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Evaluation of the composition of the binder bridges in matrix granules prepared with a small-scale high-shear granulator

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ABSTRACT

The aim of this work was to evaluate the binder bridges which can form in hydrophilic matrix granules prepared with a small-scale high-shear granulator. Matrices contained hydroxypropyl methylcellulose (HPMC) as a matrix-forming agent, together with lactose monohydrate and microcrystalline cellulose as filler. Water was used as granulating liquid. A 2^4 full factorial design was used to evaluate the effects of the operational parameters (impeller speed, chopper speed, dosing speed and wet massing time) on the granulation process. The temperature of the sample increased relevantly during the preparation in the small-scale apparatus. The same setup induced different temperature increases for different amounts of powder. This alteration enhances the solubility of lactose and decreases that of HPMC, and thus the quantities of the dissolved components can vary. Accordingly, changes in composition of the binder bridge can occur. Since exact determination of the dissolution of these materials during granulation is difficult, the consequences of the changes in solubility were examined. Differential scanning calorimetry (DSC), thermomechanical analysis (TMA) and X-ray diffraction (XRD) measurements were made to evaluate the films prepared from liquids with different ratios of soluble materials. The DSC and XRD measurements confirmed that the lactose lost its crystalline state in the film. The TMA tests revealed that increase of the quantity of lactose in the film decreased the glass transition temperature of the film; this may be attributed to the interaction of the additives. At a lactose content of 37.5%, a second glass transition appeared. This phenomenon may be indicative of a separate amorphous lactose phase.

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1. Introduction

Various solid matrix systems are currently popular because of their controlling effects on the dissolution of the active ingredients [1,2]. These matrices (mainly tablets) may be hydrophobic or hydrophilic. Hydrophilic systems can influence the rate of liberation of active pharmaceutical ingredient (API) by erosion and diffusion [3–5], but they can also exhibit relevant bioadhesive properties which can affect the site of action [6,7]. The matrix-formers that are mainly used for erodable systems are polymers with good solubility, high water uptake and properties appropriate for the formation a mucilaginous (adhesive) layer. The additional pharmaceutical excipients must be hydrophilic so as to avoid inappropriate wetting of the matrix-former and to promote the action of the matrix-former polymer.

Tablets can be prepared through the direct compression of a powder mixture containing a matrix-former or through the compression of granules (generally the matrix granules) [8]. Various methods can be used to prepare granules containing the previously mentioned components [9–12]. The most widely applied method is wet granulation, where the granulating fluid is an aqueous system. The granulating fluid can contain different binder materials (mainly macromolecular agents) or it can be a solvent of the solid component, in which case the soluble and later the solidified component too form bridges between the particles and ensure the appropriate mechanical behaviour for the agglomerates [13]. The soluble component can be any member of the powder mixture, e.g. the active agent, filler, matrix-former, etc., or a mixture of them. A number of publications have demonstrated that excipients that are strongly soluble in the liquid binder play a major role in the formation and strength of solid bridges inside a granule [14–16]. Those studies additionally dealt with the evaluation of the binder bridges, focusing on the mechanical and morphological properties of the granules, but not on the exact composition of binder

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bridges. Other papers discuss the evaluation of the solubilities of the materials, the crystallization/recrystallization processes and examination of the product formed with respect to amorphism and polymorphism [17–19]. Study of the composition and crystalline state of these individual small bridges in the granules is difficult, but an understanding of their formation is critical for optimization of the granulation process. The significance of such evaluations is highlighted by the well-known phenomenon that an amorphous form can change during storage and can indicate stability problems [20].

It was mentioned above that the hydrophilic matrix-former component can be water-soluble. Conventionally, various polysaccharides/polymers are used in the tablet formulations to retard drug release. A solution of such materials (e.g. different cellulose derivatives) is often used as a coating material. Alternatively, these can be used as a binder during conventional wet granulation binders [21,22]. It is known that a solution of these polysaccharides/polymers as binders probably on drying enables the granules to be coated by them [23] and the course of drying, they form hard film bridges [24–27]. In general, these materials are applied in high concentrations in the powder mixture during the formulation of matrix systems. A proportion of these materials dissolves in the granulation liquid and so a film or binder bridges are formed during drying, but prediction of the exact quantities is difficult. Another problem inherent in the prediction is the fact that the powder mixtures contain materials with different water uptakes and solubilities. The dissolved amounts of the components can be influenced by the quantity of the liquid and also by the operational parameters, e.g. the effectiveness of mixing or the processing time. The effects of the operational parameters on the granules or pellets formed have been studied [28–30], but the composition of the binder bridges (film) has not been evaluated.

The high-speed moving of the parts of a small-scale high-shear granulator (impeller and chopper) can cause a relevant increase in the temperature of the powder/granules. This parameter can therefore be an indirect factor during the optimization. Its importance is emphasized by the temperature-sensitive nature of the solubility of the components. In the composition under evaluation, not only the rate of dissolution, but also the quantity of materials dissolved can depend on the temperature. Hence the solution formed during granulation and after drying in the binder film can exhibit different compositions. Since exact, direct measurement of the components in the fluid formed around the solid particles and in wet granules appears impossible, it is reasonable to prepare and study the properties of free films formed from different ratios of the soluble components.

Pressures to save API are driving formulation developers toward smaller-scale laboratory processes (miniaturization), while pressure to save time puts a premium on increasingly accurate laboratory-scale tools. An appreciable number of manuscripts have dealt with miniaturization of the different technological methods and its problems [31–34]. In certain cases, it is very difficult to extrapolate the results to larger systems.

In the present work the effect of operational parameters and batch size on the temperature increase during small-scale granulation were studied. Since the solubilities of the components may change as a result of this, the main aim was the evaluation of binder bridges with different ratios of soluble materials. Such data can be informative as concerns granulation scale-up.

Table 1
Values of factors

Factor	Low-level (−)	High-level (+)
Chopper speed, X_1 (rpm)	1500	3500
Impeller speed, X_2 (rpm)	500	1000
Dosing speed, X_3 (ml/min)	5	15
Wet massing time, X_4 (min)	1	4

2. Experimental

2.1. Materials

HPMC (Pharmacoat 606, Shin-Etsu Chemical Co., Ltd., Tokyo, Japan) was used as matrix-former. Our preformulation studies indicated that the optimum concentration was 30%. Microcrystalline cellulose (Vivapur 301, Rettenmaier&Söhne GmbH, Rosenberg, Germany) was applied as a filler/binder, and α-lactose monohydrate (Ph. Eur., Hungaropharma Plc., Budapest) as a filler, each of these components was in a quantity of 35%.

2.2. Preparation of matrix granules

In the first part of the granulation, 150 g of granules was prepared in a high-shear granulator (ProCepT 4M8 granulator, ProCepT nv, Zelzate, Belgium). This apparatus is equipped with an Infrared product temperature sensor assembly. It ensures a constant control between 20 °C and 100 °C. In accordance with our previous results [35], the quantity of liquid (water) was 35–100 g of powder mixture.

During the optimization of the granulation process, the quantities of the powder mixture and the liquid were kept the same, and the technical parameters were varied. A 2^4 factorial design was applied to study the effects of the operational factors (Table 1). The experiments were performed in a randomized sequence. The granules were dried on trays at 40 °C for 24 h.

Statistica for Windows 7.1 AGA software (StatSoft Inc., Tulsa, USA) was used for the calculations. The following linear approach, containing the interactions of the factors, was used to determine the response surface. This program can also evaluate three-factor interactions, but in this study they were not investigated. They are very difficult to interpret.

$$y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{14}X_1X_4 + b_{24}X_2X_4 + b_{34}X_3X_4$$

The confidence interval in the mathematical evaluations was 95% ($p < 0.05$).

In the second part of our work, the effect of the batch size was evaluated. The same apparatus was used. The composition of the powder mixture was the same and the quantity of water was again 35–100 g of powder mixture. The operational parameters were—chopper speed: 3500 rpm; impeller speed: 1000 rpm; dosing speed: 5 ml/min; and wet massing time: 4 min. The amounts of powder taken were 50 g, 100 g, 150 g and 200 g. The dosing time had to be adjusted.

2.3. Study of granules

The sizes and the size distributions of the samples were assessed. An analytical sieve (Retsch GmbH, Haan, Germany) was used. The D10, D50 and D90 values of the samples were determined with sieving system software (Retsch EasySieve 2.0).

2.4. Evaluation of the films

Different samples were prepared for the thermoanalytical tests on the free film. Aqueous solutions containing various ratios of HPMC and lactose were produced (Table 2). They were poured into teflon dishes, and the solutions were then dried under the same

Table 2
Compositions of samples

Sample	Sign of dried film	HPMC content (%)	Lactose content (%)	HPMC/lactose ratio	Water (%)
S1	F1	5	0	–	95
S2	F2	5	1	5	94
S3	F3	5	2	2.5	93
S4	F4	5	3	1.67	92
S5	F5	5	4	1.25	91

conditions at 40 ± 2 °C for 24 h. The dried films were detached from the surface before the experiments and stored in a hermetically closed container.

The thermoanalytical examinations were carried out in part with a Mettler-Toledo DSC 821e (Mettler-Toledo GmbH, Switzerland) instrument with a dynamic method in the interval 25–300 °C, at a heating rate of 10 °C/min. Argon was used as purge gas.

For a more accurate evaluation of the behaviour of the polymer film (glass transition), thermomechanical analysis TMA was performed with a Metler Toledo TMA 40 apparatus. The heating method was dynamic in the interval 20–200 °C, and the heating rate was 10 °C/min. The glass transition temperature (T_g) was studied with STAR software. The measurements were made in triplicate.

2.5. X-ray diffraction (XRD) testing

A Bruker D8 Advance powder diffractometer (Bruker-AXS; Karlsruhe, Germany) was used for these tests. The non-pulverized samples were measured in transmission mode between Mylar foils (3.6 μm), the following conditions being applied at room temperature.

Radiation : Cu Kα1($\lambda = 1.54060$ Å) and Cu Kα2($\lambda = 1.54439$ Å)

The attachments were a Göbel mirror, a Soller slit, and a 9-position sample changer used in transmission mode. The voltage was 40 kV, the current was 30 mA, and measurements involved a Θ/Θ scan of 4–35.00° 2Θ, with a step size of 0.04° 2Θ.

3. Results and discussion

3.1. Granulation experiments

The sieving results on the granules revealed that the characteristic of particle size distribution of granules was very similar (Table 3). Apart from the fact that operational parameters were variant the differences between D10 and D90 were nearly 1500 μm.

The change of the operational factors caused an appreciable deviation in the median particle size. The D50 values of the different batches varied between 917 μm and 1478 μm.

The temperature increase during the granulation process also exhibited a great variance (4.8–18.6 °C). The variation in this parameter is significant in changing the solubility of a component, e.g. the solubility of lactose is 1 part in 4.63 parts of water at 20 °C and 1 part in 2.04 parts of water at 50 °C. The concentration of the saturated solution is therefore 17.8% at 20 °C and 32.9% at 50 °C [36].

The model for the D50 value gave $R^2 = 0.959$ and three significant factors ($p < 0.05$) (Table 4). The largest effect was observed for the dosing speed (X_3). Since the sign of this factor was negative, increase of the dosing speed caused a decrease in the particle size.

The fitting of the response surface for the temperature increase resulted in a model with $R^2 = 0.982$ and four significant factors ($p < 0.05$). Increase of the impeller speed significantly enhanced the temperature increase which was alo increased by a reduction of the dosing speed. It was clear from the evaluation of all of the factors that an increased process time caused increases in the particle size and the temperature of the sample.

To investigate the effect of the amount of powder, independent tests were performed. It was seen that an increasing amount of

Table 4
Values of coefficients

Coefficient	D50	Temperature increase
b_0	1202.19[a]	9.23[a]
b_1	−22.94	0.38
b_2	−76.56[a]	2.79[a]
b_3	−98.06[a]	−2.01[a]
b_4	17.31	1.02[a]
b_{12}	1.56	0.22
b_{13}	10.06	−0.06
b_{14}	−30.81	0.42
b_{23}	−84.31[a]	−1.19[a]
b_{24}	19.06	0.43
b_{34}	−4.94	−0.07

[a] Significant.

Table 3
Granulation parameters (in order of trials)

X_1 (rpm)	X_2 (rpm)	X_3 (ml/min)	X_4 (min)	D10 (μm)	D50 (μm)	D90 (μm)	D90 – D10 (μm)	Temperature increase (°C)
3500	500	15	4	389	1222	1879	1490	7.3
1500	500	5	1	367	1306	1932	1565	7.7
1500	1000	15	1	236	918	1879	1643	7.5
3500	1000	5	4	540	1232	2199	1659	18.6
1500	500	15	1	284	1268	1922	1638	4.8
1500	1000	15	4	359	976	1906	1547	9.7
3500	1000	5	1	532	1306	2039	1507	13.8
3500	1000	15	1	246	917	1864	1618	8.0
1500	500	15	4	347	1306	1922	1575	5.6
3500	1000	15	4	346	962	1887	1541	10.1
3500	500	5	1	315	1284	1943	1628	6.1
3500	500	5	4	464	1247	1930	1466	8.2
1500	1000	5	1	498	1216	1988	1490	13.0
1500	500	5	4	467	1333	1981	1514	7.0
3500	500	15	1	257	1264	1915	1658	4.8
1500	1000	5	4	623	1478	2396	1773	15.5

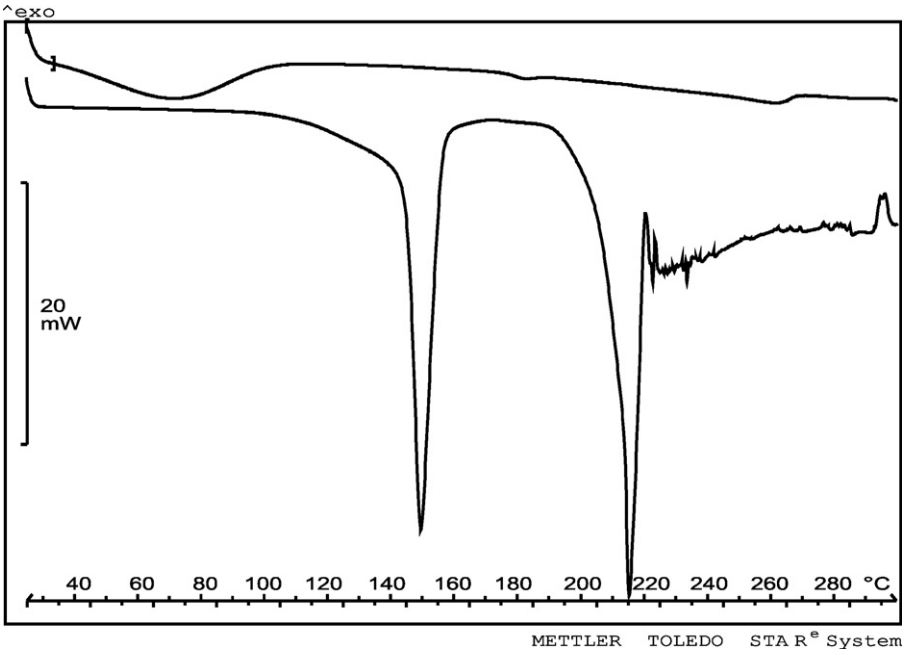

Fig. 1. DSC plot of HPMC (upper curve) and lactose monohydrate (lower curve).

powder mixure induced an increase in the dosing time (Table 5). The temperature increase was more relevant for the process with a long dosing time (higher amount of mass).

3.2. Evaluation of the films

Variation in the temperature of the sample can change the quantity and the proportions of the dissolved components, phenomena which can alter the properties of the film or binder bridge. Hence films with different compositions were prepared and evaluated.). The XRD curves of the films are typical for amorphous materials (Fig. 5

The starting components were studied first. A characteristic thermogram was observed for lactose monohydrate (Fig. 1). There was an endotherm peak at about 150 °C; this reflected the loss of crystalline water [37]. The other peak related to the melting of lactose. Above this temperature, the lactose decomposed. The differential scanning calorimetry (DSC) curve of the HPMC in this range was free from characteristic peaks. A wide endothermic peak

Table 5
Temperature increase of different samples

Amount of powder (g)	Dosing time (s)	Temperature increase (°C)
50	210	8.6
100	350	13
150	630	18.6
200	840	24.7

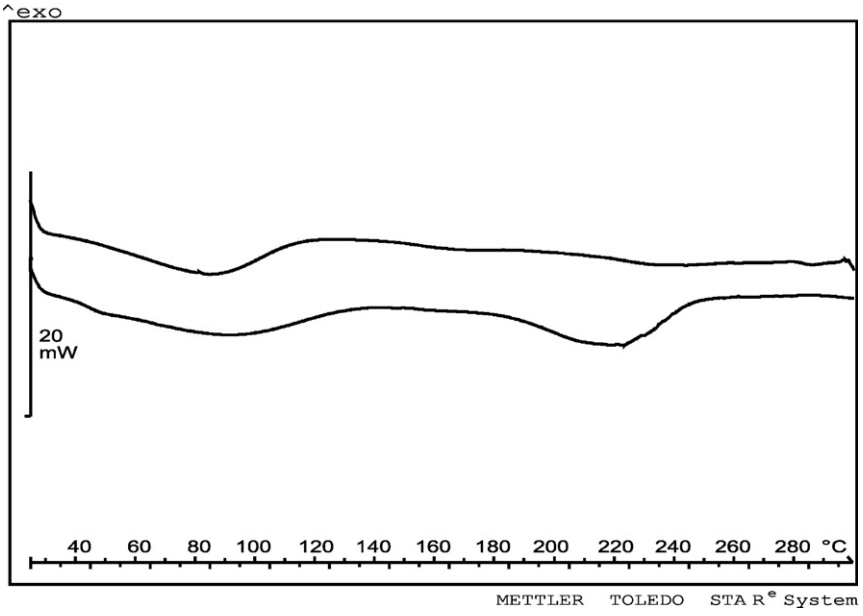

Fig. 2. DSC plots of F1 (upper curve) and F5 (lower curve).

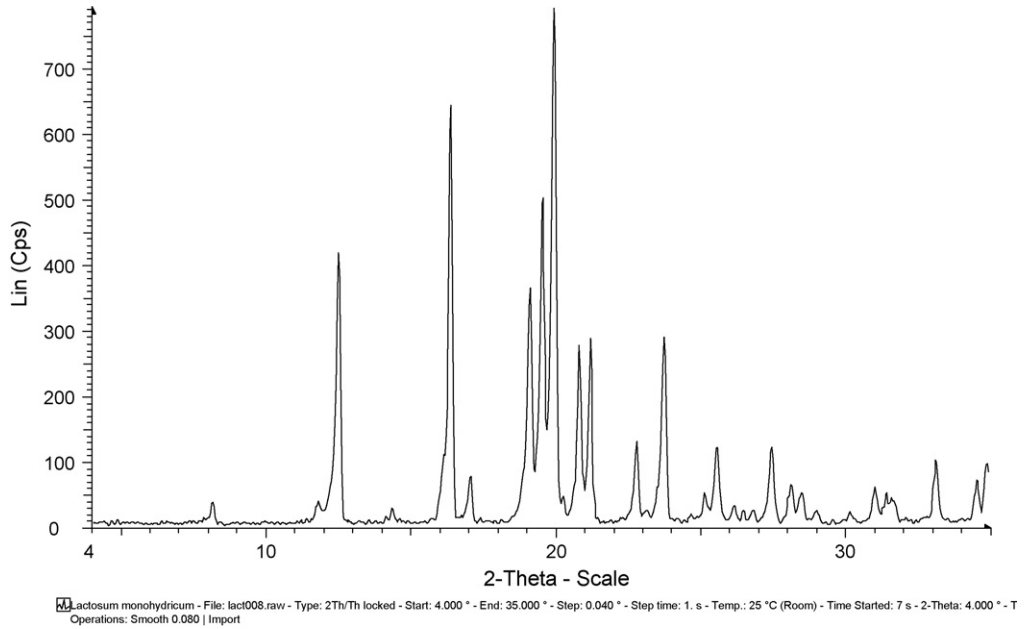

Fig. 3. XRD record of lactose monohydrate.

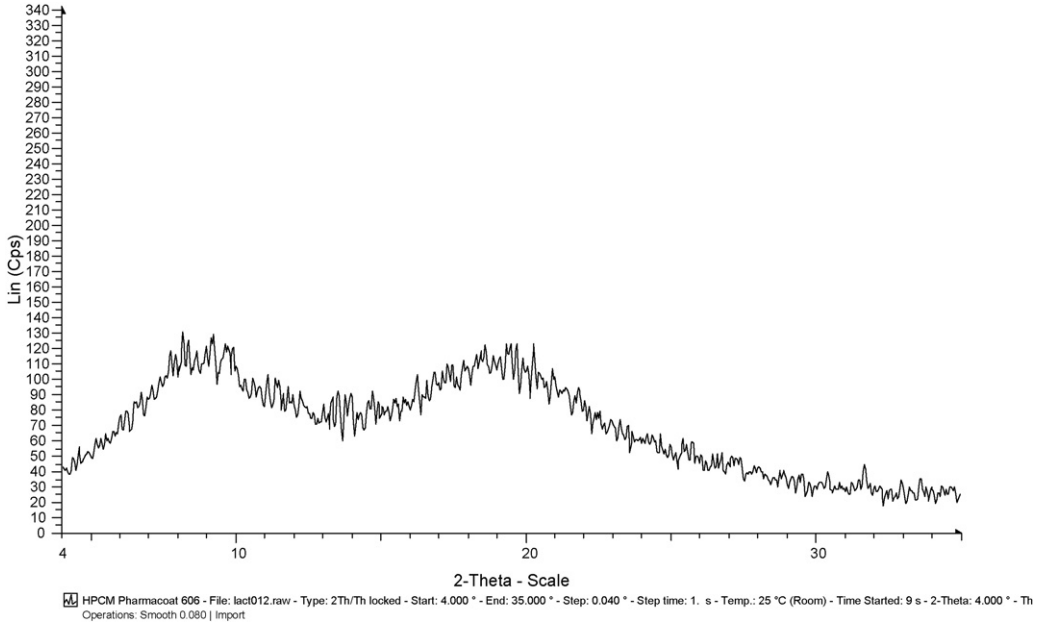

Fig. 4. XRD record of HPMC.

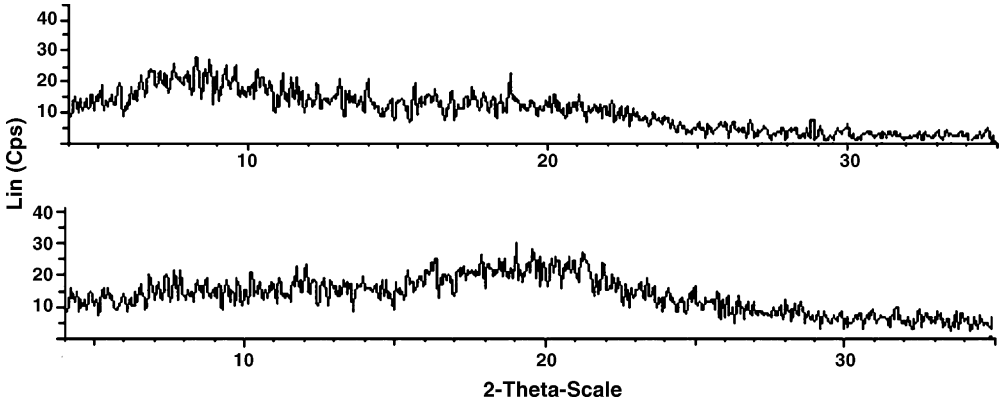

Fig. 5. XRD records of F1 (upper curve) and F5 (lower curve).

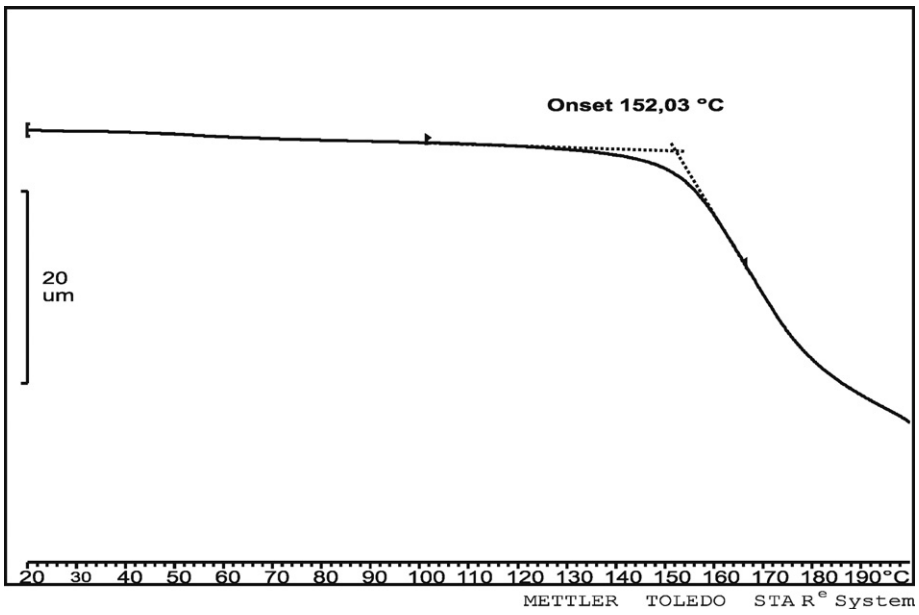

Fig. 6. TMA plot of F1.

under 100 °C can be explained by the loss of mechanically bounded water. A slight shifting of baseline was detected at higher temperature. It was the T_g of polymer.

The DSC experiments indicated similar behaviour for all films. The curves of F1 and F5 are presented in Fig. 2. The sharp characteristic peaks of lactose disappeared, but no obvious endothermic phenomenon was detected at around 210 °C for F5. Thus, the crystalline state of the lactose had evidently been lost.

XRD is a method with which to evaluate the crystallinity of the components. The crystalline state of lactose and the amorphous properties of HPMC can be seen from the curves of the starting components (Figs. 3 and 4).

Amorphous materials can be evaluated well with TMA. The TMA curve of HPMC exhibited a typical step relating to the glass transition of amorphous material (Fig. 6). At temperatures below T_g, the plot was linear. Deviation from linearity occurred as T_g was approached (onset temperature). As the temperature was increased further, the profile again became linear, indicating complete conversion to the rubbery phase. This process can be regarded as a shifting of the baseline. A change in composition altered the TMA curve of the film (Figs. 7 and 8). It can be seen that a second T_g appeared for F4 and F5.

The temperatures of onset of T_g are listed in Table 6. A decrease in the T_g of HPMC was detected for F2 and F3. Their values increased when the second step appeared for F4, and decreased for F5. These results can be interpreted in terms of changes in the structure of the film. For F2 and F3, the macromolecules and the lactose can interact, and the properties of the film then change. For F4 and F5, besides

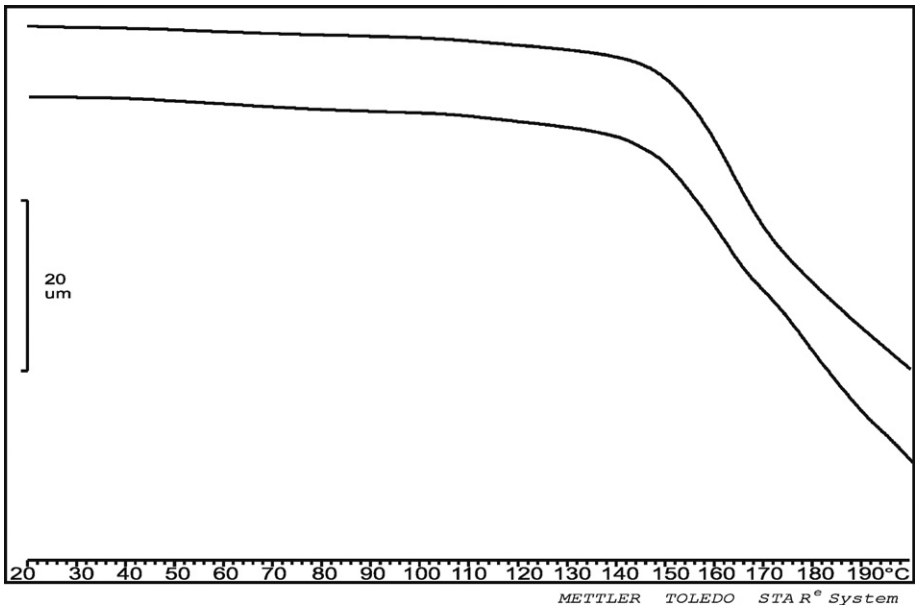

Fig. 7. TMA plots of F2 (upper curve) and F3 (lower curve).

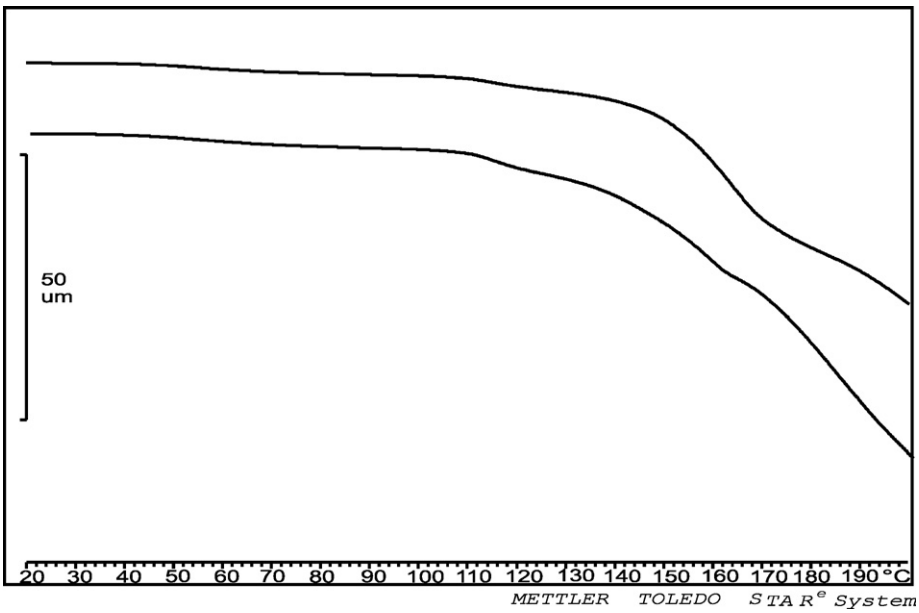

Fig. 8. TMA plots of F4 (upper curve) and F5 (lower curve).

such interactions, a new amorphous phase with a T_g appeared. It is known from the literature that the T_g of amorphous lactose is 100–120 °C, depending on the methods and conditions [38–40]. Hence, the second step probably relates to a separate amorphous lactose phase. It is well-known that the proportion of ordered and amorphous regions determines the mechanical properties of a macromolecular film [41]. The different phases can be detected in the film, as they induce inhomogeneity in it. It is also known that amorphous materials are less stable than crystalline ones and the stabilization of amorphous materials is very difficult [42].

Table 6
Temperatures of onset of glass transition ($n = 3$)

Film	T_g1 (°C)	T_g2 (°C)
F1	152.9 ± 1.0	–
F2	150.4 ± 1.2	–
F3	147.1 ± 0.6	–
F4	150.9 ± 0.8	108.3 ± 0.2
F5	143.3 ± 0.9	108.6 ± 0.5

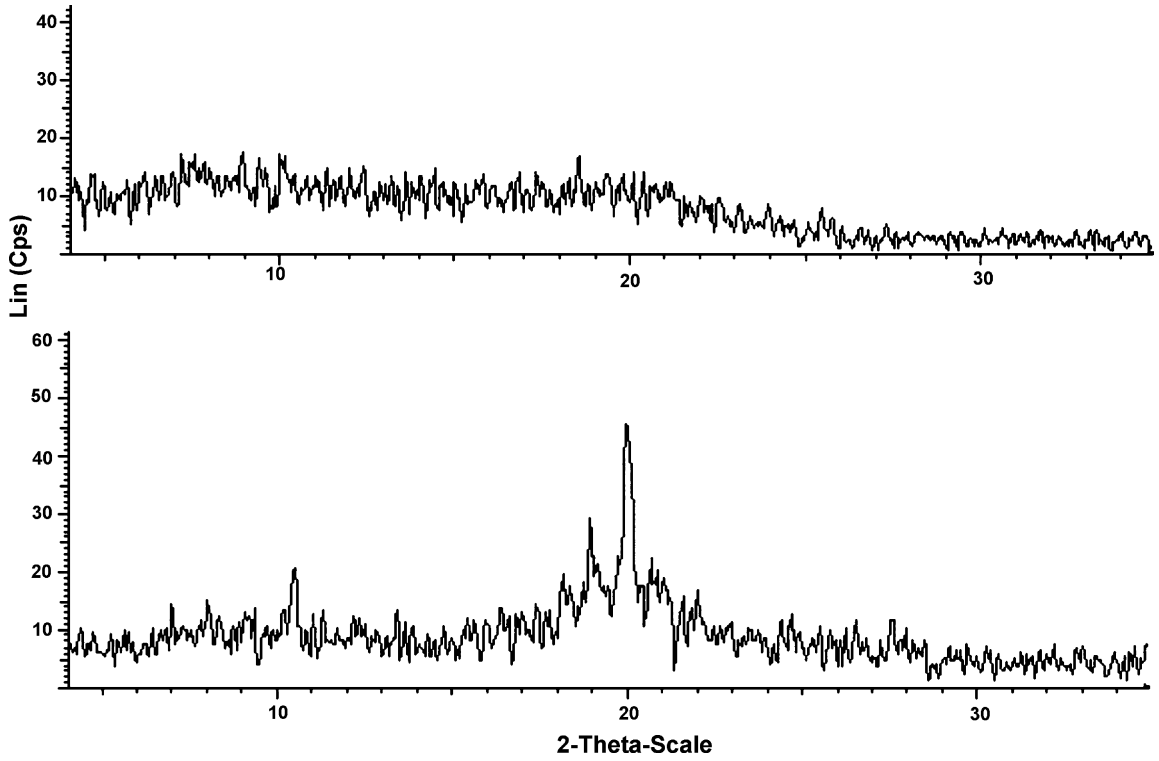

Fig. 9. XRD records of stored F1 (upper curve) and F5 (lower curve).

The individual amorphous phase of lactose changed in crystallinity during long storage (stored in a hermetically closed container at room temperature for 12 months). It was explained by X-ray diffraction study (Fig. 9). Samples with two T_gs exhibited characteristic peaks after the storage. In contrary the samples without T_g at around 110 °C did not show alteration. It can be concluded that the separate amorphous phase was partially recrystallized during the long-term storage, which can induce stability problems of product.

4. Conclusions

Not only the particle size of the granules, but also the temperature of the powder mixture changed considerably during granulation at different operational parameters. The temperature increase was an indirect factor which can influence the dissolution of the powder mixture during granulation. At higher temperatures, a higher proportion of lactose and less HPMC are dissolved. The significant factors causing a temperature increase were the impeller speed and the dosing speed. Alteration of the batch size can induce a relevant change in the temperature increase.

The crystalline behaviour of lactose disappeared in films containing lactose and HPMC, as confirmed by DSC and XRD measurements. TMA indicated that an increase of the proportion of lactose in the film decreased the T_g of the film. This can be ascribed to the interaction of the components. At a lactose:HPMC ratio of 3:5, a second glass transition appeared. This points to the formation of a separate amorphous phase of lactose. Its crystallinity was changed during the storage.

Finally, it may be stated that evaluation of the temperature increase during granulation is necessary, since the small-scale granulation procedure can induce a dramatic change in this parameter. This should be borne in mind before prediction of the parameters applied for the granulation scale-up. Direct study of the composition of every individual binder bridge formed from soluble materials in the granules is impossible, but their indirect evaluation can be useful. These data provide additional information towards an understanding of granule formation in a small-scale high-shear granulator.

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References

[1] S. Abdul, S.S. Poddar, J. Control. Release 97 (2004) 393–405.
[2] A.M. Hillary, A.W. Llojd, J. Swarbrick, Drug Delivery and Targeting for Pharmacists on Pharmaceutical Scientists, Taylor&Francis, London, 2001.
[3] P. Sriamornsak, N. Thirawong, Y. Weerapol, J. Nunthanid, S. Sungthongjeen, Eur. J. Pharm. Biopharm. 67 (2007) 211–219.
[4] C.W. Vendruscolo, I.F. Andreazza, J.L.M.S. Ganter, C. Ferrero, T.M.B. Bresolin, Int. J. Pharm. 296 (2005) 1–11.
[5] I.J. Hardy, A. Windberg-Baarup, C. Neri, P.V. Byway, S.W. Booth, S. Fitzpatrick, Int. J. Pharm. 337 (2007) 246–253.
[6] A.P. Munasur, V. Pillay, D.J. Chetty, T. Govender, Int. J. Pharm. 323 (2006) 43–51.
[7] T.S. Owens, R.J. Dansereau, A. Sakr, Int. J. Pharm. 288 (2005) 109–122.
[8] S.K. Singh, V. Naini, in: J. Swarbrick, J.C. Boylan (Eds.), Encyclopedia of Pharmaceutical Technology, vol. 1, second ed., Marcel Dekker Inc., New York, 2002.
[9] J. Herder, Å. Adolfsson, A. Larsson, Int. J. Pharm. 313 (2006) 57–65.
[10] Y. Zambito, A. Baggiani, V. Carelli, M.F. Serafini, G. Di Colo, J. Control. Release 102 (2005) 669–677.
[11] I. Özgüney, G. Ertan, T. Güneri, Il Farmaco 59 (2004) 549–555.
[12] M. Säkkinen, U. Seppälä, P. Heinänen, M. Marvola, Eur. J. Pharm. Biopharm. 54 (2002) 33–40.
[13] W. Pietsch, Agglomeration Processes, Wiley–VCH, Weinheim, 2002.
[14] L. Farber, G.I. Tardos, J.N. Michaels, Chem. Eng. Sci. 58 (2003) 4515–4525.
[15] D. Bika, G.I. Tardos, S. Panmai, L. Farber, J.N. Michaels, Powder Technol. 150 (2005) 104–116.
[16] P. Rajniak, C. Mancinelli, R.T. Chern, F. Stepanek, L. Farber, B.T. Hill, Int. J. Pharm. 334 (2007) 92–102.
[17] N. Blagden, M. de Matas, P.T. Gavan, P. York, Adv. Drug Deliver. Rev. 59 (2007) 617–630.
[18] D. Singhal, W. Curatolo, Adv. Drug Deliver. Rev. 56 (2004) 335–347.
[19] L.X. Yu, R.A. Lionberger, A.S. Raw, R. D'Costa, H. Wu, A.S. Hussain, Adv. Drug Deliver. Rev. 56 (2004) 349–369.
[20] R. Zelkó, Á. Orbán, K. Süvegh, J. Pharmaceut. Biomed. Anal. 40 (2006) 249–254.
[21] P.J. Sherrington, R. Olivier, Granulation, Heyden & Son Ltd., London, 1981.
[22] D.M. Parikh, Handbook of Pharmaceutical Granulation Technology, Marcel Dekker Inc., New York, 1995.
[23] V.R. Sinha, R. Kumria, Int. J. Pharm. 249 (2002) 23–31.
[24] K. Pintye-Hódi, P. Szabó-Révész, A. Keresztes, B. Selmeczi, Pharmazie 33 (1978) 735–737.
[25] K. Pintye-Hódi, G. Nagy, A. Keresztes, B. Selmeczi, G. Kedvessy, Pharmazie 35 (1980) 168–170.
[26] T. Kapsidou, I. Nikolakakis, S. Malamataris, Int. J. Pharm. 227 (2001) 97–112.
[27] F. Podczeck, Particle–Particle Adhesion in Pharmaceutical Powder Handling, Imperial College Press, London, 1998.
[28] E. Chevalier, M. Viana, C. Pouget, D. Chulia, Pharm. Dev. Technol. 12 (2007) 133–144.
[29] H. Vromans, H.G.M. Poels-Janssen, H. Egermann, Pharm. Dev. Technol. 4 (1999) 297–303.
[30] Á. Hegedűs, K. Pintye-Hódi, Chem. Eng. Process 46 (2007) 1012–1019.
[31] R.C. Rowe, Pharm. Sci. Technol. Today 3 (2000) 187–188.
[32] T.K. Bock, U. Kraas, Eur. J. Pharm. Biopharm. 52 (2001) 297–303.
[33] D. Ameye, E. Keleb, C. Vervaet, J.P. Remon, E. Adams, D.L. Massart, Eur. J. Pharm. Sci. 17 (2002) 247–251.
[34] E. Räsänen, O. Antikainen, J. Yliruusi, AAPS PharmSciTech. 4 (4) (2003) (article 53).
[35] J. Bajdik, G. Baki, A. Kelemen, K. Pintye-Hódi, Chem Eng. Res. Des. 86 (2008) 1–7.
[36] R.C. Rowe, P.J. Sheskey, P.I. Weller, Handbook of Pharmaceutical Excipients, 4th ed., Pharmaceutical Press, London, 2003.
[37] Á. Gombás, P. Szabó-Révész, M. Kata, G. Regdon jr., I. Erős, J. Therm. Anal. Calorim. 68 (2002) 503–510.
[38] K. Mosén, K. Bäckström, K. Thalberg, T. Schaefer, A. Axelsson, H.G. Kristensen, Eur. J. Pharm. Biopharm. 64 (2006) 206–211.
[39] D.J. Burnett, F. Thielmann, J. Booth, Int. J. Pharm. 287 (2004) 123–133.
[40] J. Berggren, G. Frenning, G. Alderborn, Eur. J. Pharm. Sci. 22 (2004) 191–200.
[41] K.H. Bauer, K. Lehmann, H.P. Osterwald, G. Rothang, Coated Pharmaceutical Dosage Forms, Medpharm GmbH Scientific Publishers, Stuttgart, 1988.
[42] J. Berggren, G. Alderborn, Eur. J. Pharm. Sci. 21 (2004) 209–215.