rather than additional moisture sorption.

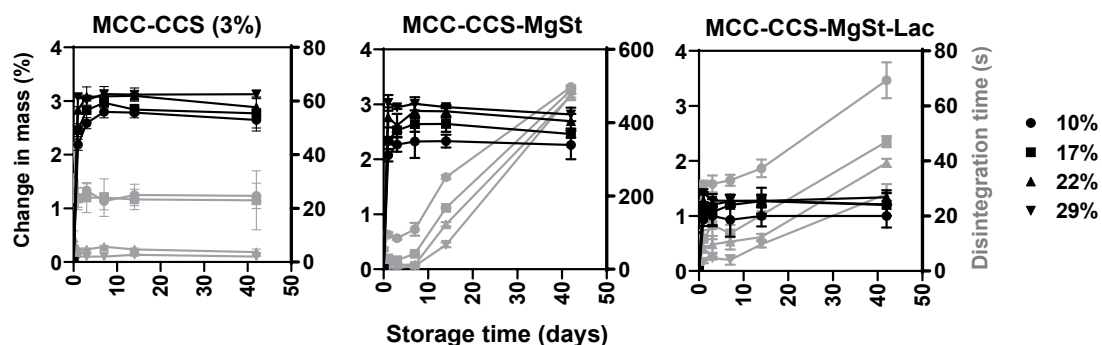


Figure 6.13: Change in mass and disintegration time during storage at 50°C/75% RH. Disintegration times: Grey lines, change in mass: black lines (n = 3, mean ± SD).

6.4.3 Linking disintegration to liquid absorption rate and mechanical changes

Plotting disintegration time against k across all formulations and porosities revealed a clear inverse relationship for MgSt and lactose formulation (Figure 6.14). As k declined, disintegration time rose. This suggests that surface wetting and initial water uptake are crucial to disintegration performance after storage. In low- k samples, delayed hydration prevents or slows CCS activation, which depends on rapid swelling to disrupt the matrix. In the MCC-CCS formulation, k remained relatively stable over the 42-day storage period, and the disintegration time did not change substantially. The consistency of k values and disintegration performance suggests that the surface and pore structure of these tablets remained accessible to water throughout storage. This confirms the

resilience of the MCC-CCS matrix, where CCS continues to function as an efficient wicking and swelling agent, initiating rapid matrix breakup once wetted.

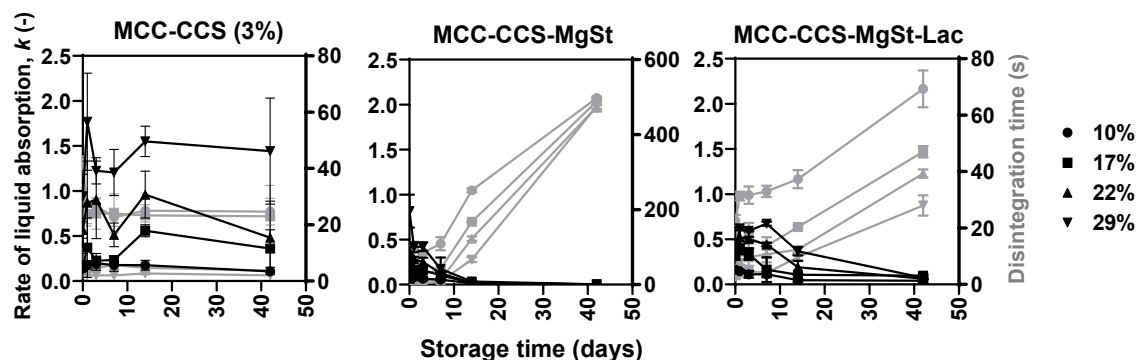


Figure 6.14: Disintegration times and liquid uptake rate of tablets after storage at 50°C/75% RH over time; disintegration times: Grey lines, liquid absorption rate: black lines ($n = 3$, mean $\pm$ SD).

In contrast, plotting disintegration time against tensile strength showed no consistent trend beyond the initial storage period (Figure 6.15). Tensile strength dropped early (mostly by day 1) and then plateaued, while disintegration time continued to rise, particularly from day 14 to 42 in MgSt tablets. This suggests that while mechanical weakening may initially contribute, it is not the primary factor affecting tablet disintegration over time. Instead, water penetration and wetting kinetics are more predictive of the disintegration performance of these formulations under 50°C/75% RH.

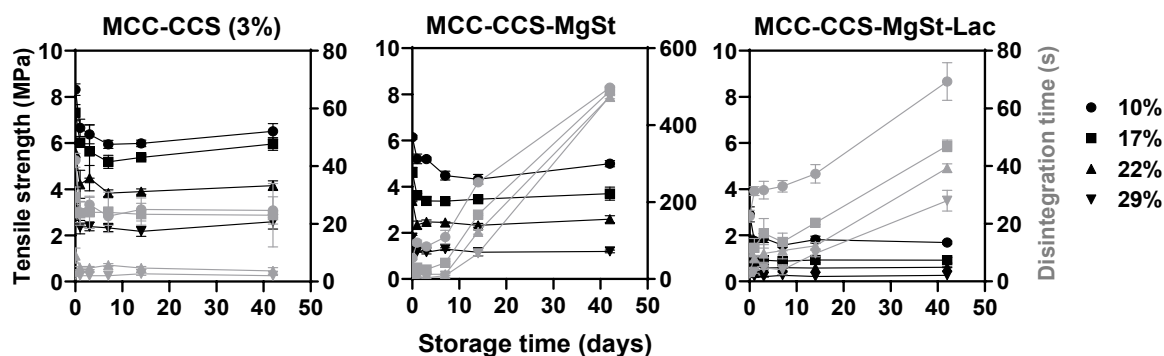


Figure 6.15: Disintegration times and tensile strength of tablets after storage at 50°C/75% RH over time; disintegration times: Grey lines, tensile strength: black lines (n = 3, mean $\pm$ SD).

6.4.4 The effect of excipients on tablets' physical stability

A summary of the observed and proposed mechanisms, along with their temporal progression, is illustrated in Figure 6.16, which presents a timeline of structural changes and excipient-specific contributions during exposure. The mechanisms underlying changes in the physical properties of tablets can generally be distinguished based on whether the excipients are swelling, soluble, or lubricants.

For swelling materials, such as disintegrants and MCC, exposure to high humidity promotes premature and irreversible expansion as the particles absorb moisture from the environment (Chapter 4). Upon removal from storage, this irreversible expansion and moisture uptake result in a decrease in particle density, reflected in reduced tablet porosity and tensile strength. The latter can be explained by the loss of interparticle bonding as swollen particles disrupt the compact structure. Furthermore, partial loss of disintegrant efficiency is expected, since a fraction of the swelling capacity is consumed during storage. Nevertheless, in this study, both MCC and MCC-CCS formulations remained

relatively stable. Liquid absorption and swelling kinetics were largely unaffected, and only negligible changes in disintegration time were observed during the first day of storage.

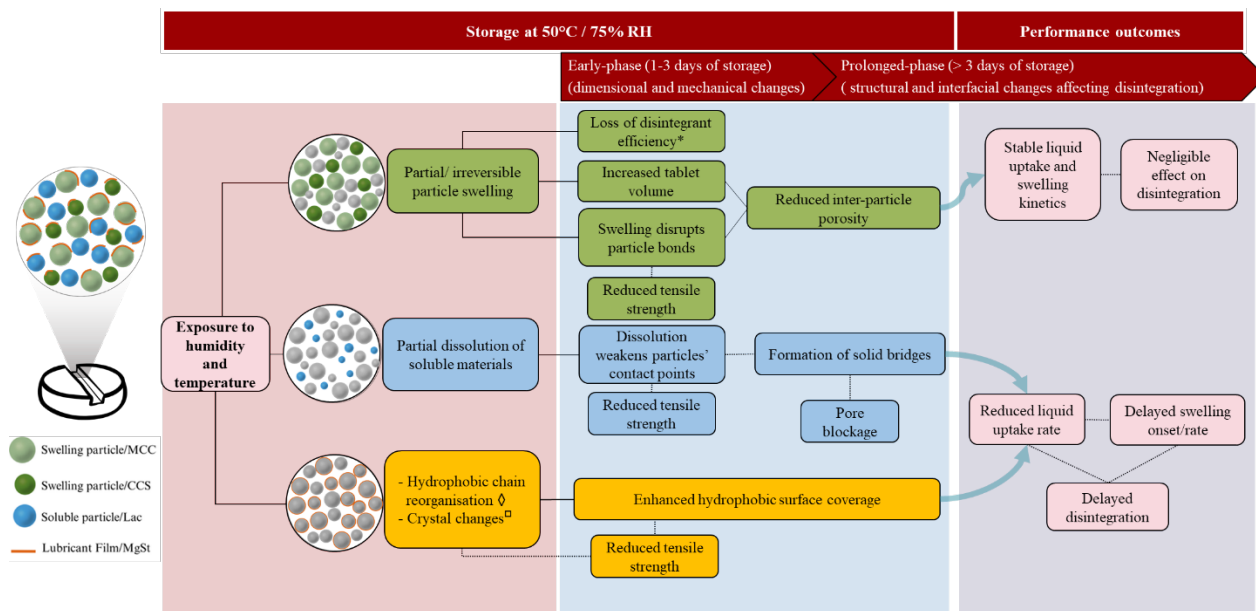


Figure 6.16: Summary of humidity-induced changes in IR tablet formulations, presented as a timeline of structural/interfacial changes and performance outcomes. (*Bauhuber et al., 2021; Marshall et al., 1991; $\diamond$ Rapp et al., 1995; $\square$ Calahan, 2020; Yamamoto et al., 2017).

For lubricant materials, the changes were far more pronounced. Tablets containing MgSt exhibited a complete inhibition of liquid uptake and swelling, as evidenced by sessile drop measurements. These observations suggest the formation of a continuous hydrophobic surface layer during storage, resulting in disintegration times after 42 days that were approximately 150 times longer than those before storage. While the literature has proposed various hypotheses for the influence of humidity and temperature on MgSt, none fully explain the extent of these changes. Our findings provide strong evidence that

MgSt plays a dominant role in controlling storage-induced instability, far beyond its traditional role as a processing aid. For soluble materials, such as lactose, accelerated humidity conditions can induce partial dissolution of particles, weakening interparticle contacts and decreasing tensile strength. Subsequent recrystallisation upon removal from storage can create new solid bridges, which may slow disintegration.

Taken together, these results challenge the prevailing emphasis in the literature, where most storage-induced changes have been attributed to disintegrants or binders. Our study shows instead that the most significant instability arose from MgSt. The influence of MgSt has often been underestimated; yet, under storage conditions, it can dominate tablet behaviour, altering moisture uptake, swelling, and disintegration to a far greater extent than swelling or soluble excipients.

6.5 Conclusion

This chapter highlights the significant impact of MgSt on the stability and disintegration behaviour of IR tablets under humid storage conditions. Inclusion of MgSt at a concentration of 1% hindered liquid uptake and reduced swelling capability, leading to pronounced disintegration delays, particularly at lower porosities. Formulations containing lactose alongside MgSt exhibited moderated yet notable increases in disintegration time, as lactose initially enhanced water uptake but subsequently contributed to structural densification through recrystallisation and pore blockage. Porosity played a key role in shaping tablet behaviour both before and after storage. Higher porosity consistently enhanced moisture uptake, liquid absorption rates, and swelling kinetics across all formulations, thereby facilitating faster disintegration.

However, in MgSt-containing tablets, this advantage diminished over time. After extended storage, the effect of porosity on wettability and disintegration became negligible, suggesting that surface hydrophobic film formation had overridden the benefits of structural porosity.

Beyond mechanistic insights, this study also demonstrates that the previously developed moisture uptake predictive framework can be extended to multi-component systems. Tablet-based DVS measurements, scaled to storage conditions, accurately reproduced uptake across porosities with high R^2 values. A single r_{sor} -scaling factor calibrated from MCC was sufficient for all systems, confirming that rate differences are method-dependent rather than intrinsic formulation effects. By contrast, EMC scaling varied with formulation due to handling artefacts and physical instabilities, such as the brittleness of lactose-containing tablets.

Kinetic analysis revealed two complementary pathways underlying storage-induced changes. In the early exposure-driven pathway, tensile strength responded on the same timescale as moisture uptake, with DVS-derived sorption rates successfully predicting weakening kinetics across formulations and porosities. In the prolonged exposure-driven pathway, long-term disintegration behaviour was governed not by tensile strength but by progressive changes in wetting and swelling, where decreases in liquid absorption rate constants (k) and delays in swelling onset times ($S_{t,0}$) reliably predicted functional impairment. Together, these findings demonstrate that moisture sorption controls the timescale of mechanical weakening, while surface wetting and swelling processes drive the progressive evolution of disintegration performance during storage.

6.6 Future implications

The findings of this chapter demonstrate that the impact of MgSt on tablet performance extends beyond its immediate lubricating function and evolves during storage through moisture-driven surface effects. The ability of MgSt to hinder liquid uptake and progressively override the benefits of high porosity indicates that lubricant selection and processing cannot be evaluated solely based on initial tablet performance. Instead, the time-dependent development of hydrophobic surface barriers must be considered when designing formulations intended to maintain rapid disintegration after storage. These results highlight the need to reconsider conventional lubrication strategies for humidity-sensitive immediate-release tablets. Approaches such as reducing lubricant exposure at the particle surface, for example, through punches and die external lubrication, shortened or staged blending, or partial replacement of MgSt with alternative lubricants, may mitigate the formation of continuous hydrophobic films. In addition, combining MgSt with small amounts of hydrophilic excipients may offer a route to balancing lubrication efficiency with sustained wettability, particularly in high porosity systems where liquid access is critical for performance.

The extension of the DVS-based predictive framework to multi-component formulations demonstrates its potential applicability beyond simplified systems. The ability to predict moisture uptake kinetics across porosities using a single rate scaling factor suggests that early-stage, tablet-based DVS measurements can be used to screen complex formulations efficiently. This offers an opportunity to identify formulations at

risk of long-term disintegration failure using minimal material and short experimental times.

The identification of distinct early and prolonged instability pathways has direct implications for stability strategy design. Early mechanical weakening driven by moisture sorption may be predicted using short-term DVS measurements, while later-stage functional failure is better anticipated through parameters describing wetting and swelling kinetics. Incorporating both pathways into stability assessment frameworks may enable more mechanistic, time-resolved prediction of tablet performance under storage.

While the study offers insights into excipient-specific responses and porosity effects under stress conditions, several limitations must be acknowledged. The excipient selection and levels were fixed, which limits the generalisability of the findings to broader formulation spaces. The study also focused on placebo tablets and did not assess interactions with APIs that may influence disintegration dynamics. Moreover, only a single accelerated storage condition (50°C/75% RH) was tested, which may not capture the full range of environmental conditions relevant to real-world scenarios. Finally, although disintegration changes were thoroughly investigated, the corresponding dissolution performance was not evaluated, which limits the direct assessment of functional bioavailability outcomes.

7. General conclusion and future work

7.1 General conclusion

This thesis systematically investigated the influence of excipient properties, formulation composition, and structural attributes on the physical stability and disintegration performance of directly compressed placebo formulations designed for IR under humid storage conditions. By combining DVS measurements with real storage studies (Jar method), this work bridges particle- and tablet-level observations, connecting short-term sorption behaviour with long-term storage outcomes to provide an integrated understanding of how temperature and RH influence tablet physical stability.

The research followed a stepwise design that progressively increased in complexity. Chapter 4 examined the moisture sorption behaviour at the excipient level, identifying hygroscopicity and irreversible swelling for CCS and SSG, and partial reversibility for MCC. Chapter 5 linked these findings to simplified tablet systems (MCC and MCC-CCS) across four porosities, showing how particle swelling translates into porosity reduction, tensile strength loss, and changes in tablet stability. This chapter also established scaling factors that connect short-term DVS sorption data to long-term jar storage, thereby bridging the behaviour of powder and tablets across both length and time scales. Chapter 6 extended the framework to more complex, multi-component formulations, introducing MgSt and lactose. Here, the interplay between hydrophobic lubrication and soluble filler highlighted excipient-excipient interactions and demonstrated the robustness, as well as the boundaries, of the predictive scaling approach.

Across these studies, two distinct mechanistic pathways of instability were identified:

1. Rapid, early exposure-driven changes: tensile strength loss occurred within the first day of storage, tightly coupled to moisture uptake. During this stage, the disintegration time also began to increase, albeit to a lesser extent.
2. Slower, prolonged exposure-driven changes: disintegration times continued to evolve across 42 days, even after tensile strength had plateaued, governed by changes in wetting and swelling dynamics.

At the particle level, moisture sorption behaviour was found to be highly dependent on both RH and temperature. Elevated humidity increased the EMC and promoted swelling in hygroscopic materials such as CCS, SSG, and MCC, whereas temperature accelerated sorption and desorption kinetics while generally reducing EMC. Swelling behaviour followed the order $CCS > SSG > MCC$ and was driven by humidity rather than temperature. Maximum swelling was reached within the first day of storage, and changes were largely irreversible, with MCC exhibiting partial reversibility, while CCS/SSG showed no reversibility. These findings emphasise the need to account for early-stage physical changes in accelerated stability studies and demonstrate that excipient-specific responses to moisture uptake and swelling are critical when predicting long-term stability and designing humidity-sensitive formulations.

At the tablet level, porosity and the presence of swelling excipients emerged as key determinants of humidity-induced changes. Higher porosity facilitated faster liquid absorption and swelling, translating into faster disintegration in freshly prepared tablets. However, these advantages diminished in certain formulations after storage, especially those containing MgSt, where the formation of hydrophobic surface films restricted

wetting efficiency and masked the benefits of porosity. The inclusion of MgSt at 1% consistently reduced liquid ingress and swelling capacity, producing a pronounced delay in disintegration, particularly at lower porosities. The addition of lactose alongside MgSt initially improved wetting and disintegration due to its solubility, but with prolonged storage, it promoted structural densification through recrystallisation, partially offsetting the early advantages. In contrast, formulations without MgSt preserved porosity-dependent disintegration trends throughout storage. Importantly, across all formulations, liquid absorption rate constants were found to be stronger predictors of disintegration performance after storage than tensile strength, which dropped rapidly within the first day but no longer correlated with progressive changes in disintegration. These observations highlight that storage outcomes are governed not only by the choice of excipients but also by their interactions and the mechanistic pathways through which moisture exposure alters microstructure and function.

Collectively, this thesis establishes a predictive framework that connects excipient-scale moisture sorption and swelling data to bulk tablet stability outcomes. By demonstrating scaling between DVS and real-storage behaviour, the work shows that long-term performance can be inferred from short-term, small-scale experiments. This approach offers the potential to reduce material demands, shorten stability studies, and support the rational design of more robust formulations. Besides addressing multiple knowledge gaps in this thesis, the results have clear industrial relevance, informing excipient selection, formulation design, and predictive stability assessment strategies that align with regulatory expectations.

7.2 Limitations and outlook of the present work

The experimental scope of this thesis is intentionally focused on immediate-release tablet formulations manufactured by direct compression and evaluated under a defined storage condition. While this controlled approach enabled systematic investigation of moisture-induced physical changes over time, the use of a single storage condition limits direct comparison with environments of differing relative humidity or temperature. As such, the findings should be interpreted in terms of mechanistic understanding rather than as absolute predictions across all possible storage scenarios.

The excipient space explored in this work is limited in scale and was selected to support mechanistic clarity. The primary focus was placed on swellable excipients in order to isolate moisture-driven changes in particle and tablet structure. However, the framework was challenged by the inclusion of excipients with other physicochemical properties. In particular, lactose was incorporated as a soluble filler and MgSt as a hydrophobic lubricant, enabling evaluation of framework applicability beyond purely swellable systems. The results demonstrate that although the dominant mechanisms governing moisture-induced changes differ between swellable, soluble, and hydrophobic excipients, the overarching framework linking particle-level moisture sorption behaviour to time-dependent changes in tablet structure and performance remained valid.

Nevertheless, the conclusions drawn from this study should be interpreted within the context of a limited number of excipients and direct compression formulations. Extension to a wider excipient palette, including materials with differing solubility, hygroscopicity, and functionality, would further strengthen assessment of the framework's generality.

Similarly, while direct compression provides a well-controlled system for establishing particle-to-tablet relationships, the influence of additional process steps associated with dry and wet granulation remains outside the scope of the present work.

The methodology developed in this thesis therefore provides a foundation for future studies extending beyond the defined experimental boundaries. Application of the same framework to alternative storage conditions, granulated systems, and more complex formulation architectures would enable systematic evaluation of how process history and environmental exposure influence moisture sorption kinetics, structural evolution, and mechanical stability. Rather than aiming to deliver universally applicable conclusions across all formulation types and conditions, this work should be viewed as an enabling investigation. Its primary contribution lies in establishing a structured experimental and analytical framework that links particle-scale moisture sorption behaviour with tablet-scale changes under real storage conditions.

7.3 Innovative contributions and methodological advances

A key innovative contribution of this thesis lies in the strategic repurposing of established pharmaceutical characterisation techniques for applications beyond their conventional scope. In current pharmaceutical practice, DVS is widely used to characterise moisture sorption behaviour of powders, primarily to classify hygroscopicity, assess amorphous content, or support excipient and API selection. Its application is typically restricted to equilibrium moisture uptake at the material level, with limited direct linkage to tablet-scale. In this thesis, DVS was systematically extended from its traditional powder-based application to the investigation of intact tablets. By incorporating tablets directly into the

DVS workflow, it was possible to quantify moisture uptake kinetics while preserving tablet structure, porosity, and compaction history. This enabled particle-scale sorption behaviour to be directly connected to the tablet sorption behaviour under real storage conditions. Importantly, this approach transforms DVS from a materials screening tool into a predictive method for assessing physical stability at the tablet level, demonstrating its potential for a completely new application area within formulation development.

A further methodological advance was achieved through adaptation of the sessile drop technique. Conventionally, sessile drop measurements are employed to obtain static or quasi-static contact angle values, providing a single point descriptor of surface wettability. Such measurements are commonly used for comparative screening but offer limited insight into the dynamic processes governing liquid penetration and tablet activation. In the present work, the sessile drop method was reinterpreted as a time-resolved kinetic tool. By tracking the full temporal evolution of droplet absorption alongside surface swelling of compacted porous tablets, the technique enabled quantitative analysis of liquid uptake rates and swelling dynamics rather than a single wettability parameter. Applied in this manner, sessile drop analysis was extended from a surface characterisation method to a dynamic probe of liquid–solid interactions that are directly relevant to disintegration and early-stage tablet performance. When combined with DVS-derived moisture sorption kinetics and traditional mechanical characterisation, this approach provided a coherent and mechanistically informed picture of how moisture and liquid ingress jointly govern physical stability and functionality.

Collectively, these methodological adaptations demonstrate how widely used pharmaceutical apparatus can be reinterpreted and integrated to generate new insight without the need for bespoke instrumentation. Beyond their application within this thesis, the approaches presented have clear potential for adoption in both academic and industrial contexts, particularly where rapid, resource-efficient, and predictive assessment of moisture- and liquid-mediated effects is required.

7.4 Future work

The pharmaceutical industry is moving toward more science-based, model-informed approaches that aim to accelerate the development of new drug products. Stability testing remains one of the most time- and resource-intensive stages of formulation development, often delaying the introduction of new medicines. Any reduction in this timeline through predictive, mechanistic, and data-driven strategies can therefore have a substantial impact on how quickly effective treatments reach patients. The framework established in this thesis aligns with this industrial direction by demonstrating how small-scale, accelerated studies can be used to anticipate long-term physical stability. Such science-driven methodologies offer the potential to reduce reliance on extended empirical studies, strengthen the scientific basis of stability prediction, and support faster, knowledge-based design of robust pharmaceutical products. Building on these principles, several specific research directions are recommended:

1. Linking Physical Changes to Drug Release Performance

Future studies should extend the current framework to include dissolution testing alongside disintegration, thereby allowing for a direct assessment of how storage-induced

changes in structure and wettability affect bioavailability. Establishing quantitative correlations between liquid absorption rate constants, swelling onset times, and in vitro dissolution rates will enable more robust predictive models that connect mechanical and functional performance under storage conditions.

2. Broader Excipient and Formulation Space

Expanding predictive modelling to encompass a broader range of excipient types, including additional swelling disintegrants and binders, will enhance the generality of the framework. Systematically varying excipient concentrations, such as lubricant (MgSt) mixing time, grade and levels, can also help to define threshold effects and identify optimal compositions that balance lubrication efficiency with rapid disintegration.

3. API-Excipient Interactions

A logical next step is to evaluate how APIs influence the moisture sorption, swelling, and mechanical stability of the systems studied in this thesis. Particular attention should be given to whether API properties, such as solubility, hygroscopicity, or crystallinity, alter the scaling relationships established between particle-level and tablet-level behaviour.

4. Multiple Storage Conditions and Time Scales

Validation of the established scaling factors across a broader range of temperature and humidity combinations, including ICH-recommended conditions, would provide stronger evidence for generalisability. Incorporating additional intermediate time points and very short-term measurements into stability protocols would also help capture rapid-onset changes that occur within the first days of storage.

5. Integrating Tablet-analysed DVS with Physical Change Monitoring

To further strengthen DVS as a predictive tool, it is essential to examine whether tablets analysed directly in the DVS exhibit the same physical changes as those observed under real-storage conditions. Confirming that reductions in tensile strength, swelling capacity, and disintegration behaviour are reproducible within the DVS environment would reinforce its role in predicting long-term stability from short-term measurements.

6. Advanced Surface and Microstructural Characterisation

Finally, employing high-resolution analytical techniques such as Raman spectroscopy, atomic force microscopy, or time-of-flight secondary ion mass spectrometry (ToF-SIMS) can provide detailed insights into surface film formation and crystallisation during storage. Complementary 3D imaging methods, such as X-ray micro-computed tomography, would allow quantitative evaluation of pore structure and connectivity changes over time, further elucidating how microstructural evolution governs functional performance.

By addressing these research directions, future work can build upon the findings of this thesis to develop a more comprehensive and predictive understanding of how formulation, process, and environmental factors together define the long-term stability and performance of IR tablets.

Appendices

Appendix A

Additional Data for Chapter 4

Summary

This appendix presents supporting information for Chapter 4, including additional data obtained from the moisture sorption/desorption experiments and the storage-induced particle size swelling analysis.

Table A.1: The recorded datalogger storage conditions (mean $\pm$ SD) (The 25°C/30% RH represents the Laboratory equilibration condition).

Target storage condition	Actual storage condition
50°C/75% RH	49.8°C $\pm$ 0.3/ 77.7% RH $\pm$ 1.3
25°C/75% RH	24.9°C $\pm$ 0.4/ 77.7% RH $\pm$ 1.3
50°C/30% RH	49.8°C $\pm$ 0.3/ 32.4% RH $\pm$ 0.9
25°C/30% RH	20.4°C $\pm$ 0.6/ 26.4% RH $\pm$ 3.5

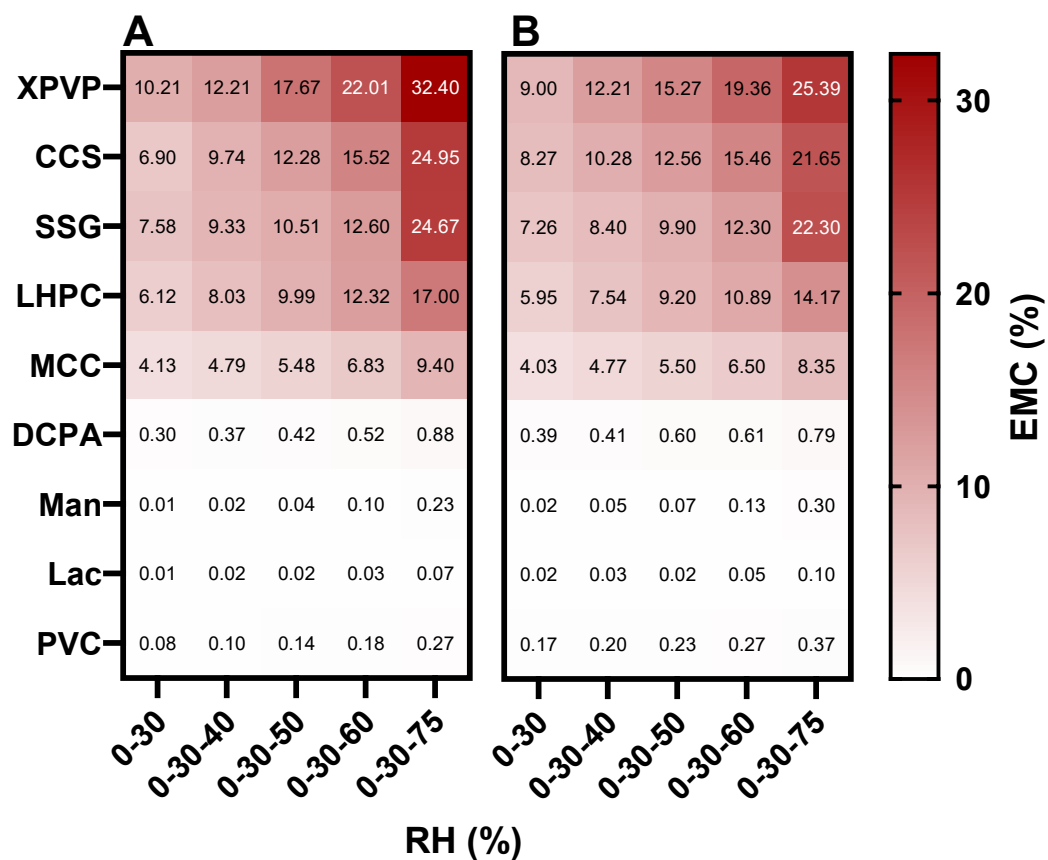


Figure A.1: Equilibrium moisture content of excipients at (A) 25°C and (B) 50°C, presented relative to the dry reference mass at 0% RH. (0-30% RH represents an average of 4 measurements).

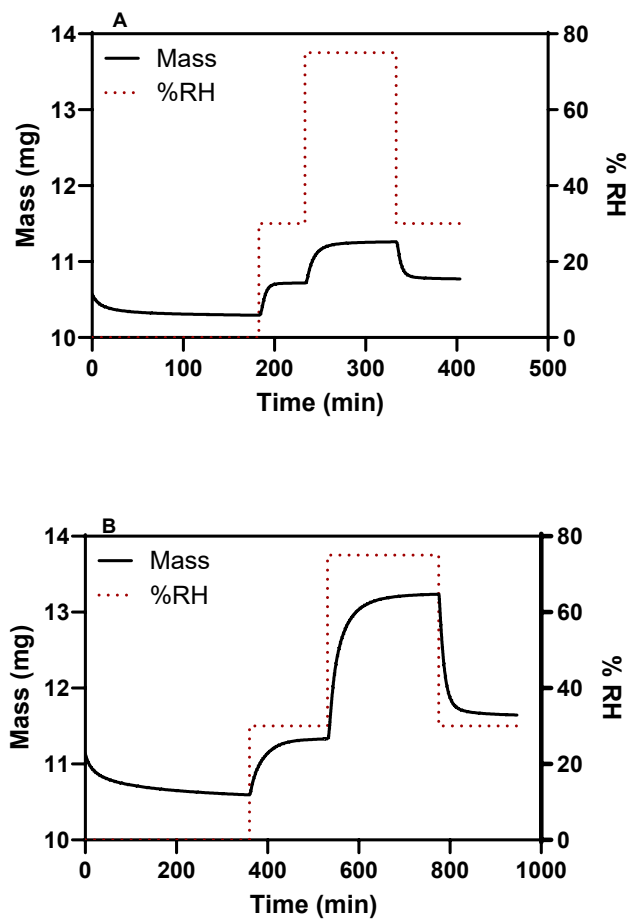


Figure A.2: Moisture sorption and desorption- time profile of (A) MCC and (B) CCS at 25°C.

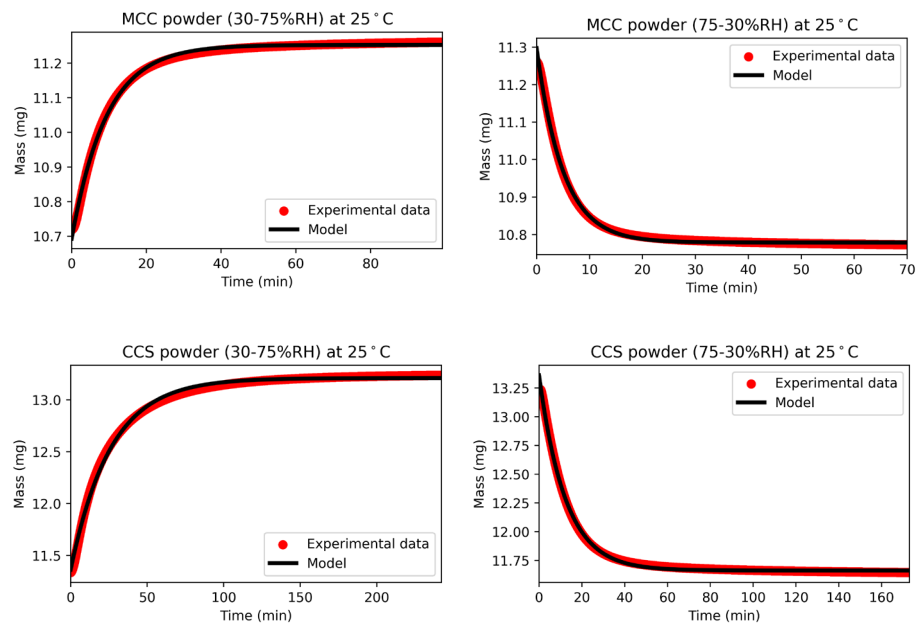


Figure A.3: Moisture sorption and desorption of MCC and CCS at 25°C over time as predicted by the model vs. experimental measurements.

Table A.2: The Prediction performance of the moisture sorption kinetic rate constant model at 25°C.

Excipient	RH% step	r_{sor} (s ⁻¹)	R ²	RMSE
Lactose	0-30	0.1799	0.7159	0.0004
	30-40	0.3958	0.9652	0.0001
	30-50	0.1870	0.9725	0.0001
	30-60	0.1596	0.9638	0.0001
	30-75	0.1812	0.993	0.0002
L-HPC	0-30	0.0981	0.9957	0.0082
	30-40	0.0510	0.9928	0.0034
	30-50	0.0774	0.9979	0.0040
	30-60	0.0819	0.9973	0.0072
	30-75	0.0747	0.99726	0.0124
SSG	0-30	0.0601	0.9944	0.0155
	30-40	0.0879	0.9991	0.0014
	30-50	0.1313	0.9395	0.0143
	30-60	0.1155	0.9927	0.0108
	30-75	0.0162	0.9926	0.0330
CCS	0-30	0.0341	0.9975	0.0071
	30-40	0.0312	0.9982	0.0025
	30-50	0.0564	0.9989	0.0040
	30-60	0.0657	0.9989	0.0061
	30-75	0.0384	0.9951	0.0267
MCC	0-30	0.2239	0.9988	0.0024
	30-40	0.2199	0.9977	0.0007
	30-50	0.2343	0.9965	0.0016
	30-60	0.1507	0.9901	0.0046
	30-75	0.1073	0.9971	0.0059

DCPA	0-30	0.7432	0.9975	0.0003
	30-40	0.5365	0.9961	0.0001
	30-50	0.4753	0.9986	0.0001
	30-60	0.4041	0.9975	0.0002
	30-75	0.1973	0.9987	0.0005
Mannitol	0-30	1.0403	0.7410	0.0002
	30-40	0.9518	0.9416	4.7E-5
	30-50	0.5647	0.9912	0.0001
	30-60	0.3072	0.9970	0.0001
	30-75	0.2902	0.9937	0.0004
XPVP	0-30	0.0865	0.9899	0.0182
	30-40	0.0349	0.9960	0.0054
	30-50	0.0521	0.9989	0.0054
	30-60	0.0497	0.9992	0.0078
	30-75	0.0414	0.9973	0.0235

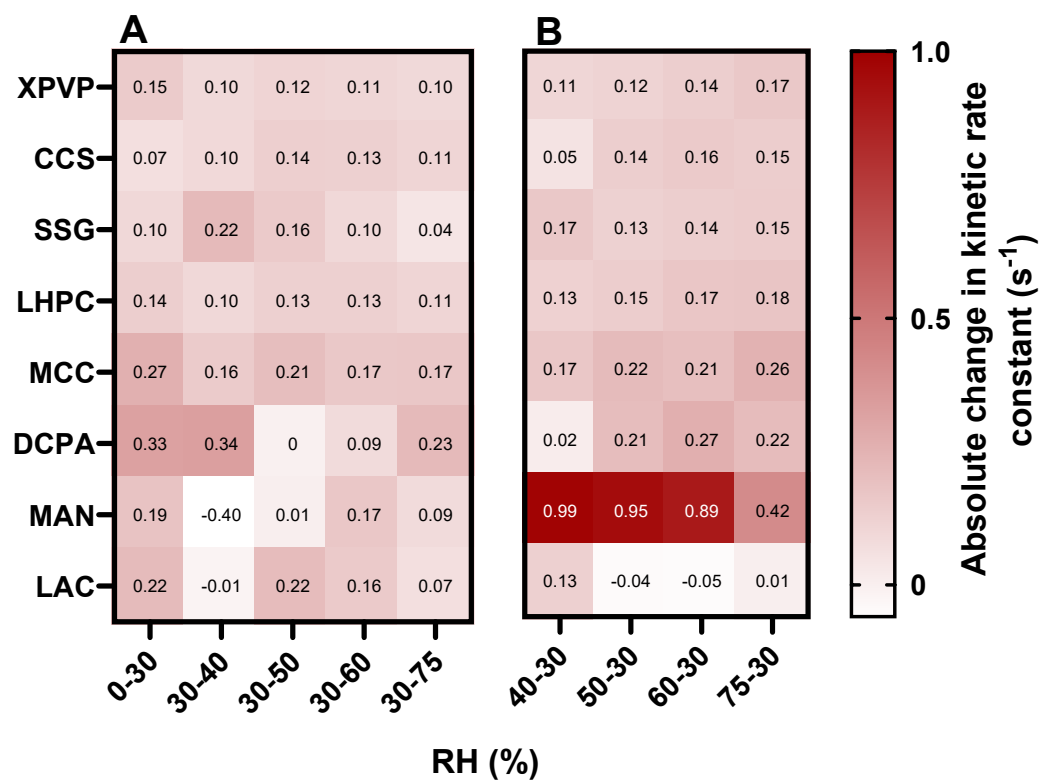
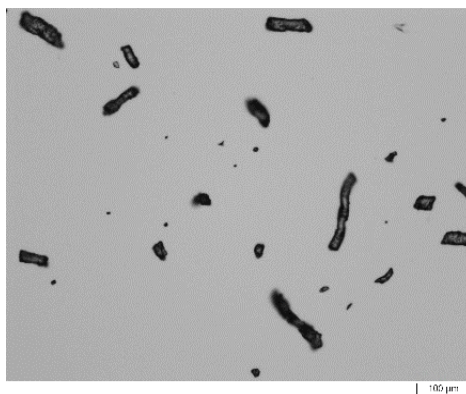
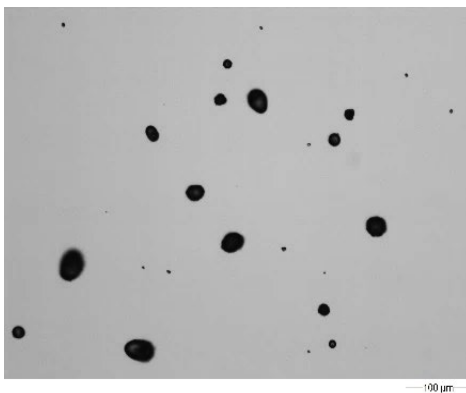


Figure A.4: Absolute change in kinetic rate constant from 25°C to 50°C of the tested excipients in (A) moisture sorption and (B) desorption as a function of % RH steps.

CCS



SSG



MC

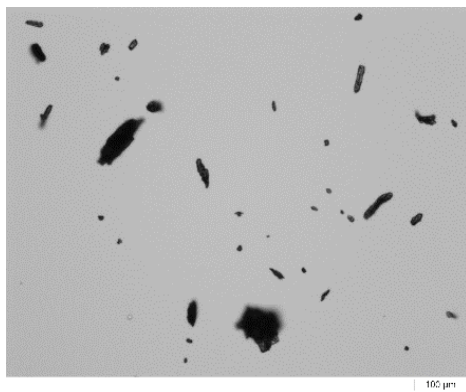


Figure A.5: Field of view images of swelling excipients studied using 10X lens.

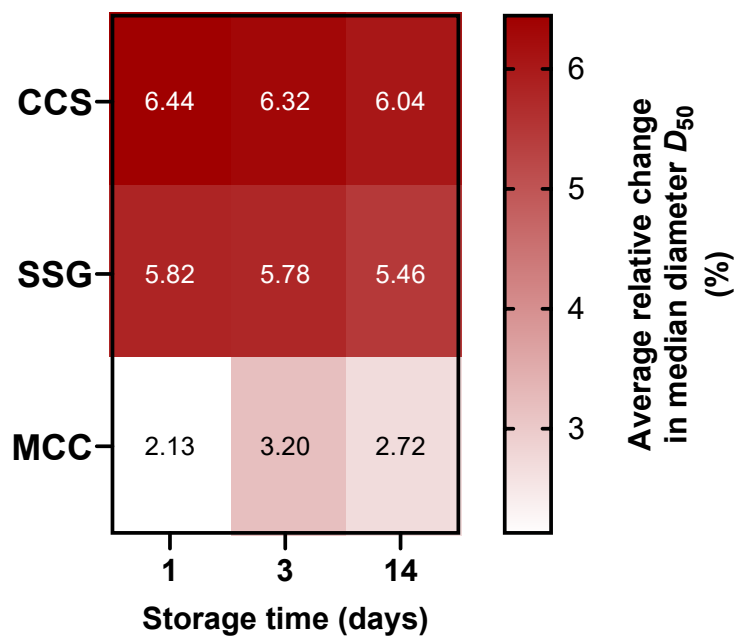


Figure A.6: The average relative change in volume-based diameter D_{50} of the studied excipients after storage at 50°C/75% RH, showing all time points: 1, 3, and 14 days (n = 3).

Table A.3: Relative change in volume-based diameter (D_{50}) of the studied excipients after storage at 50°C/30% RH (n = 3).

Storage time (days)	1		3		14	
Material	Mean	SD	Mean	SD	Mean	SD
CCS	6.44	1.39	6.32	1.94	6.04	0.68
SSG	5.82	0.61	5.78	0.15	5.46	0.81
MCC	2.13	1.13	3.20	1.17	2.72	0.54

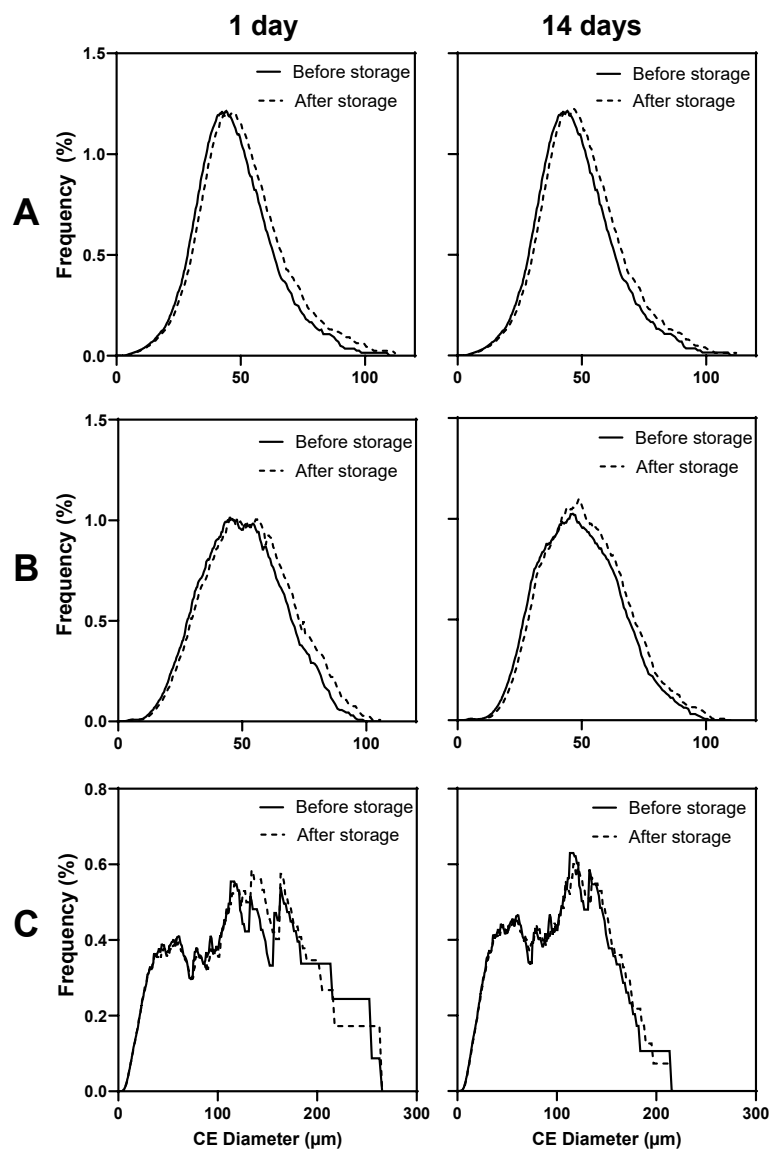


Figure A.7: The change in number-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 25°C/75% RH for 1 and 14 days. (The example shown at each time point represents one of the samples analysed for this time point, CED smoothed over 50 points).

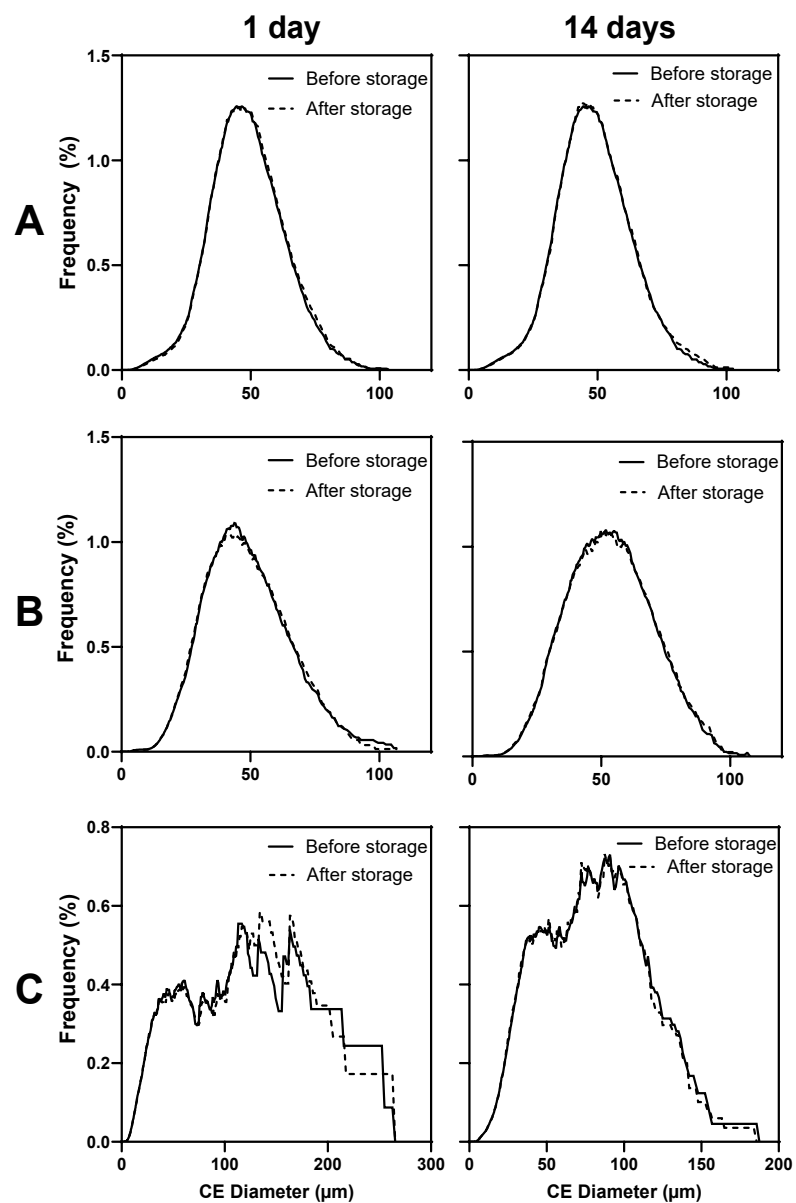


Figure A.8: The change in number-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 50°C/30% RH for 1 and 14 days. (The example shown at each time point represents one of the samples analysed for this time point, CED smoothed over 50 points).

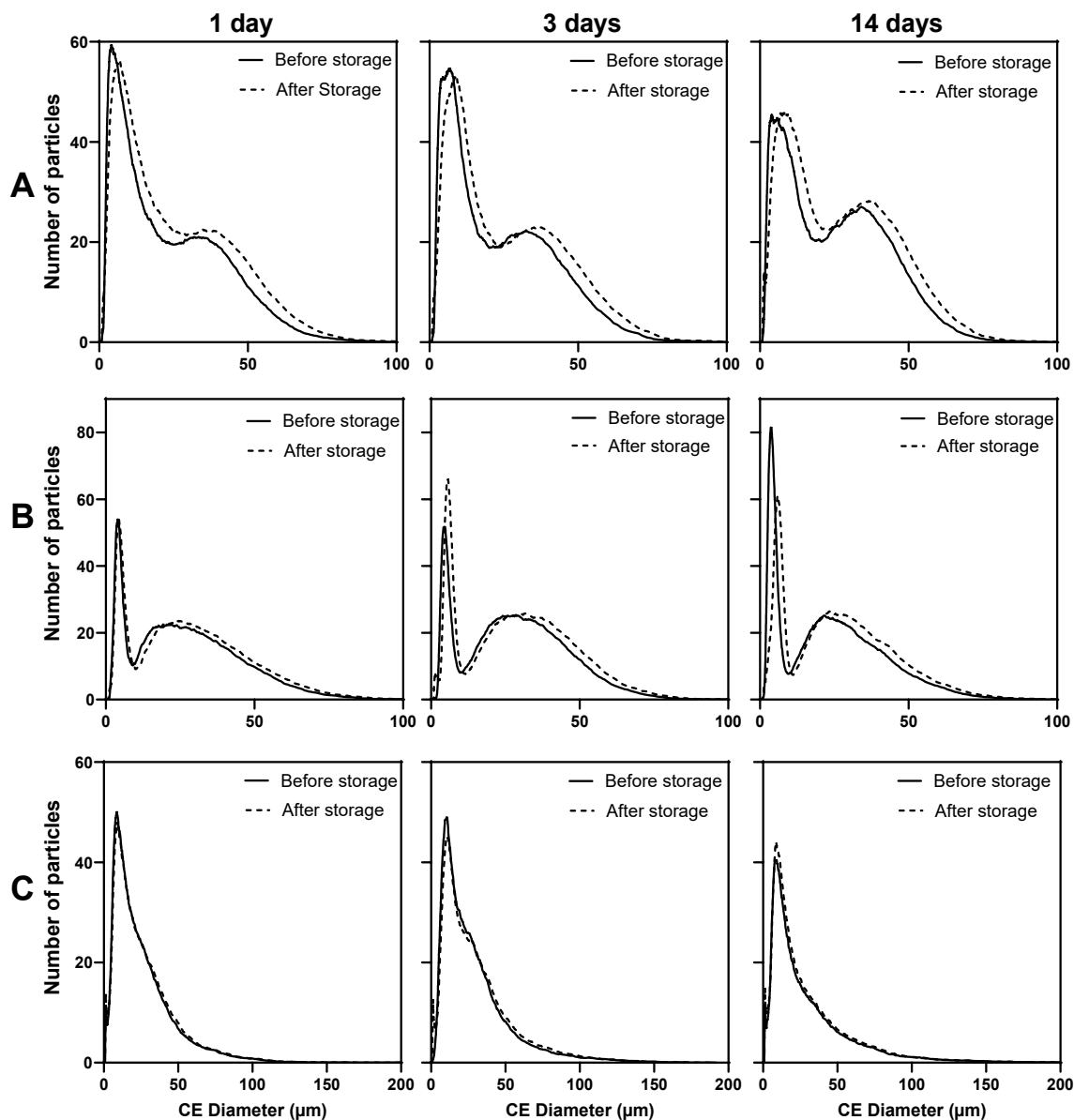


Figure A.9: The change in number-based size distributions of (A) CCS, (B) SSG, and (C) MCC particles after storage at 50°C/75% RH for 1,3 and 14 days. (The example shown at each time point represents one of the samples analysed for this time point, CED smoothed over 50 points).

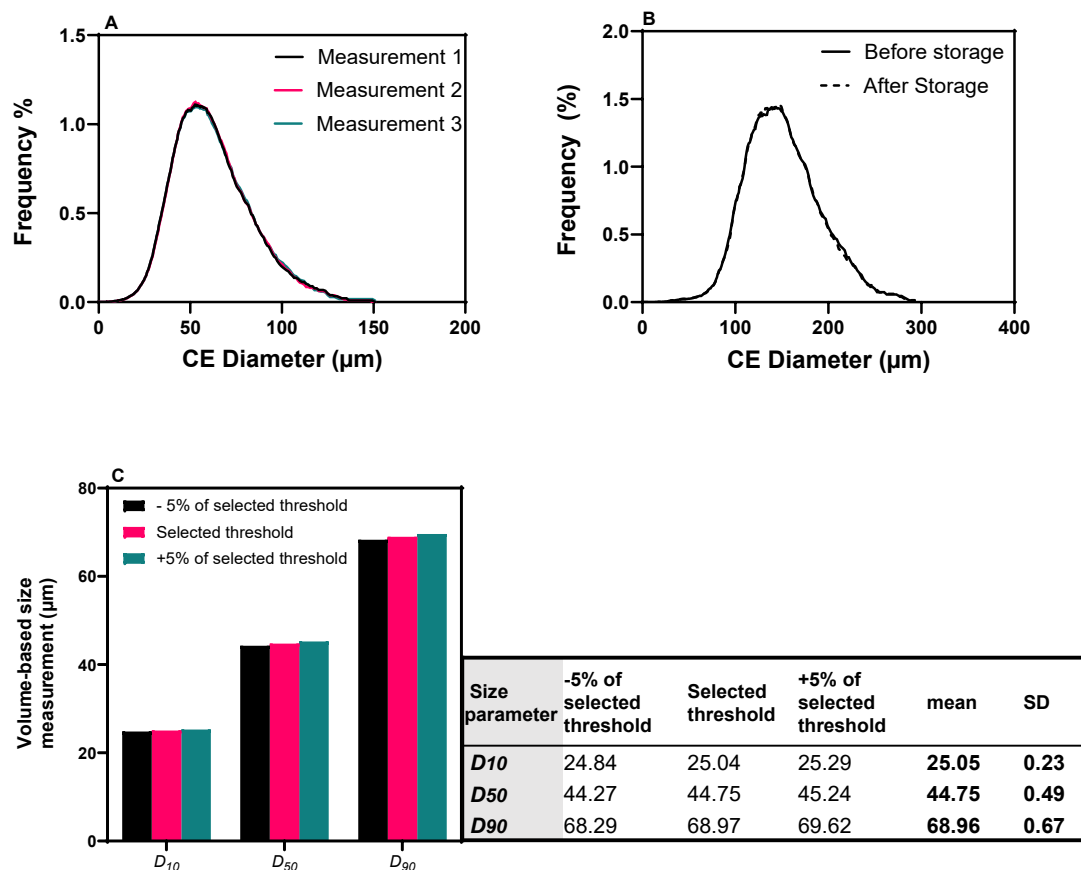


Figure A.10: Measures to evaluate the Reliability of Morphologi4 in particle size Analysis. (A) Demonstrating the repeatability of measurements for the same sample. (B) Utilising PVC powder as a control material after storage at 50°C/75% RH for 3 days. (C) Investigating the threshold effect on CCS particle size analysis to assess the robustness of the study under storage conditions.

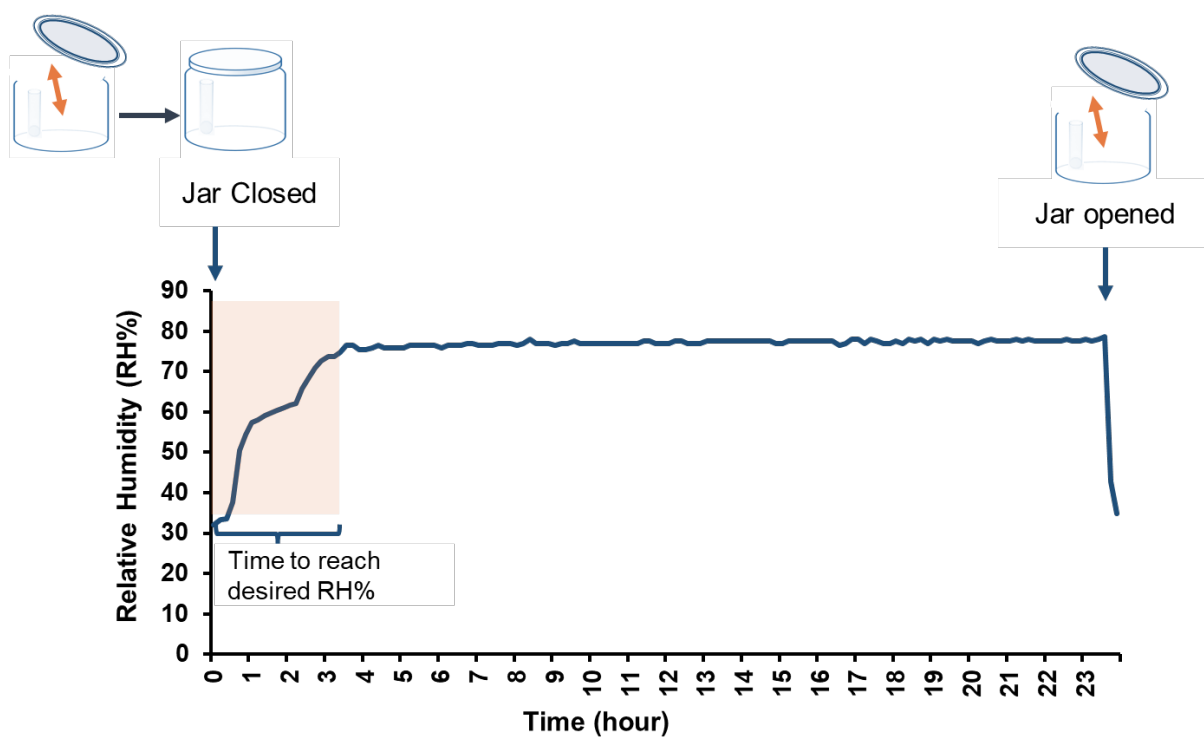


Figure A.11: The time needed to establish the required 75% RH inside jars (data shown were extracted from a data logger inside one of the jars intended for 1-day storage).

Appendix B

Additional Data for Chapter 5

Summary

This Appendix provides additional data and analyses to complement the main findings presented in Chapter 5. It includes means with standard deviations of the measured properties, additional DVS data for powders and tablets, raw material analyses, and performance evaluation of the moisture sorption model. It also provides data on the equilibration of tablet weight and volume after removal from storage, correlations from terahertz analysis, and other supplementary findings relevant to the study.

Table B.1: The average values of mass, volume, tensile strength, terahertz measured refractive index and loss coefficient with standard deviation(SD) of MCC and MCC-CCS tablets before and after storage (n = 3).

MCC tablets																	
		Before storage								After storage							
Tablet porosity		10%		17%		22%		29%		10%		17%		22%		29%	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tablets mass (mg)																	
Storage time (days)	1	50.58	0.49	50.23	0.88	50.68	0.31	49.70	0.26	51.53	0.50	51.25	1.06	51.58	0.25	51.05	0.30
	3	49.43	0.15	50.00	0.79	49.83	0.17	49.53	0.26	50.83	0.15	51.40	0.63	51.40	0.08	50.88	0.43
	7	50.48	1.40	50.18	0.79	50.18	0.15	49.90	0.24	51.90	1.34	51.45	0.68	51.68	0.33	51.15	0.29
	14	50.68	0.59	50.05	1.27	50.30	0.29	49.90	0.22	52.08	0.61	51.45	1.28	51.78	0.25	51.20	0.14
	42	50.63	0.64	50.35	0.79	50.60	0.80	49.95	0.19	52.05	0.81	51.83	0.83	52.13	0.71	51.38	0.30
Tablet volume (mm3)																	
Storage time (days)	1	35.91	0.12	38.16	0.30	40.10	0.19	45.45	0.25	36.44	0.53	38.85	0.73	41.08	0.70	46.68	0.92
	3	35.76	0.18	37.97	0.37	40.06	0.15	45.41	0.34	36.52	0.66	38.83	0.82	41.04	0.70	46.73	0.93
	7	35.81	0.22	37.92	0.40	40.11	0.17	45.50	0.25	36.67	0.76	38.84	0.75	41.14	0.64	46.83	0.88
	14	35.81	0.12	38.00	0.34	40.11	0.12	45.55	0.28	36.72	0.66	38.94	0.74	41.13	0.75	46.83	0.99
	42	35.80	0.09	38.10	0.18	40.10	0.19	45.60	0.25	36.67	0.63	39.02	0.65	41.13	0.88	46.93	0.93
Tablet porosity (%)																	
Storage time (days)	1	9.72	0.73	15.64	19.00	19.00	0.63	29.91	0.53	4.39	0.49	10.91	0.92	15.05	0.67	26.76	0.57
	3	11.40	0.62	15.58	20.28	20.28	0.43	30.08	0.49	6.78	0.36	11.25	1.60	16.51	0.76	27.10	0.46
	7	9.65	2.10	15.17	19.82	19.82	0.45	29.70	0.26	5.31	2.49	10.88	1.37	16.00	0.74	26.70	0.26
	14	9.29	1.35	15.59	19.62	19.62	0.61	29.78	0.28	4.93	1.31	11.31	1.58	15.88	0.65	26.77	0.44
	42	9.35	1.14	15.29	19.12	19.12	1.27	29.79	0.18	5.02	1.33	10.97	1.04	15.48	1.31	26.85	0.28

THz effective refractive index																	
Storage time (days)	1	1.79	0.00	1.73	0.02	1.70	0.01	1.60	0.01	1.78	0.01	1.72	0.01	1.68	0.00	1.58	0.00
	3	1.78	0.01	1.73	0.01	1.69	0.00	1.60	0.01	1.76	0.01	1.72	0.01	1.67	0.01	1.58	0.01
	7	1.79	0.01	1.74	0.01	1.69	0.01	1.60	0.00	1.77	0.02	1.72	0.01	1.68	0.00	1.59	0.01
	14	1.79	0.01	1.73	0.02	1.70	0.01	1.61	0.00	1.78	0.02	1.72	0.02	1.68	0.01	1.59	0.01
	42	1.79	0.02	1.73	0.02	1.70	0.01	1.61	0.01	1.78	0.02	1.72	0.02	1.69	0.02	1.59	0.01
THz loss coefficient																	
Storage time (days)	1	24.33	0.49	22.25	0.78	21.61	0.76	18.12	0.90	25.13	1.20	22.86	1.23	21.78	0.75	18.56	0.89
	3	23.30	0.90	22.08	0.99	20.75	0.85	17.96	0.78	24.18	1.09	22.81	0.68	21.31	1.26	18.46	0.98
	7	24.10	1.28	22.25	1.12	20.92	0.84	17.82	0.24	24.97	1.35	23.05	1.76	21.62	1.49	18.94	1.34
	14	24.99	0.57	22.39	0.83	21.73	0.49	18.58	0.58	25.99	0.67	23.88	0.57	22.33	0.42	19.39	0.46
	42	24.67	0.42	22.65	0.63	21.29	1.24	18.54	0.53	26.50	1.52	25.01	0.78	23.88	1.30	20.31	0.87
Tensile strength (MPa)																	
Storage time (days)	1	9.82	0.72	7.11	0.70	5.33	0.26	3.47	0.08	6.84	0.58	5.15	0.24	4.39	0.17	1.84	0.27
	3									6.62	0.69	5.02	0.46	4.45	0.08	1.72	0.25
	7									6.45	0.68	5.06	0.13	3.82	0.34	1.79	0.34
	14									5.94	0.49	5.01	0.22	3.93	0.21	1.79	0.16
	42									5.44	0.41	4.43	0.70	3.66	0.48	2.15	0.15
MCC-CCS tablets																	
		Before storage								After storage							
Tablet porosity		10%		17%		22%		29%		10%		17%		22%		29%	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tablets mass (mg)																	
Storage time (days)	1	49.53	0.46	49.40	0.45	50.38	0.05	48.28	0.97	50.48	0.69	50.68	0.48	51.93	0.13	49.68	0.95
	3	49.45	0.25	49.78	0.40	50.68	0.10	48.60	0.57	50.90	0.42	51.28	0.34	52.40	0.29	49.98	0.46
	7	49.55	0.42	49.40	0.42	50.55	0.52	47.95	0.97	51.03	0.53	51.00	0.54	52.15	0.45	49.55	0.83
	14	49.33	0.36	49.88	0.31	50.65	0.24	48.40	0.62	50.75	0.34	51.38	0.29	52.25	0.10	49.90	0.42
	42	49.60	0.08	49.33	0.19	50.83	0.10	48.20	1.30	51.10	0.00	50.90	0.12	52.43	0.21	49.83	1.42

Tablet volume (mm ³)																	
Storage time (days)	1	36.14	0.49	38.36	0.30	40.26	0.33	45.70	0.29	36.78	0.76	39.31	0.84	41.37	1.07	47.12	1.10
	3	36.01	0.39	38.30	0.41	40.32	0.44	45.56	0.33	36.96	0.84	39.42	0.99	41.52	1.18	47.17	1.09
	7	35.91	0.35	38.35	0.35	40.30	0.34	45.51	0.25	37.00	0.98	39.40	1.03	41.56	1.15	47.17	1.09
	14	36.02	0.44	38.35	0.27	40.25	0.42	45.55	0.23	37.14	0.96	39.59	1.02	41.55	1.17	47.22	1.25
	42	36.04	0.49	38.35	0.27	40.40	0.46	45.61	0.10	37.10	1.05	39.54	0.98	41.75	1.17	47.27	1.15
Tablet porosity (%)																	
Storage time (days)	1	12.32	0.38	17.60	1.39	19.94	0.67	32.42	1.20	7.79	0.33	13.77	1.27	16.51	0.71	29.67	1.12
	3	12.12	1.12	16.84	1.06	19.58	0.98	31.74	0.93	8.29	0.39	13.37	1.32	16.42	0.81	29.27	0.86
	7	11.71	1.19	17.57	1.19	19.75	0.93	32.59	1.06	8.32	0.61	14.17	1.22	16.70	1.06	30.21	1.31
	14	12.38	0.85	16.79	0.27	19.49	0.88	32.02	0.77	9.04	0.81	13.57	0.36	16.50	0.76	29.77	0.91
	42	11.94	1.17	17.70	0.62	19.50	1.03	32.38	1.97	8.47	0.45	14.41	0.59	16.52	0.82	30.06	1.98
THz effective refractive index																	
Storage time (days)	1	1.78	0.01	1.73	0.02	1.70	0.01	1.59	0.01	1.76	0.01	1.71	0.01	1.68	0.01	1.57	0.01
	3	1.79	0.02	1.73	0.01	1.71	0.01	1.59	0.01	1.76	0.01	1.71	0.01	1.68	0.01	1.57	0.01
	7	1.79	0.01	1.73	0.02	1.70	0.01	1.59	0.01	1.76	0.01	1.71	0.00	1.68	0.01	1.56	0.01
	14	1.79	0.01	1.74	0.00	1.71	0.01	1.59	0.00	1.76	0.01	1.72	0.01	1.69	0.01	1.57	0.01
	42	1.78	0.02	1.72	0.01	1.71	0.02	1.59	0.02	1.76	0.01	1.71	0.00	1.69	0.01	1.57	0.02
THz loss coefficient																	
Storage time (days)	1	25.54	1.43	23.17	1.11	21.96	0.66	18.52	1.04	25.05	1.15	23.26	1.23	22.30	1.03	18.53	0.98
	3	24.75	1.42	22.67	0.67	22.30	0.96	18.41	0.78	25.14	1.52	23.66	0.86	22.54	1.25	18.55	0.90
	7	24.42	1.24	23.27	1.40	22.27	1.36	18.50	0.59	25.81	1.89	23.82	1.43	22.87	1.34	18.56	1.29
	14	24.90	1.02	23.08	1.22	22.56	1.13	18.71	0.53	25.87	0.21	24.64	0.47	23.49	0.42	19.20	0.76
	42	24.90	1.34	23.02	1.20	22.43	1.32	18.38	0.98	27.59	1.31	25.46	0.88	24.27	0.90	19.91	1.20
Tensile strength (MPa)																	
Storage time (days)	1	8.31	0.67	6.37	0.35	4.72	0.31	2.25	0.44	7.13	0.42	6.43	0.76	4.50	0.63	2.23	0.13
	3									7.13	0.42	5.94	0.83	4.64	0.57	2.29	0.16
	7									7.19	0.35	6.25	0.79	4.84	0.19	2.19	0.96
	14									7.10	0.56	5.80	0.28	4.29	0.65	2.24	0.03
	42									5.55	0.53	4.23	0.46	3.64	0.15	1.41	0.27

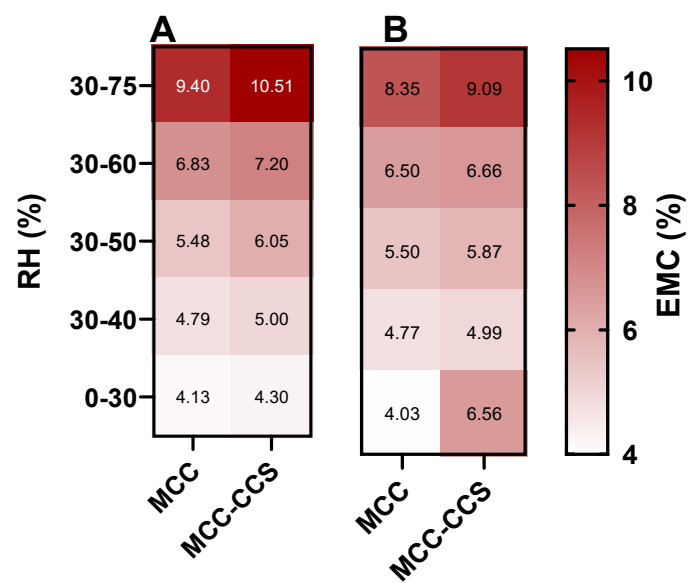


Figure B.1: EMC (%) of the two formulations at (A) 25°C and (B) 50°C relative to the dry mass of the powder at the end of 0% RH.

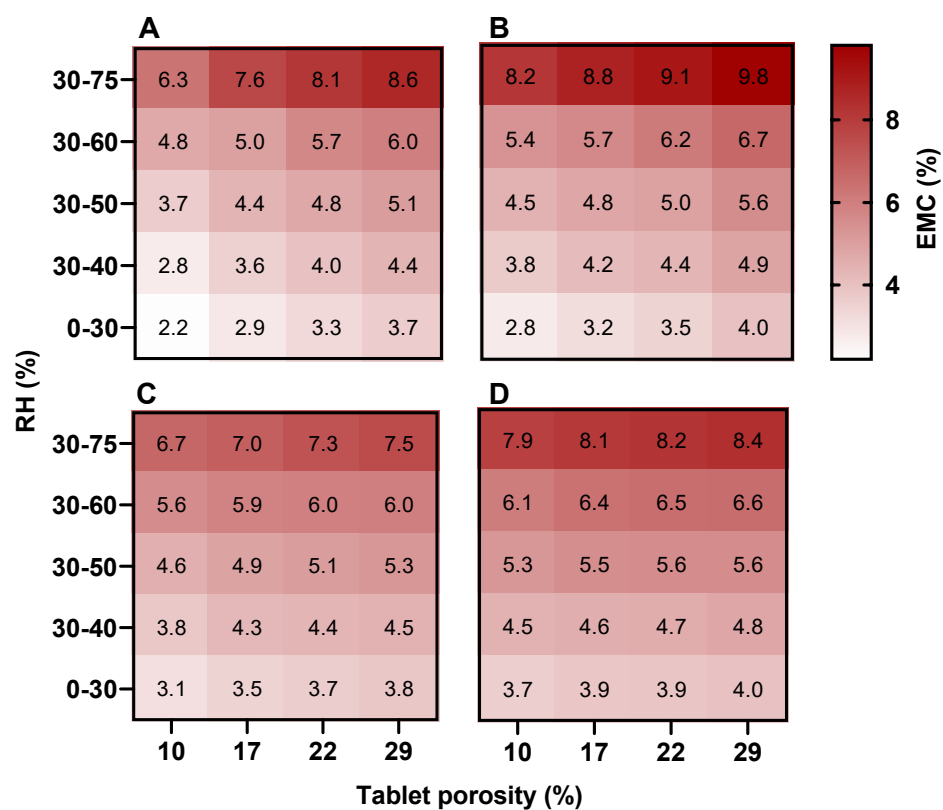


Figure B.2: Moisture uptake of tablets at 25°C (A and B) and 50°C (C and D), presented as EMC (%) relative to the dry mass of tablets at the end of 0% RH. (A) and (C) represent MCC tablets, while (B) and (D) represent MCC-CCS (8%) tablets.

Table B.2: The Prediction performance of the moisture sorption kinetic rate constant model at 25°C and 50°C.

Tablet/ Porosity	Temperature	25°C		50°C	
	RH% step	R ²	RMSE	R ²	RMSE
MCC tablets 10%	0-30	0.990	0.025	0.993	0.029
	30-40	0.998	0.004	0.998	0.004
	30-50	0.997	0.009	0.997	0.010
	30-60	0.997	0.016	0.998	0.012
	30-75	0.997	0.029	0.998	0.018
MCC tablets 17%	0-30	0.996	0.023	0.999	0.013
	30-40	0.998	0.004	0.998	0.004
	30-50	0.998	0.008	0.999	0.004
	30-60	0.997	0.016	0.998	0.011
	30-75	0.998	0.028	0.999	0.042
MCC tablets 22%	0-30	0.998	0.017	0.999	0.012
	30-40	0.999	0.003	0.997	0.004
	30-50	0.999	0.007	0.999	0.004
	30-60	0.997	0.016	0.998	0.009
	30-75	0.998	0.027	0.999	0.013
MCC tablets 29%	0-30	0.999	0.010	0.998	0.017
	30-40	0.999	0.002	0.997	0.004
	30-50	0.999	0.005	0.999	0.004
	30-60	0.997	0.015	0.999	0.006
	30-75	0.997	0.030	0.999	0.011
MCC-CCS (8%) tablets 10%	0-30	0.995	0.024	0.998	0.020
	30-40	0.998	0.004	0.997	0.005
	30-50	0.997	0.010	0.998	0.009
	30-60	0.997	0.018	0.997	0.015
	30-75	0.998	0.032	0.999	0.015

MCC-CCS (8%) tablets 17%	0-30	0.997	0.021	0.999	0.014
	30-40	0.999	0.004	0.998	0.004
	30-50	0.998	0.008	0.999	0.007
	30-60	0.996	0.019	0.998	0.012
	30-75	0.998	0.033	0.999	0.013
MCC-CCS (8%) tablets 22%	0-30	0.998	0.019	0.999	0.013
	30-40	0.999	0.004	0.998	0.004
	30-50	0.998	0.008	0.999	0.007
	30-60	0.996	0.019	0.999	0.011
	30-75	0.998	0.033	0.999	0.016
MCC-CCS (8%) tablets 29%	0-30	0.999	0.012	0.998	0.015
	30-40	0.999	0.003	0.998	0.004
	30-50	0.999	0.005	1.000	0.003
	30-60	0.996	0.018	1.000	0.005
	30-75	0.997	0.035	1.000	0.009

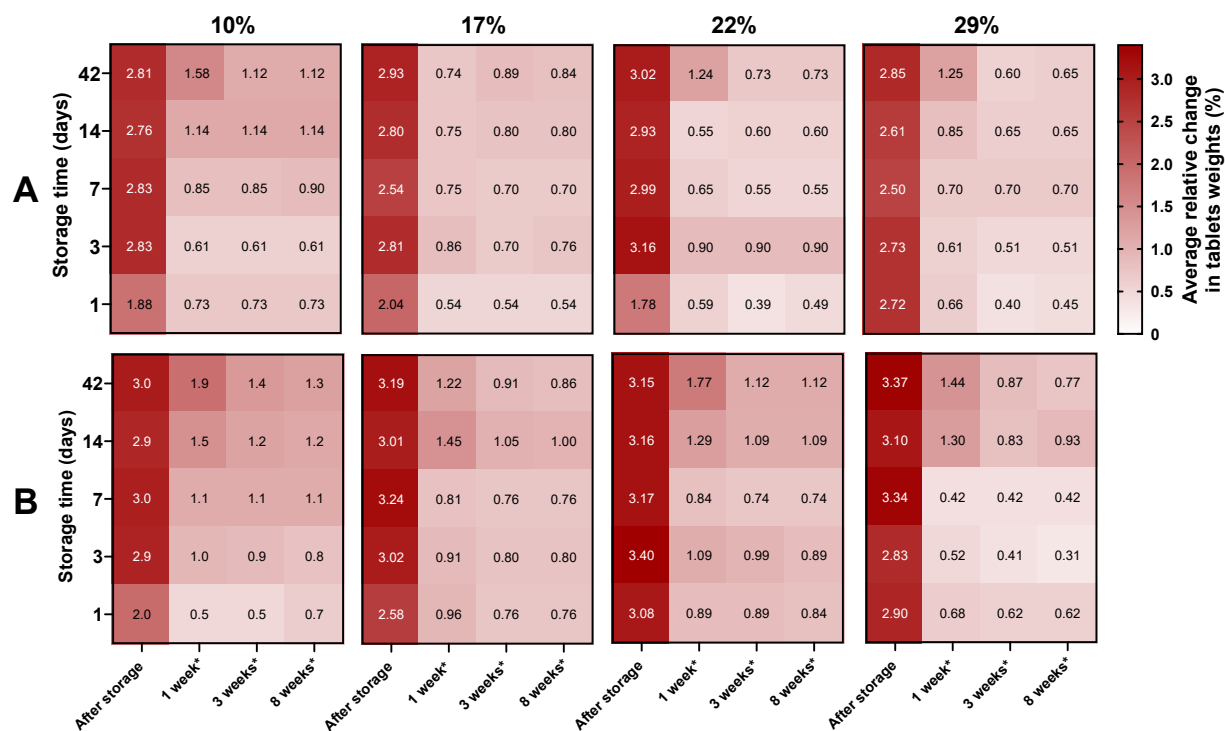


Figure B.3: Equilibration of tablet's weight after removal from storage at 50°C/75% RH compared to the weight of tablets before storage. A and B represent MCC and MCC-CCS (8%) tablets of different porosities, respectively (n = 3).

* Resting duration after removal from storage.

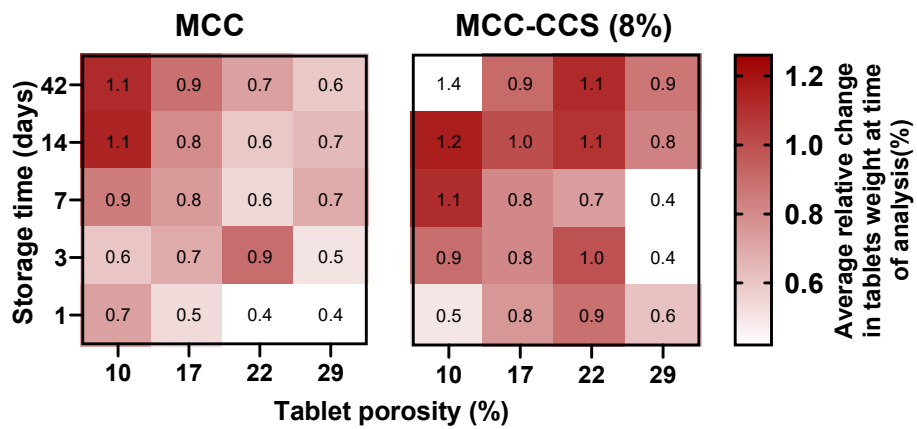


Figure B.4: Average relative change in tablet weight at the time of analysis, relative to the weight of tablets before storage (n = 3).

Table B.3: The Prediction performance of the moisture sorption kinetic rate constant model for tablets stored at 50°C/75% RH.

Tablet formulation	Porosity (%)	$r_{\text{sor-real}}$ (day⁻¹)	R²	CI (±)	RMSE
MCC	10	0.206	0.716	0.206	0.347
	17	1.493	0.929	0.710	0.139
	22	2.012	0.859	1.741	0.212
	29	2.517	0.921	2.094	0.146
MCC-CCS (8%)	10	1.118	0.962	0.351	0.107
	17	1.319	0.924	0.619	0.166
	22	1.537	0.976	0.417	0.096
	29	2.457	0.947	1.588	0.132

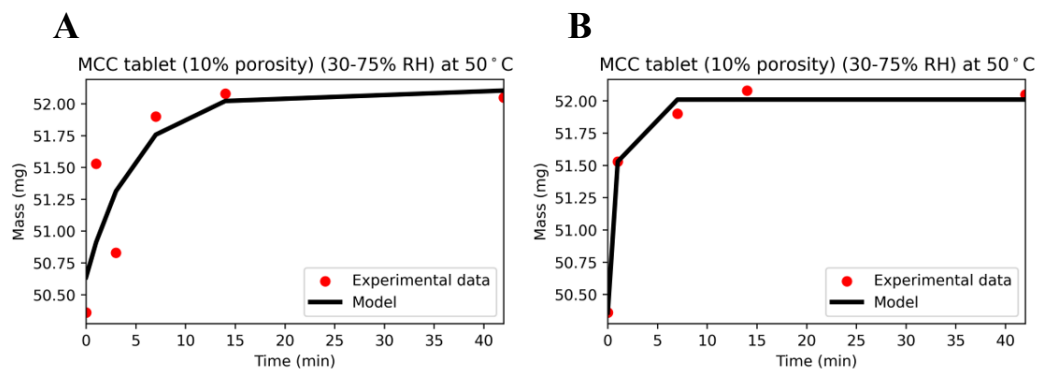


Figure B.5: Moisture sorption profile of MCC tablets at 10% porosity (30–75% RH, 50°C). (A) Experimental dataset showing a single anomalous day-3 average (normalised to the initial masses of all tablets before storage, M_0 , intended to be stored across all time points), resulting in reduced model fit ($R^2 = 0.72$). (B) Improved regression ($R^2 = 0.991$) obtained when the day-3 point is excluded, confirming that the poor initial fit was due to an averaging artefact rather than inconsistent behaviour.

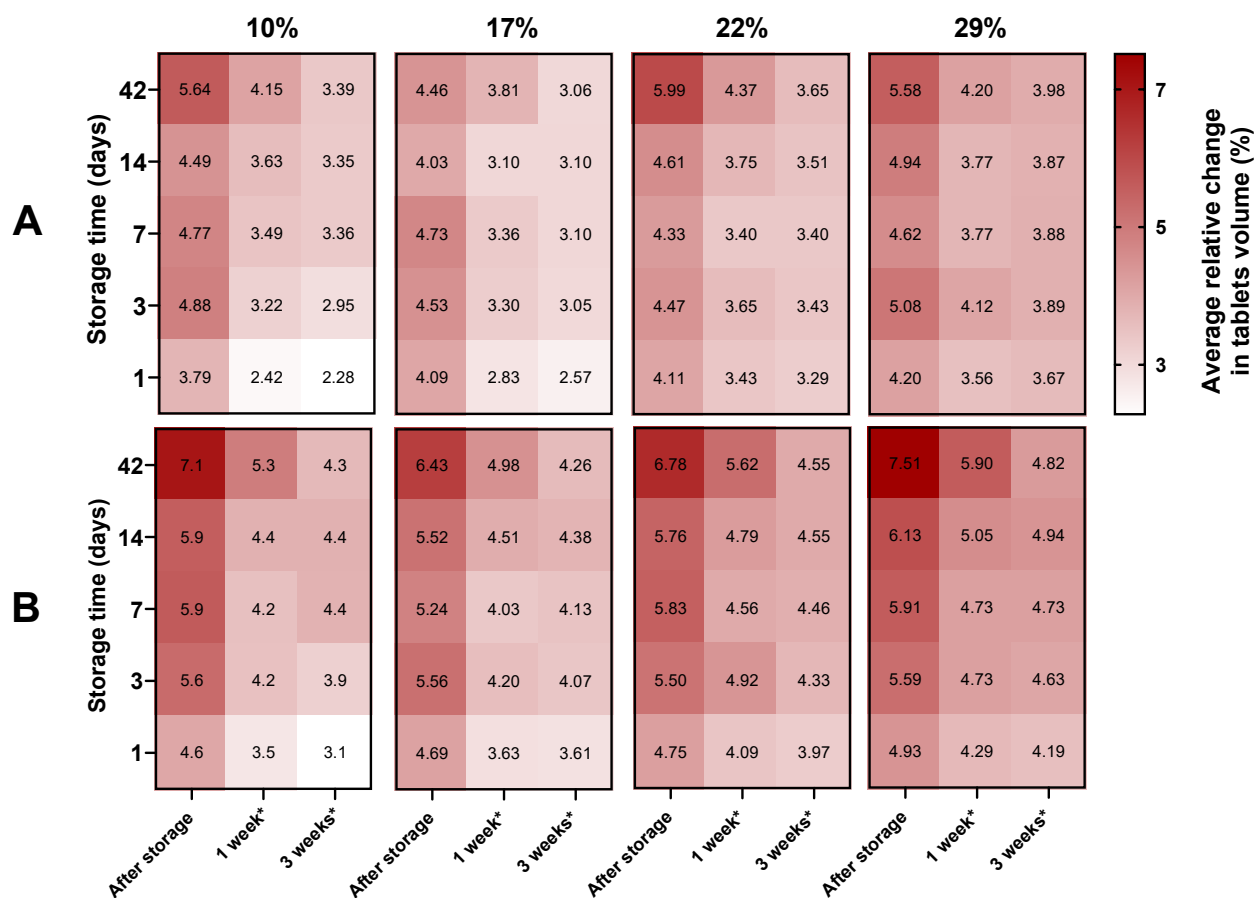


Figure B.6: Equilibration of tablet's volume after removal from storage at 50°C/75% RH compared to the volume of tablets before storage. A and B represent MCC and MCC-CCS (8%) tablets of different porosities, respectively (n = 3).

* Resting duration after removal from storage.

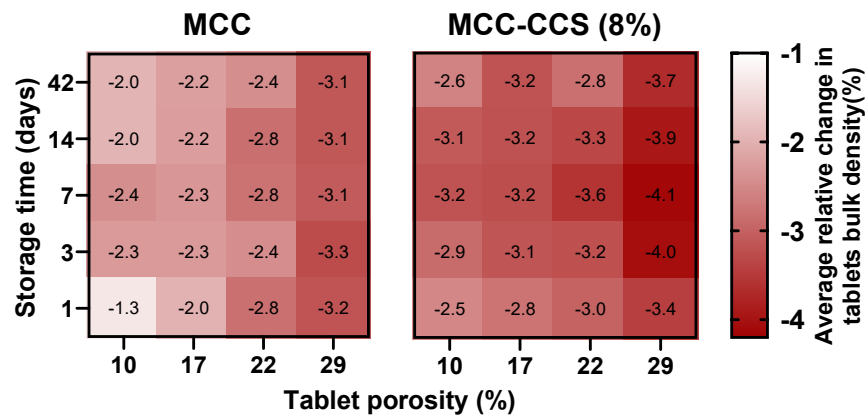


Figure B.7: The average relative change in tablets' bulk density (%), relative to the bulk density of tablets before storage (n = 3).

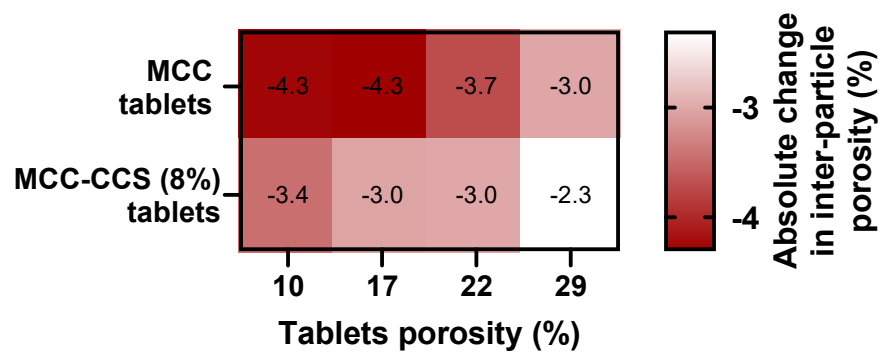


Figure B.8: The absolute change in inter-particle porosity of the tested tablets after storage at 50°C/75% RH for 42 days (n = 3).

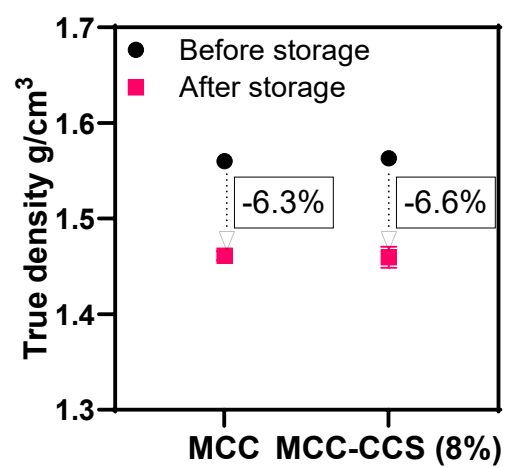


Figure B.9: The true density of formulations before and after storage at 50°C/75% RH. (The numbers in squares represent the average relative change in the true density after storage).

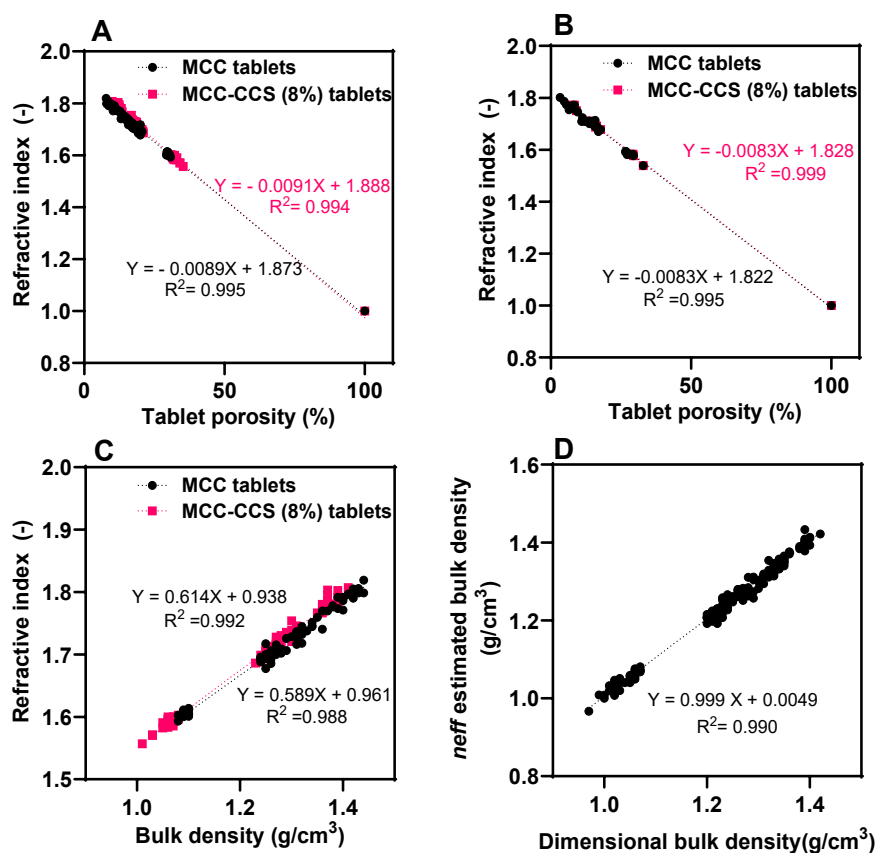


Figure B.10: Linear correlation between the refractive index and tablet porosity (A) before storage and (B) after storage. The point (100,1) represents the powder of the same composition as the tablets. Additionally, (C) shows the linear correlation between the refractive index and bulk density of tablets before storage, while (D) compares the bulk density derived from the refractive index to the bulk density calculated using the tablets' dimensions.

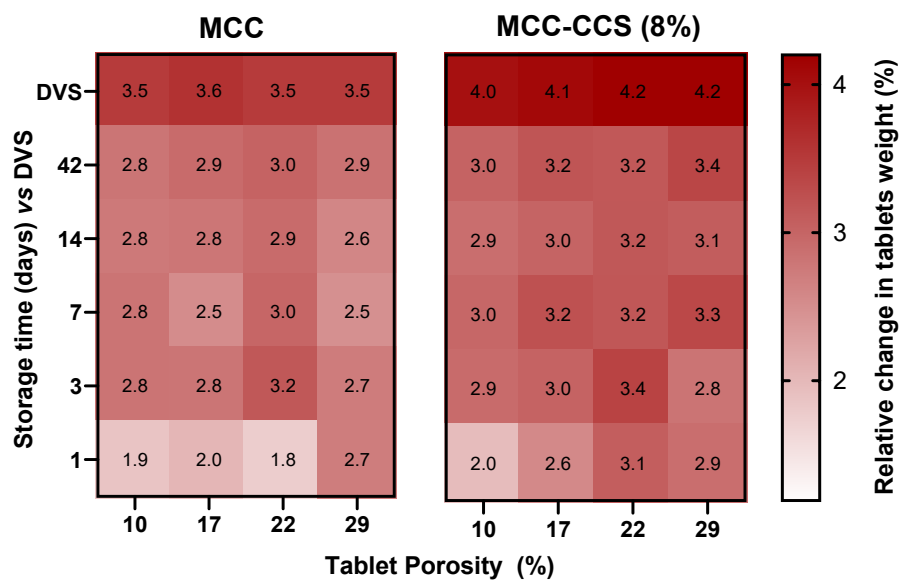
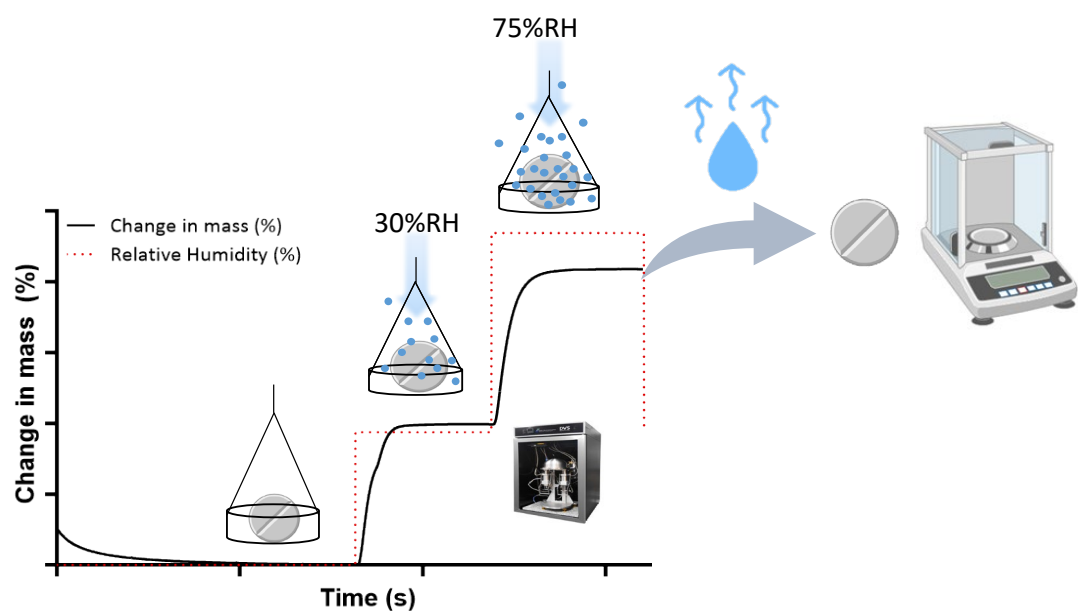


Figure B.11: The average relative change in tablet weight after removal from storage compared to DVS measurements ($n = 3$).



Formulation and tablet porosity (%)	Mass at 30% RH	Mass at 75% RH (inside DVS)	Mass after removal from DVS	Moisture lost during transfer (mg)
MCC (29%)	48.3	49.9	49.5	0.4
MCC-CCS (8%) (29%)	48.9	50.9	50.6	0.3

Figure B.12: Moisture loss observed during the transfer of tablets from the DVS for weight measurement. (The above diagram is for illustration purposes only).

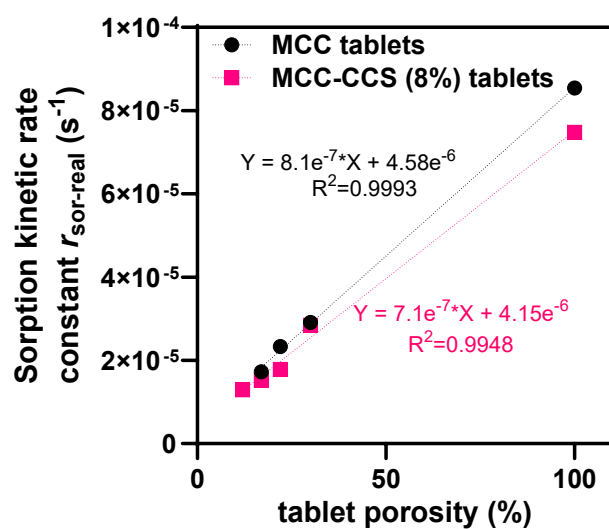


Figure B.13: Sorption kinetic rate constants of the tested tablets at 50°C/75% RH, including powder data estimated using the scaling factor from DVS data.

Table B.4: The Prediction performance of the moisture sorption kinetic rate constant model to predict the tablet mass at each time point after storage at 50°C/75% RH.

The reference point for calculating the EMC*	Tablet formulation	Porosity (%)	R ²	RMSE
DVS powder EMC equation	MCC	10	0.478	0.470
		17	0.656	0.305
		22	0.700	0.310
		29	0.627	0.317
	MCC-CCS (8%)	10	0.722	0.288
		17	0.791	0.275
		22	0.901	0.196
		29	0.815	0.247
DVS tablet EMC equation	MCC	10	0.593	0.415
		17	0.918	0.149
		22	0.858	0.213
		29	0.910	0.156
	MCC-CCS (8%)	10	0.929	0.146
		17	0.912	0.178
		22	0.964	0.118
		29	0.943	0.137

*DVS powder and tablet equations applied in the analysis are presented in Figure 5.7 in Chapter 5.

Appendix C

Additional Data for Chapter 6

Summary

This supporting information provides additional data and analyses to complement the main findings presented in Chapter 6. It includes true density measurements of the excipient powders, evaluation of the moisture sorption model and tensile strength loss model, and additional sessile drop images.

Table C.1: The true density (ρ_{true}) of the excipients used in the study.

Material	ρ_{true} (g/cm³)
MCC	1.56
CCS	1.60
MgSt	1.11
Lac	1.54

Table C.2: The average values of mass and volume of tablets* before and after storage at 50°C/75% RH (n = 3).

MCC-CCS (3%) tablets																	
		Before storage								After storage							
Tablet porosity		10%		17%		22%		29%		10%		17%		22%		29%	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tablets mass (mg)																	
Storage time (days)	1	48.80	0.70	51.53	0.47	51.63	0.81	52.00	0.10	49.87	0.74	52.80	0.46	53.10	0.87	53.60	0.10
	3	48.93	0.35	51.80	0.36	51.93	0.93	51.93	0.31	50.20	0.40	53.27	0.35	53.53	0.96	53.50	0.36
	7	48.87	0.81	51.70	0.36	51.83	0.40	52.23	0.93	50.23	0.84	53.23	0.40	53.43	0.40	53.87	0.91
	14	49.07	0.81	51.63	0.35	51.67	0.75	52.33	0.32	50.43	0.85	53.10	0.40	53.27	0.75	53.97	0.29
	42	49.10	0.10	51.83	1.22	52.00	0.78	52.23	0.67	50.40	0.10	53.27	1.14	53.50	0.79	53.87	0.72
Tablet volume (mm ³)																	
Storage time (days)	1	35.87	0.23	39.53	0.30	41.23	0.00	45.95	0.00	37.04	0.11	41.04	0.20	43.44	0.11	48.63	0.11
	3	35.74	0.20	39.73	0.11	41.30	0.11	45.95	0.00	37.03	0.10	41.52	0.21	43.62	0.11	48.82	0.30
	7	35.87	0.11	39.53	0.11	41.50	0.11	45.95	0.00	37.24	0.20	41.39	0.02	43.93	0.03	49.15	0.11
	14	35.74	0.20	39.53	0.11	41.36	0.11	45.88	0.11	37.32	0.30	41.59	0.13	43.90	0.19	49.21	0.11
	42	35.54	0.20	39.66	0.20	41.36	0.23	45.81	0.11	37.47	0.11	41.42	0.22	44.09	0.00	49.08	0.20
MCC-CCS-MgSt tablets																	
		Before storage								After storage							
porosity		10%		17%		22%		29%		10%		17%		22%		29%	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tablets mass (mg)																	
Storage time (days)	1	49.80	0.26	51.33	0.15	50.63	0.38	50.63	0.47	50.83	0.29	52.53	0.15	52.03	0.46	52.17	0.42
	3	49.97	0.35	51.43	0.78	50.90	0.36	50.90	0.53	51.10	0.30	52.73	0.78	52.23	0.47	52.40	0.53
	7	50.17	0.51	51.80	0.61	50.93	0.46	50.97	0.15	51.33	0.55	53.17	0.55	52.40	0.44	52.50	0.10
	14	50.07	0.45	51.70	1.04	51.03	0.12	50.83	0.38	51.23	0.45	53.07	1.02	52.50	0.10	52.33	0.38
	42	50.17	0.95	51.43	1.16	50.77	0.40	50.90	0.35	51.30	0.87	52.70	1.21	52.13	0.35	52.33	0.32

Tablet volume (mm ³)																	
Storage time (days)	1	36.65	0.11	40.25	0.20	41.82	0.00	47.32	0.00	37.87	0.29	41.92	0.27	43.83	0.11	49.88	0.00
	3	36.78	0.11	40.32	0.11	42.02	0.00	47.52	0.00	38.03	0.18	42.11	0.11	43.95	0.01	50.14	0.12
	7	36.78	0.11	40.45	0.20	41.95	0.11	47.45	0.11	38.10	0.09	42.04	0.11	44.12	0.01	50.27	0.20
	14	36.72	0.20	40.19	0.11	41.89	0.11	47.39	0.11	38.16	0.20	42.09	0.11	44.30	0.01	50.47	0.20
	42	36.65	0.30	40.06	0.20	41.95	0.11	47.32	0.00	38.43	0.28	42.57	0.11	44.35	0.10	50.47	0.20
MCC-CCS-MgSt-Lac tablets																	
		Before storage								After storage							
Tablet porosity		10%		17%		22%		29%		10%		17%		22%		29%	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tablets mass (mg)																	
Storage time (days)	1	50.00	0.70	49.90	0.10	49.77	0.31	49.50	0.72	50.47	0.70	50.47	0.06	50.40	0.30	50.20	0.72
	3	49.93	0.71	49.90	0.26	49.83	1.21	49.57	0.21	50.43	0.81	50.43	0.15	50.43	1.21	50.20	0.17
	7	50.17	0.42	49.97	0.42	49.83	0.29	49.63	0.06	50.63	0.38	50.57	0.42	50.47	0.32	50.27	0.12
	14	50.03	0.61	49.87	0.91	49.77	0.32	49.60	0.20	50.53	0.68	50.50	0.92	50.40	0.35	50.23	0.12
	42	50.07	0.47	50.00	0.17	49.83	0.51	49.60	0.40	50.57	0.38	50.60	0.17	50.50	0.46	50.20	0.36
Tablet volume (mm ³)																	
Storage time (days)	1	36.26	0.11	38.88	0.00	41.56	0.11	46.21	0.11	37.09	0.06	40.01	0.02	42.96	0.18	48.16	0.30
	3	36.32	0.00	38.94	0.11	41.76	0.23	46.21	0.11	37.23	0.03	40.15	0.11	43.02	0.11	47.90	0.19
	7	36.13	0.00	39.14	0.11	41.56	0.11	46.21	0.11	37.21	0.15	40.30	0.11	43.21	0.11	48.03	0.11
	14	36.26	0.23	39.27	0.34	41.63	0.20	46.14	0.00	37.44	0.39	40.60	0.30	43.44	0.11	48.09	0.19
	42	36.46	0.23	38.94	0.11	41.63	0.20	46.21	0.11	37.84	0.37	40.74	0.11	43.43	0.10	48.28	0.20

*Pure MCC tablets data are available in Table B.1 in Appendix B.

Table C.3: EMC of powder blends determined by DVS at 50°C and 30-75% RH.

Powder blend	Change in mass (%)
MCC	4.21
MCC-CCS	4.74
MCC-CCS-MgSt	5.25
MCC-CCS-MgSt-Lac	2.61

Table C.4: Prediction performance of the moisture sorption kinetic rate constant model for tablets and powder blends analysed by DVS at 50°C and 30-75% RH. The 100% porosity corresponds to powder blend measurements.

Tablet formulation	Porosity (%)	$r_{\text{sor-DVS}}$ (s ⁻¹)	R ²	RMSE
MCC	10	0.029	0.998	0.018
	17	0.055	0.999	0.042
	22	0.080	0.999	0.013
	29	0.094	0.999	0.011
	100	0.279	0.999	0.003
MCC-CCS (3%)	10	0.036	0.999	0.016
	17	0.044	0.998	0.020
	22	0.050	0.998	0.021
	29	0.056	0.999	0.020
	100	0.221	0.989	0.012
MCC-CCS-MgSt	10	0.032	0.998	0.021
	17	0.048	0.999	0.018
	22	0.054	0.999	0.019
	29	0.067	0.999	0.019
	100	0.198	0.992	0.011
MCC-CCS-MgSt-Lac	10	0.066	0.999	0.009
	17	0.098	0.999	0.011
	22	0.110	0.999	0.006
	29	0.127	0.999	0.007
	100	0.324	0.996	0.004

Table C.5: Prediction performance of the moisture sorption kinetic rate constant model for tablets stored at 50°C/75% RH using the jars method.

Tablet formulation	Porosity (%)	$r_{\text{sor-real}}$ (day ⁻¹)	R ²	CI (±)	RMSE
MCC	10	0.206	0.716	0.206	0.347
	17	1.493	0.929	0.710	0.139
	22	2.012	0.859	1.741	0.212
	29	2.517	0.921	2.094	0.146
MCC-CCS (3%)	10	1.014	0.981	0.221	0.071
	17	1.325	0.988	0.240	0.062
	22	1.622	0.979	0.426	0.087
	29	2.016	0.947	1.025	0.144
MCC-CCS-MgSt	10	0.936	0.986	0.173	0.054
	17	1.119	0.910	0.554	0.160
	22	1.582	0.956	0.601	0.115
	29	1.926	0.990	0.389	0.056
MCC-CCS-MgSt-Lac	10	1.747	0.909	1.045	0.058
	17	2.266	0.947	1.313	0.052
	22	2.546	0.984	0.945	0.030
	29	3.244	0.991	1.410	0.023

Table C.6: Prediction performance of tensile strength kinetic rate constant model for tablets stored at 50°C/75% RH using the jars method.

Tablet formulation	Porosity (%)	r_{TS} (day ⁻¹)	R ²	CI (±)	RMSE
MCC	10	1.503	0.931	0.704	0.369
	17	1.621	0.938	0.750	0.210
	22	0.444	0.877	0.256	0.195
	29	2.478	0.947	1.631	0.140
MCC-CCS (3%)	10	1.027	0.945	0.384	0.187
	17	1.278	0.885	0.746	0.235
	22	1.510	0.876	0.982	0.206
	29	2.699	0.889	3.040	0.092
MCC-CCS-MgSt	10	0.847	0.839	0.568	0.235
	17	1.504	0.934	0.686	0.111
	22	1.865	0.948	0.867	0.079
	29	2.535	0.959	1.513	0.045
MCC-CCS-MgSt-Lac	10	2.273	0.953	1.241	0.096
	17	2.645	0.997	0.448	0.017
	22	2.882	0.989	1.075	0.011
	29	3.641	0.917	6.703	0.021

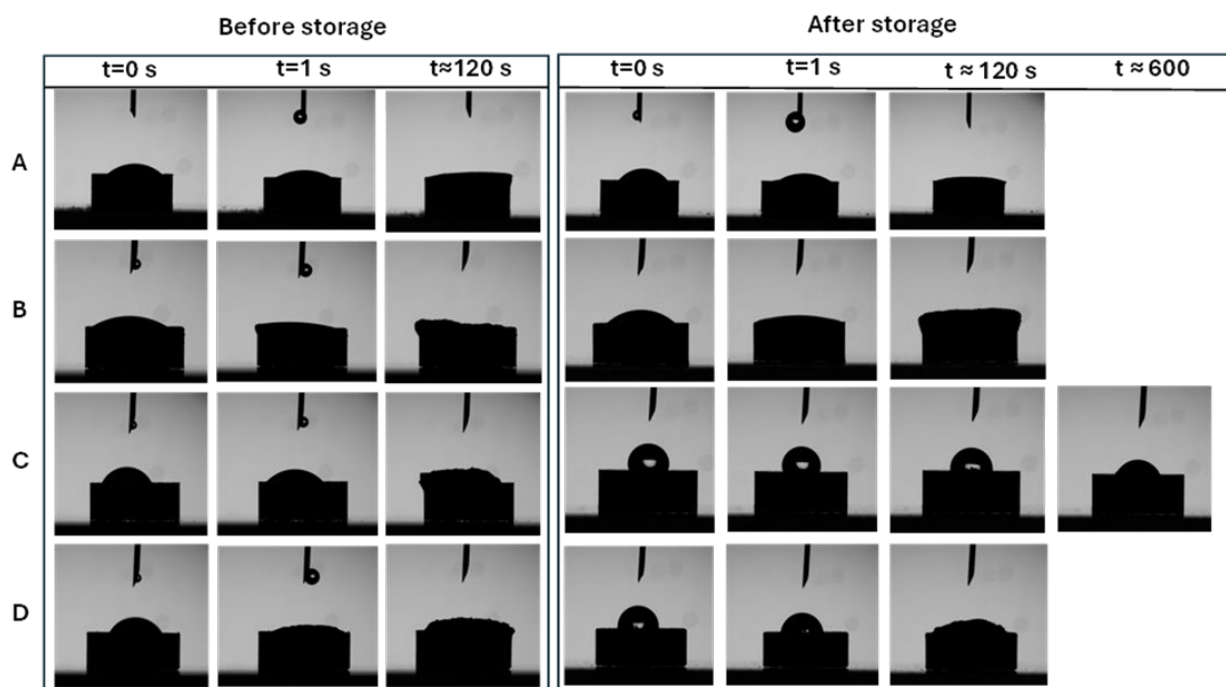


Figure C.1: Sessile drop images of the (A) MCC, (B) MCC-CCS (3%), (C) MCC-CCS-MgSt, and (D) MCC-CCS-MgSt-Lac, 17% porosity tablets as a function of time.

Table C.7: Prediction performance of the moisture sorption kinetic rate constant model using a single r_{sor} -scaling factor derived from MCC across all formulations to predict the tablet mass at each time point after storage at 50°C/75% RH.

Tablet formulation	Porosity (%)	R²	RMSE
MCC-CCS (3%)	10	0.956	0.107
	17	0.967	0.102
	22	0.930	0.158
	29	0.867	0.227
MCC-CCS-MgSt	10	0.978	0.067
	17	0.898	0.170
	22	0.881	0.189
	29	0.844	0.224
MCC-CCS-MgSt-Lac	10	0.673	0.110
	17	0.946	0.053
	22	0.963	0.046
	29	0.964	0.046

Table C.8: Prediction performance of the moisture sorption kinetic rate constant model to predict the tablet mass at each time point after storage at 50°C/75% RH.

The reference point for calculating the EMC*	Tablet formulation	Porosity (%)	R ²	RMSE
DVS- powder EMC	MCC	10	0.478	0.470
		17	0.656	0.305
		22	0.700	0.310
		29	0.627	0.317
	MCC-CCS (3%)	10	0.850	0.197
		17	0.897	0.180
		22	0.942	0.144
		29	0.934	0.160
	MCC-CCS-MgSt	10	0.470	0.329
		17	0.687	0.297
		22	0.872	0.196
		29	0.963	0.109
	MCC-CCS-MgSt-Lac	10	-0.193	0.210
		17	0.676	0.129
		22	0.879	0.083
		29	0.902	0.075
DVS- tablet EMC	MCC	10	0.593	0.415
		17	0.918	0.149
		22	0.858	0.213
		29	0.910	0.156
	MCC-CCS (3%)	10	0.975	0.081
		17	0.979	0.081
		22	0.944	0.142
		29	0.879	0.217
	MCC-CCS-MgSt	10	0.978	0.068
		17	0.899	0.169
		22	0.886	0.185
		29	0.849	0.220
	MCC-CCS-MgSt-Lac	10	0.683	0.109
		17	0.946	0.052
		22	0.962	0.046
		29	0.963	0.046

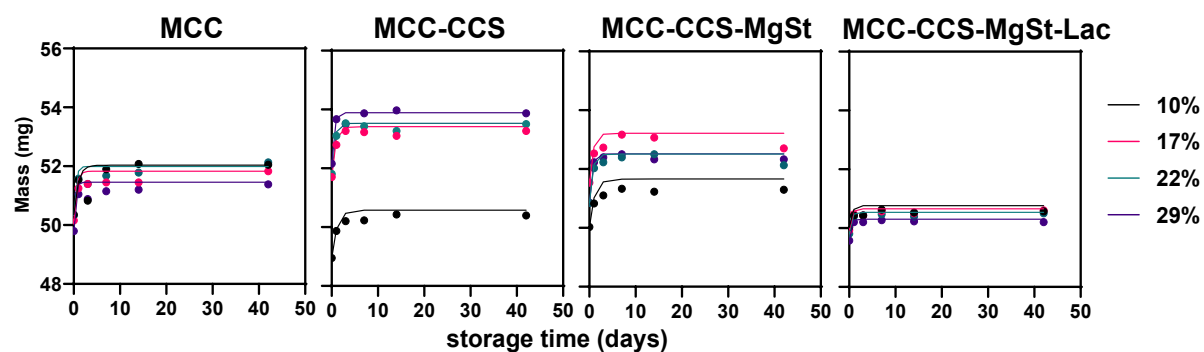


Figure C.2: Predicted (lines) and experimental (points) moisture uptake of tablets at 50°C/75% RH using powder-based DVS-derived scaling.

Table C.9: Prediction performance of the tensile strength kinetic rate constant model to predict the tensile strength at each time point after storage at 50°C/75% RH.

r_{TS} reference	Tablet formulation	Porosity (%)	r_{TS}	R^2	RMSE
The coupling equations between r_{TS} and $r_{sor-real}$ in Figure 6.12	MCC	10	0.813	0.892	0.462
		17	1.366	0.935	0.215
		22	1.762	0.798	0.249
		29	2.315	0.936	0.156
	MCC-CCS	10	0.894	0.941	0.194
		17	1.463	0.883	0.237
		22	1.869	0.873	0.208
		29	2.438	0.890	0.091
	MCC-CCS-MgSt	10	1.057	0.824	0.246
		17	1.513	0.934	0.111
		22	1.838	0.946	0.081
		29	2.295	0.958	0.045
	MCC-CCS-MgSt-Lac	10	2.163	0.953	0.096
		17	2.707	0.997	0.018
		22	3.096	0.989	0.011
		29	3.647	0.917	0.021
$r_{TS} = r_{sor-real}$	MCC	10	1.096	0.921	0.395
		17	1.824	0.936	0.212
		22	2.345	0.774	0.264
		29	3.072	0.945	0.145
	MCC-CCS	10	0.856	0.939	0.198
		17	1.322	0.885	0.235
		22	1.655	0.875	0.207
		29	2.121	0.888	0.092
	MCC-CCS-MgSt	10	0.890	0.828	0.243
		17	1.241	0.929	0.116
		22	1.491	0.934	0.089
		29	1.842	0.953	0.048
	MCC-CCS-MgSt-Lac	10	1.842	0.950	0.099
		17	2.328	0.997	0.017
		22	2.675	0.989	0.011
		29	3.167	0.917	0.021

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