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Evaluation of phenomena occurring during the preparation of matrix granules by the hot melt technique

János Bajdik · Anita Korbely · Klára Pintye-Hódi

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Abstract The aim of this study was to evaluate the applicability of hot melt granulation for the formulation of a pH-sensitive intelligent tablet containing heat- and moisture-sensitive components. An appropriate combination of magnesium trisilicate, aluminium hydroxide, sodium bicarbonate, and basic butylated methacrylate copolymer (Eudragit E PO) exhibited a good disintegration profile, but poor processibility. Hot melt granulation was applied with the aid of polyethylene glycol 2000 to increase the tablettability. The effects of the composition and the process on the properties of the granules and tablets formed were assessed with thermoanalytical and conventional testing methods. The heating of mixtures containing basic butylated methacrylate copolymer (Eudragit E PO) below its glass transition caused a relevant change in the wettability of the granules. This was induced by an alteration in the microstructure of the agglomerates. Tablets prepared from the granules containing an appropriate ratio of polymers exhibited an appropriate mechanical and disintegration profile. The thermal behaviour of the mixture of polymers cannot be predicted from the properties of the starting materials. Their interaction, demonstrated by DSC, can cause significant structure-forming problems in the matrices. The parameters of the granules and tablets varied with the quantity of the polymer applied. With an appropriate combination of polymers, hot melt granulation can be a suitable method for the preparation of intermediates for the formulation of controlled-release antacid tablets. Thermal analysis can promote an understanding of the process and determination of its operational parameters.

J. Bajdik · A. Korbely · K. Pintye-Hódi (✉)
Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6, Szeged H-6720, Hungary
e-mail: klara.hodi@pharm.u-szeged.hu

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Introduction

The acidity of the gastric juice becomes excessive in various gastrointestinal diseases. In these cases, administered gastric antacids act locally to reduce the acidity of the stomach contents. Their components (mainly magnesium and aluminium salts) can bind different components, e.g. phosphates or active agents such as tetracyclines, digoxin and sulphonamides. If the antacid is used in excess, its potential side-effects may be severe, e.g. milk-alkali syndrome, renal calculi, bone problems, intestinal effects, neurotoxicity [1–5].

Elevation of the pH from 1.0 to 3.5 eliminates 99% of the hydrogen ions in the stomach, and very little proteolytic activity will persist after this level is achieved. It is known that higher values can be reached with antacids [6]. At pH >4.5, the pepsin activity is markedly decreased, and it is completely inactivated at pH >6 [7]. Since the low pH of the stomach normally kills ingested microorganisms, antacids increase the vulnerability to infection [8]. In view of this situation, the application of antacid components with controlled release is a reasonable demand.

The aim of our current project was the formulation of matrix systems with a local antacid effect. These monolytic systems must be intact if the contents of the stomach are less acidic, but rapid disintegration must occur if necessary. The excess of the active agent is eliminated without release from the matrix of the dosage form. Accordingly, the potential unwanted effects of the unliberated components need not be taken into account. It is known that there is periodic

interdigestive activity in the gastrointestinal tract, which is important for the regular mechanical and enzymatic cleansing of the gastrointestinal lumen and may serve to remove indigestible and/or foreign material, and to prevent bacterial overgrowth or the pathological activation of enzymes [9]. The interdigestive migrating motor complex is a cyclical contraction sequence with an average duration of approximately 7 min that sweeps through the stomach and small intestine about every 90 min during fasting in healthy people [10]. If the tablets remain intact until this time, the possibility of unwanted effects can be decreased.

The optimum composition of the main active components (aluminium hydroxide and magnesium trisilicate), the acrylic matrix former basic butylated methacrylate copolymer (Eudragit E PO) and effervescent sodium bicarbonate was determined earlier. The best tablets exhibited disintegration time >4 h in the stomach at pH 3, but of <15 min at pH 1.2 [11]. Preparation of this intelligent tablet by means of direct compression was difficult, since the processibility (flowability and compressibility) of the powder was insufficient. In this case, therefore, intermediates must be prepared [12]. This was also a very difficult step, since the applied components are not appropriate for wet granulation. Sodium bicarbonate is sensitive to water [13], whilst the other components are only insoluble in water and the water uptake of the micronized matrix former is very poor. It is not possible to achieve even wettability of the powder mixture without decomposition of the ingredients. An alternative granulation method is the hot melt technique [14, 15]. In this case, heat-sensitive materials cannot be used, a problem that can arise for sodium bicarbonate, but only at higher temperature [13]. Accordingly, the use of a binder with a low melting point, and hence a low temperature of granulation, can solve this problem. The glass transition temperature of the matrix former is known to be nearly 55 °C [16]. Polyethylene glycol 2000 exhibits a similar melting point [13], and can therefore be a potential binder. Its effects on the properties of the granules and tablets formed were evaluated with conventional testing methods used in pharmaceutical technology (flowability, compressibility, wettability, particle size analysis, friability and disintegration of tablets) and differential scanning calorimetry (DSC). The aims of these tests were to promote an understanding of the granulation process and to assess its applicability for these components.

Materials and methods

Materials

The antacid components (Ph. Eur.) were aluminium hydroxide (AH), magnesium trisilicate (MT) and sodium bicarbonate (SB), all obtained from Hungaropharma Plc. (Budapest, Hungary). The matrix-forming agent [basic butylated methacrylate copolymer, Eudragit® E PO (EE)] was a gift from Degussa Pharma Polymers (Darmstadt, Germany). Polyethylene glycol 2000 (PEG 2000) (Fluka Chemie GmbH, Buchs, Switzerland) was applied as a binder during the melt granulation.

Hot melt granulation

To obtain a homogeneous mixture, the powder was blended at 50 rpm for 10 min with a Turbula mixer (W.A. Bachofen, Basel, Switzerland). Granules were prepared from these blends in a high-shear granulator (ProCepT 4M8 granulator, ProCepT nv, Zelzate, Belgium). The temperature applied during the process was determined by the results of the thermoanalytical measurements. A jacketed glass vessel was used and a thermostat (Julabo F12, Julabo Labortechnik GmbH, Seelbach) was applied to ensure the permanent temperature. A pre-warming was applied to attain the equilibrium temperature of the powder. This was 5–7 °C lower than the set value. The operational parameters were as follows:

Impeller speed: 1000 rpm
Chopper speed: 4000 rpm
Process time at the equilibrium temperature: 10 min
Mass of powder mixture: 150 g
Applied temperature: 70 °C
Granules were dried on trays under ambient conditions (25 ± 2 °C) for 24 h.

Preparation of tablets

The compositions of the granules are detailed in Table 1. Granules were compressed into tablets with a Korsch EK0 eccentric tablet machine (Emil Korsch Maschinenfabrik, Berlin, Germany). The punches were convex and measured 13 mm in diameter. The compression force applied was 15 ± 2 kN. The number of tablets manufactured was 500 ± 20 pieces.

Evaluation of powder mixtures

A Powder Testing System PTG-1 (Pharma Test Apparatebau GmbH, Hainburg, Germany) was applied to determine the flow time of 100 mL of sample. A Teflon tunnel was used with an orifice 10 mm in diameter. A stirrer was operated at 25 rpm, if necessary. Three parallel experiments were performed.

A STAV 2003 Stampfvolumeter (Engelsmann A.G., Ludwigshafen, Germany) was utilized for the determination of densities [tapped (ρ_∞) and loose (ρ_0)] and consequently the compressibility. Carr's index was calculated from these results [17]. Three parallel tests were carried out.

Table 1 Compositions of samples

	S0[a]/mg	S1/mg	S2/mg	S3/mg	S4/mg	S5/mg
AH	135	135	135	135	135	135
MT	135	135	135	135	135	135
SB	50	50	50	50	50	50
EE	100	100	100	100	100	–
PEG 2000	–	–	50	100	150	100
Total	420	420	470	520	570	420

[a] Prepared by direct compression

$$\text{Carr's index} = \frac{\rho_\infty - \rho_0}{\rho_\infty} \times 100.$$

The sizes of the granules were assessed after drying. An analytical sieve (Retsch GmbH, Haan, Germany) was used for these experiments. The D50 values of the samples were determined with sieving system software (Retsch EasySieve 2.0).

An Enslin apparatus with a glass filter 5 cm in diameter and a pipette with 0.01 mL accuracy were used in the evaluation of the water uptake of the mixtures. 0.25 g of each powder was tested; three parallel experiments were performed. Heat treatment of the starting component was also performed in a moisture analyser (HR73 Halogen Moisture Analyser, Mettler-Toledo GmbH, Greifensee, Switzerland). The temperature and time applied were the same as during granulation (70 °C for 10 min). The water uptake of these powders was also determined.

Evaluation of tablets

The times required for tablet disintegration were measured with an Erweka ZT 71 (Erweka GmbH) apparatus; 12 tablets were evaluated at each pH. The active agent can alter the pH of the medium. The pH of the test liquid was checked with a pH-tester (WinLab pH-Meter, Windaus-Labortechnik GmbH & Co. KG, Clausthal-Zellerfeld, Germany). The test liquids (700 mL) were changed every 20 min to ensure constant pH (the deviation of the pH was <0.3). The test was carried out in four solutions with different pH. The pH was adjusted with phosphate buffer according to Ph. Eur.

The directly compressed tablets disintegrated in the liquid pH 3.0 in more than 4 h. Accordingly, the study stopped at this pH.

The compositions of the disintegration media are the following:

Solution of pH 1.2

hydrochloric acid
sodium hydroxide
water

Phosphate buffer solution of pH 2.0

disodium hydrogen phosphate
potassium dihydrogen phosphate
water
phosphoric acid

Buffer solution of pH 2.5 R1

dilute phosphoric acid
dilute sodium hydroxide solution
water

Phosphate buffer solution of pH 3.0 R1

potassium dihydrogen phosphate
phosphoric acid
water.

The friability tests were performed in an Erweka friabilator (Erweka GmbH) according to Ph. Eur. The breaking strength has been determined in the Heberlein (Flisa, Le Locle) apparatus.

DSC studies

The thermoanalytical examinations were carried out with a Mettler-Toledo DSC 821e (Mettler-Toledo GmbH, Switzerland) instrument. Dynamic methods were used, with a heating rate of 10 °C min^{-1}. The interval was 25–200 °C for the testing of the interactions of the polymers, and 0–200 °C for the study of the behaviour of sodium bicarbonate. Argon was used as a purge gas. Ten milligram samples were added to the aluminium pans (40 μL). The curves were evaluated with STAR[e] Software. The investigated samples were the following:

- Polymer mixtures in different ratios:
  - basic butylated methacrylate copolymer (Eudragit E PO): PEG 2000 = 2:1
  - basic butylated methacrylate copolymer (Eudragit E PO): PEG 2000 = 2:2
  - basic butylated methacrylate copolymer (Eudragit E PO): PEG 2000 = 2:3
- PEG 2000.

Results and discussion

DSC studies

In the first step before the granulation, the maximum temperature that can be used during the process was determined. DSC revealed that the heat-induced decomposition of SB started above 80 °C (Fig. 1) [18]. The

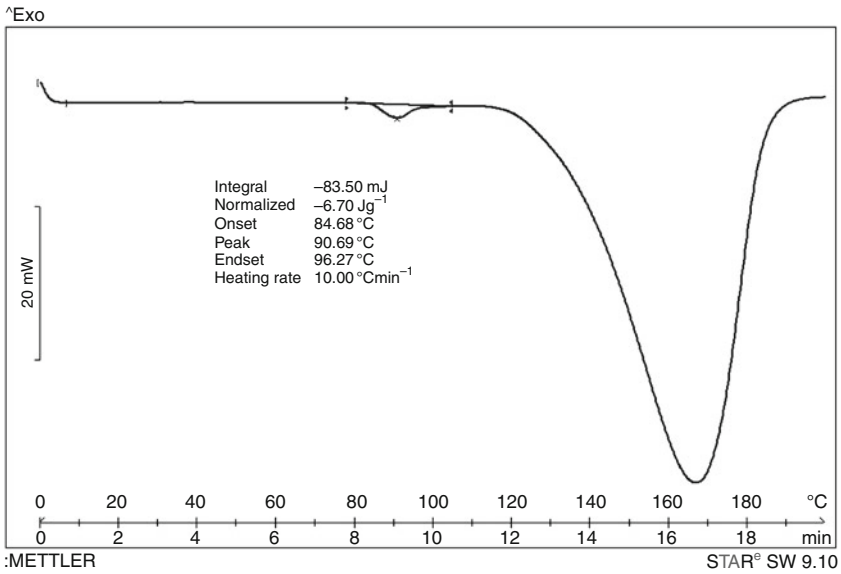

Fig. 1 DSC curve of SB

Table 2 Parameters of granules

Samples	Flowing time/s	Bulk density/g cm^{-3}	Carr's index/%	Enslin number/mL g^{-1}	D50/mm
S0	157.8 ± 8.9[a]	0.313 ± 0.005	30.4 ± 0.8	0.41 ± 0.04	–
S1	153.6 ± 15.4[a]	0.387 ± 0.007	26.4 ± 0.8	1.62 ± 0.05	0.154
S2	80.3 ± 6.4[a]	0.448 ± 0.008	26.7 ± 1.7	1.19 ± 0.03	0.215
S3	8.5 ± 2.3	0.742 ± 0.001	9.3 ± 0.6	0.74 ± 0.02	0.242
S4	4.1 ± 0.2	0.719 ± 0.001	3.5 ± 0.3	0.66 ± 0.03	0.376
S5	60.4 ± 3.6[a]	0.537 ± 0.007	19.2 ± 0.8	1.03 ± 0.02	0.169

[a] With stirring at 25 rpm

temperature for the granulation must therefore be below this temperature. The temperature of the powder mixture exhibited a lower value than that of the wall of the heated container of the granulator, and the melting points and glass transitions of the macromolecular components must also be considered. The temperature applied must therefore be in the interval 65–80 °C. The temperature chosen for the granulation was 70 °C.

Flowing and wetting properties of the granules

The parameters of the granules were compared with the properties of the powder mixture (Table 2). Free flowing of the powder without stirring was detected only for S3 and S4. Increase of the ratio of PEG 2000 and EE decreased not only this parameter, but also the Carr's index, and increased the particle size and the bulk density, and hence the performance of the granulation. The particle size was not determined for S0, since in this case only the separation of the starting components can be attained. The heating of the powder mixture without PEG 2000 caused less relevant alterations in the flowability and compressibility of the starting composition, but the wettability was changed significantly ($p < 0.05$). This parameter was 4 times higher for the heat-treated sample. A modification was revealed without the same change in compressibility. Independent heat treatment of the individual components was therefore performed under the conditions of the granulation. The alterations induced in the wettability were compared (Table 3). The weight loss induced by this treatment was highest for AH. During the water uptake test, this amount of water must be considered, but the relative change was also calculated. There was no obvious relationship between

Table 3 Wettability of the components

Components	Enslin number/ mL g^{-1}	Weight loss induced by heating/%	Enslin number after heating/ mL g^{-1}	Relative change of Enslin number/%
AH	4.73 ± 0.16	8.10	5.27 ± 0.02	11.1
MT	1.37 ± 0.02	6.49	1.59 ± 0.02	16.1
SB	0.45 ± 0.03	0.23	0.49 ± 0.05	8.9
EE	0.03 ± 0.01	0.63	0.16 ± 0.04	533.3

the loss on drying and the relative change in water uptake. The highest change in water uptake was detected for the poorly wetting EE. This component lost its microparticulate individuality, and formed a hard layer. This was powderized before this test. Such a phenomenon can cause slight sticking of the particles, but its relevance was low, and it caused only a slight modification in the compressibility. Alterations in wettability cannot be explained merely by the changes in wettability of the separate components. In the powder mixture, the wettability of the materials with poor water uptake properties predominated. The enrichment of certain components on the surface of other components is well known [19], and their properties therefore become more important. During the heating of this blend, the microstructure of the powder mixture and its agglomerate also changed. The softening of this polymer caused a rearrangement of this component in the powder mixture and accordingly the properties of the active agents became dominant.

The use of PEG 2000 alone without EE led to poorer flowability and compressibility than for S4, but to better properties than for the sample prepared without PEG 2000. The difference in the wetting was interesting, since for S3 and S4 this parameter was lower than for the two endpoint compositions (S1 and S5). This can be explained by interactions (between the active agent and polymers and/or between the polymers) occurring during the formulation.

Properties of tablets

Tablets were prepared from the granules and their properties were compared with those of the comprimates obtained by direct compression [11] (Tables 4 and 5). The composition without PEG 2000 exhibited poorer friability and retardation (extended release of the active ingredients) than those of the starting composition. The pH-sensitive disintegration profile was decreased. The tablets prepared from granules produced without the matrix former displayed weak mechanical properties, and broke during the test. The quickest disintegration was observed for S2, where the pH-sensitive effect was negligible. The best disintegration profile was that of S4. The properties of the granules were also best for this composition. It can be concluded that there was no obvious connection between the wettability of the sample and the disintegration. The slowest disintegration was detected for the sample that exhibited the poorest wettability, but this tendency was not valid for all the cases. The changes in the inner structure of the matrix were such that their prediction was impossible from the parameters of the starting components. This may involve interactions between the components induced by the heating.

Table 5 Dimensions of tablets

Samples	Thickness/mm	Diameter/mm
S0	3.36 ± 0.02	13.06 ± 0.01
S1	3.46 ± 0.05	13.10 ± 0.01
S2	3.61 ± 0.02	13.11 ± 0.02
S3	3.64 ± 0.02	13.13 ± 0.02
S4	3.77 ± 0.02	13.06 ± 0.02
S5	2.97 ± 0.02	13.14 ± 0.01

Investigation of the possible interactions between the polymers

The DSC curve of EE demonstrated a shift of the baseline at nearly 55 °C, but no other event after this (Fig. 2). This phenomenon may be responsible for the changes in the parameters of the S1 granules and consequently of these tablets. The previous wettability test indicated a significant alteration in the distribution of soft EE in the agglomerate. PEG 2000 exhibited a melting peak at a similar temperature. The possibility of the interaction of the polymers during the granulation was evaluated by the thermal analysis of powder blends containing these components in the appropriate ratios. The mixture of the polymers exhibited not only shifts in the peaks to higher temperatures, but changes in their shape. An important alteration was found at the 2:1 ratio of EE and PEG 2000, the polymer ratio of the S2 composition, which exhibited the poorest disintegration profile. The process induced by the interaction

Table 4 Parameters of tablets

Samples	Friability/%	Breaking strength/*N*	Disintegration at pH			
			1.2/min	2.0/min	2.5/min	3.0/min
S0	0.21	174.3 ± 9.6	12.56 ± 0.66	16.88 ± 1.76	145.52 ± 8.64	183.43 ± 4.51
S1	2.55	59.1 ± 14.6	7.48 ± 0.58	9.84 ± 0.82	27.83 ± 6.75	38.87 ± 4.58
S2	1.81	36 ± 6.5	4.82 ± 0.55	4.56 ± 0.47	6.37 ± 1.83	10.89 ± 2.18
S3	0.29	54.6 ± 3.3	13.74 ± 0.62	15.00 ± 0.34	50.58 ± 4.51	80.82 ± 7.96
S4	0.21	101.5 ± 14.2	16.96 ± 0.67	17.40 ± 0.96	64.14 ± 3.59	107.42 ± 6.58
S5	Broken	32.1 ± 4.3	4.18 ± 0.28	4.81 ± 0.17	11.86 ± 3.15	37.38 ± 1.34

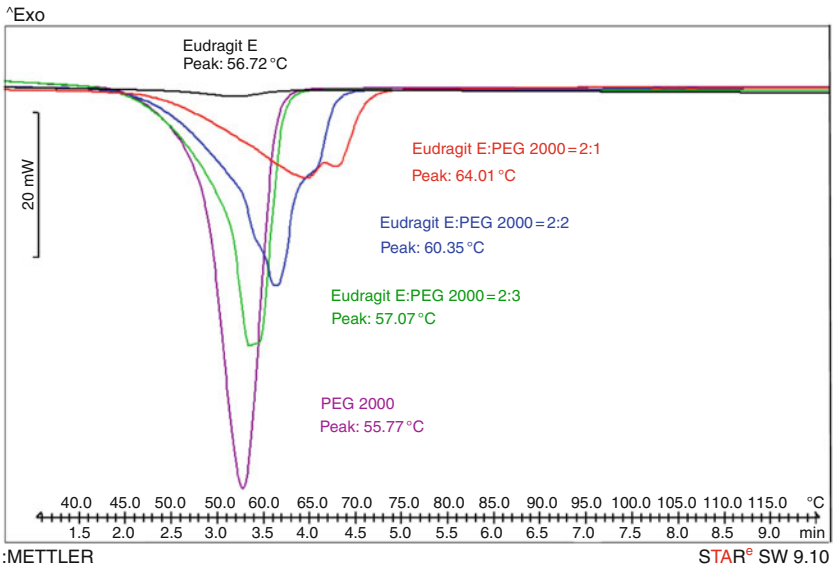

Fig. 2 DSC curves of polymers and their mixtures

cannot be completed at the temperature of granulation. For the definite occurrence of this phenomenon, a temperature of >80 °C should be applied during the formulation, where the risk of decomposition of the active agent is relevant. The cause of the poor properties of the tablets can therefore be explained by the incomplete formation of the structure-building component. The decision to ignore this composition in our matrix system was supported by the DSC experiments. The S4 polymer ratio exhibited a uniform peak which was quantitatively formed at the temperature of granulation. This ratio ensured the properties of the tablets and granules. In this case, not only the favourable effect of the binder, but also the synergistic effect of the rate-limiting polymer was detected.

Conclusions

It can be concluded that hot melt granulation can be applied for the preparation of matrix granules to enhance the production of controlled-release antacid tablets. The temperature of the hot melt granulation and the problems that arise during this process can be evaluated by means of thermal analysis. The heating of mixtures containing EE below its glass transition caused a relevant change in the wettability of the mixtures. This is induced by an alteration in the microstructure of the agglomerates. Tablets prepared from the granules containing EE and PEG 2000 in a ratio of 2:3 exhibited an appropriate mechanical and disintegration profile. The relationship of the two polymers can be tested via DSC. The behaviour of the mixture of polymers cannot be predicted from the properties of the pure starting materials; this method confirmed their interaction, which can cause important structure-forming problems in the matrices. There were good correlations between the parameters of the granules/tablets and the determined interactions. If this thermally induced alteration in the polymer blend is not completely finished at the temperature of the granulation, the properties of the matrices are insufficient.

This information can increase our understanding of the phenomena that occur during hot melt granulation. A well-designed process allows application of this technique for the formulation of a pH-sensitive intelligent solid dosage form containing heat- and moisture-sensitive components.

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