AAPS PharmSciTech, Vol. 12, No. 4, December 2011 (© 2011)
DOI: 10.1208/s12249-011-9698-7

Research Article

Theme: Advanced Technologies for Oral Controlled Release
Guest Editors: Michael Repka, Joseph Reo, Linda Felton, and Stephen Howard

Effect of Different Excipients on the Physical Characteristics of Granules and Tablets with Carbamazepine Prepared with Polyethylene Glycol 6000 by Fluidized Hot-Melt Granulation (FHMG)

Radosław Kraciuk[1] and Malgorzata Sznitowska[2,3]

Received 23 February 2011; accepted 13 September 2011; published online 23 September 2011

Abstract. The objective of this study was to investigate the properties of granules and tablets with carbamazepine which were prepared employing a fluidized hot-melt granulation (FHMG) technique. The FHMG process was carried out at 65°C. Macrogol 6000 (PEG 6000) was used as a binder at the content 10% (*w*/*w*) of the granulated mass. Granules containing up to 70% (*w*/*w*) of the drug and 20–90% (*w*/*w*) of a filler (lactose, mannitol, calcium hydrogen phosphate (Di-Cafos), pregelatinized starch, and microcrystalline cellulose (MCC)) were produced. When the drug content was 30% (*w*/*w*), the yield of the process was satisfying (>95%) and flowability of the granules was better than placebo granules or drug-loaded granules prepared by wet granulation. Type of a filler had strong impact on physical properties of granules, and size distribution of the particles was the most homogenous when lactose or Di-Cafos were used. The FHMG technique enabled preparation of granules with better compressability compared with the wet-granulated product or with non-granulated powders. Tablets with shorter disintegration time than 10 min were obtained with 2.0% crospovidone added as a disintegrant. In comparison to tablets prepared from the wet-granulated mass, employment of the FHMG method resulted in tablets with faster dissolution of carbamazepine (more than 80% of the drug released within 15 min). This was achieved with mannitol or lactose/MCC, as fillers.

KEY WORDS: carbamazepine; dissolution; fluidized hot-melt granulation; macrogol; tablets.

INTRODUCTION

Granulation is an important process in the production of solid dosage forms: tablets and capsules. Granules for tabletting are either prepared by wet methods, which utilize liquid in the process, or by dry methods, where no liquid is utilized.

High shear mixer granulation and fluidized-bed granulation are the most common wet methods. In high shear granulation, blending and wetting is accomplished by spraying the binder solution (in water or organic solvent) into powders subjected to a high mechanical agitation with an impeller and chopper. Mixing, densification, and agglomeration of the wetted materials are achieved through shearing and compaction forces exerted by the impeller. Fluidized-bed granulation is a process by which granules are produced by spraying a binder solution onto a fluidized powder bed. Generally, granulation requires drying and screening, which are costly in terms of time, space, and equipment and adds complexity (1).

An alternative to wet granulation is dry granulation. The dry granulation process is used to form granules without using a liquid (solution); this is especially applicable if the product to be granulated is sensitive to moisture and heat. Forming granules without moisture requires powder compaction and densification. Dry granulation can be conducted on a tablet press using slugging tooling or, more often, on a roller compactor. The powders are compacted into a ribbon or small pellets between rollers and milled with a low-shear mill (2)

Melt granulation, or thermoplastic granulation, is based on agglomeration carried out by means of a binder material, which is solid at room temperature and softens and melts at higher temperature (i.e., 50–90°C). When melted, the action of the binder liquid is similar to that in a wet-granulation process. Water-soluble binders used for melt granulation are macrogols (polyethylene glycols (PEG)). The binder is added either in a powder form to the starting material at ambient temperature, followed by heating the binder above its melting

[1] Pharmaceutical Works Polpharma SA, 19 Pelplińska, 83-200 Starogard Gdański, Poland.
[2] Department of Pharmaceutical Technology, Medical University of Gdańsk, 107 Hallera, 80-416 Gdańsk, Poland.
[3] To whom correspondence should be addressed. (e-mail: msznito@gumed.edu.pl)

point, or in a molten form to heated materials (3). Using PEG, solid dispersions can be prepared by dissolving a drug in the molten PEG binder.

Fluidized hot-melt granulation (FHMG) is an alternative to the hot-melt granulation; however, it is still an underdeveloped process in the pharmaceutical industry. Granules prepared by FHMG technique use a fluidized-bed system only. The melting material and other powders are added to the fluidized bed and then the inlet temperature is set to an appropriate value to start granulation by melting. In melt granulation, mixing with the drug may be performed by spraying the molten excipient to the drug powder or by heating both components together; in either case, the system is cooled to a solid state with the molten excipient acting as a binder (4,5).

This technique is very simple and easily controlled. In general, FHMG is a suitable method for the preparation of granules for tabletting because the lack of shear force during granulation results in porous granules with a low strength (6). This process may allow the generation of granules of a suitable size and the generation of a compression profile for subsequent processing into solid forms (5). It was reported that in contrast to the product obtained from FHMG process, the granules prepared by hot-melt granulation are dense and very hard, so their tabletting properties are extremely poor (6).

A significant advantage of both melt granulation methods is that a judicious choice of the granulation excipient may enable the formulator to manipulate the drug dissolution rate from the corresponding dosage form. This may be performed in terms of producing slow-release formulations. In this case, hydrophobic excipients, such as the stearic acid or triglycerides, may be utilized. Alternatively, hydrophilic materials, such as the polyethylene glycol or poloxamer 188, may be used. These polymers may enhance the dissolution rate of poorly soluble drugs (especially if solid dispersion is formed) yielding, thereby, the possibility of enhanced bioavailability. However, these benefits must be balanced against the possibility of thermolabile drug degradation and the absence of a core knowledge base within the pharmaceutical industry with regard to the optimization of the melt granulation process (7). Considering that the scaling-up problem seems to be limited, it is surprising that the hot-melt granulation technique is not more widespread in production. However, the FHMG technique is still at a very low level of development.

In our study, we have been testing the application of FHMG methodology for processing granules and tablets with carbamazepine by means of different excipients: lactose, mannitol, calcium hydrogen phosphate, pregelatinized starch, and microcrystalline cellulose. As a binder, macrogol 6000 (PEG 6000) was used in the amount of 10% (*w*/*w*) of the total powder mass. In this study, the binder is not sprayed but it is initially present in the form of discrete particles within the fluidized bed that are melted while the fluidization temperature is simultaneously increased. The goal of this study was to assess the usefulness of different fillers. The size of granules, flowability, and compressibility were determined in relation to the carbamazepine content. Besides, the quality of granules was compared with those prepared by means of wet granulation and the tablets made of two types of granules, as well as by the direct compression, were also considered in comparative studies.

MATERIALS AND METHODS

Materials

The following substances were used for the preparation of granules: carbamazepine (100% particles below 20 μm and not less than 90% below 10 μm—Polpharma, Starogard Gdanski, Poland), macrogol 6000 (polyethylene glycol, PEG 6000; melting point at 61.6°C, 95% particles between 32 and 500 μm Clariant, Burgkirchen, Germany), lactose (50–300 μm; Granulac 200, Meggle, Wasserburg, Germany), mannitol (95% particles between 50 and 500 μm; Pearlitol 200 SD, Roquette, Lestrem, France), calcium hydrogen phosphate (Di-Cafos; 95% particles below 50 μm; Chemisha Fabric, Budenhein, Germany), pregelatinized starch (Starch 1500, Colorcon, Indianapolis, USA), microcrystalline cellulose (MCC; 95% particles below 200 μm; Vivapur Type 101, JRS Pharma, Weissenborn, Germany).

The following excipients were used to improve the tabletting compression: magnesium stearate (Peter Greven Nederland, Venlo, the Netherlands), crospovidone (Polyplasdone XL-10, ISP Global Technologies, Calvert City, USA), and colloidal anhydrous silica (Aerosil 200, Evonik Degussa Group, Frankfurt, Germany).

Granulation

Granulation experiments were performed in a fluidized-bed granulator (GPCG-3.1, Glatt, Dresden, Germany). The unit consisted of a container suitable for a batch size of 1,000 g (the vessel volume was 5 L). Two batches of each formulation were prepared.

The PEG 6000 (binder) content in all formulations was 10% (*w*/*w*). In placebo granules, 90% (*w*/*w*) of the mass consisted of a filler. The following excipients were tested as fillers: lactose, 50:50 mixture of microcrystalline cellulose and lactose (MCC/lactose), Di-Cafos, mannitol, pregelatinized starch, or microcrystalline cellulose (the latter two were used only in the preliminary studies). Granules with carbamazepine contained 30%, 45%, or 70% (*w*/*w*) of the drug and 60%, 45%, or 20% (*w*/*w*) of a filler, respectively.

The PEG 6000 was blended with other powders, and the mixture was introduced to the fluidized bed. The air flow was adjusted to ensure a good flow of powders and then the inlet temperature was set at the maximum temperature of 90°C. The powders were heated to 65°C, and this temperature was maintained for 10 min (6). Afterwards, the material contained in the fluidized bed was cooled to 45°C by decreasing inlet temperature to 20°C. The resulting granules were manually sieved through 1.5 mm sieve.

For comparison purposes, the granules (batches of 1 kg) of the same composition, containing 30% (*w*/*w*) of carbamazepine, 10% (*w*/*w*) of PEG as a binder and 60% (*w*/*w*) of mannitol, or MCC/lactose as fillers were also produced by means of wet granulation. In this process, performed in a granulator (FGS granulator, Erweka, Heusenstamm, Germany), PEG 6000 was used as a 33% (*w*/*w*) aqueous solution. The liquid was added to the stirred powders within 5 min, and

the wetted and granulated mass was passed through a 3.15-mm screen mesh. The granules were dried on a tray at 40°C until a 2% moisture level was achieved. After drying, the granules were manually sieved through 1.5 mm sieve.

Tabletting

Before tabletting, magnesium stearate (0.5%, *w*/*w*), colloidal anhydrous silica (1.0%, *w*/*w*), and crospovidone (2.0%, *w*/*w*) were added to granules and the material was carefully mixed. The tablets were formed in a rotary tablet press machine (C-50, Kilian, Köln, Germany) equipped with 12-mm spherical punches, with a working speed approximately 4,500 tablets/h. The main pressure on the tablet machine was adjusted to produce tablets with a hardness of approximately 70 N and a thickness of approximately 5.9 mm.

For comparison purposes, carbamazepine (30%, *w*/*w*) tablets were also produced from granules prepared by wet granulation as well as by the direct compression of powders. Final composition of the tablets was the same as for the tablets produced from granules prepared by FHMG.

Analysis

Particle size distribution in granules after drying and milling was determined by a sieve shaker (AS 200, Retsch, Haan, Germany) with mounted sieves of 1,000, 500, 300, 100, and 50 μm.

Tap density (weight of sample/final volume), initial density (weight of sample/initial volume), and compressibility index commonly known as Carr's index ($[(\text{initial volume} - -\text{final volume})/\text{initial volume} \times 100]$) were determined for granules using TT2 tester (Sotax, Basel, Switzerland) according to USP I method.

The flowability of granules was determined by means of FT 300 flow tester (Sotax, Basel, Switzerland) with six combinations of vibration and pre-vibration settings. Mean values were calculated automatically by a tester.

The results of these tests were presented as a mean value for two batches, and the difference between batches was expressed as a relative deviation.

The hardness and thickness of tablets was determined using tablet hardness testers (TBH 300 MP and TBH 30 MP, Erweka, Heusenstamm, Germany). The friability of tablets was determined in F1 tester (Sotax, Allschwil/Basel, Switzerland), on 20 tablets, in the apparatus running for 4 min at a speed of 25 rpm. Disintegration time was determined in water at 37°C by means of a disintegration tester with disks (ZT 74, Erweka, Heusenstamm, Germany). The time recorded was the time required for the last out of six tablets to disintegrate.

Dissolution profiles were determined in a pharmacopoeial paddle apparatus (Erweka, Heusenstamm, Germany), with a rotating speed of 75 min^{-1}. Sodium lauryl sulfate 1.0% (*w*/*w*) solution was used as a dissolution medium at 37±0.5°C. An analysis of carbamazepine in a dissolution medium was performed spectrophotometrically (UV/Vis spectrophotometer V-530, Jasco, Tokyo, Japan) at the wavelength of 280 nm.

The results were presented as means of the values measured for six tablets, and the variablility was expressed as relative standard deviation (RSD%).

RESULTS

Process Remarks

During FMHG processing of placebo granules (PEG 6000 10% (*w*/*w*) and a filler), it was observed that the internal wall of fluid bed dryer was clean when microcrystalline cellulose, lactose or pregelatinized starch were used as fillers. When calcium hydrogen phosphate, mannitol, and MCC/lactose were used, a small amount of dust was observed at the top of the fluid bed dryer.

When granules containing 30% (*w*/*w*) of carbamazepine were processed, the fluid bed dryer was clean and the yield of the process was practically at 100%. However, when the drug content was 45% and 70% (*w*/*w*), the granules adhered to the dryer's wall.

Particle Size Distribution in Granules

The size of placebo granules prepared with different fillers is presented in Fig. 1a. The granules with Di-Cafos are the most homogeneous since 90% of particles were in the range between 100 and 300 μm. With other fillers, the sizes of granules were distributed within the entire range; for example, the content of particles above 1,000 μm was 5.0–6.4% and between 100 and 300 μm was—13.1–43.95%. In mannitol granules, practically no particles with size lower than 50 μm were observed while in other granules this fraction was at 7.8–8.6%.

Figure 1b shows the particle size in carbamazepine 30% (*w*/*w*) granules. For granules prepared with MCC/lactose, the least homogenous was the size, with 15% of particles bigger than 1,000 μm and almost 10% of particles smaller than 50 μm. For all fillers, a large portion of carbamazepine granules (29.7–47.6%) was in the range of 500–1,000 μm.

The results for two batches of each formulation were similar: less than 10% deviation between particular mass fractions representing at least 10% of the total mass was noted.

Granules Density, Compressibility, and Flowability

The physical properties of placebo and carbamazepine granules produced in FHMG process are presented in Table I.

Among all the placebo granules, those prepared with Di-Cafos have the best flowability, measuring 19.5 g/s. Corresponding values for lactose granules are almost twice as low. For granules with Di-Cafos, and particularly with lactose, the lowest values of Carr's index can also be observed. On the other hand, granules with mannitol and MCC/lactose have very low flowability while Carr's index were smaller than for the other two placebo formulations.

Better flowability can be observed for granules with 30% (*w*/*w*) of carbamazepine than for placebo granules with the same filler. Anyhow, as in the placebo formulation, also the drug-containing granules with lactose and Di-Cafos have better flowability than the other two types of granules (Table I). On the other hand, no significant difference was noted in Carr's index determined for placebo granules and the granules with 30% of carbamazepine.

All granules with 45% and 70% of carbamazepine have significantly lower flowability than the corresponding formulations with 30% of carbamazepine. Only for composition

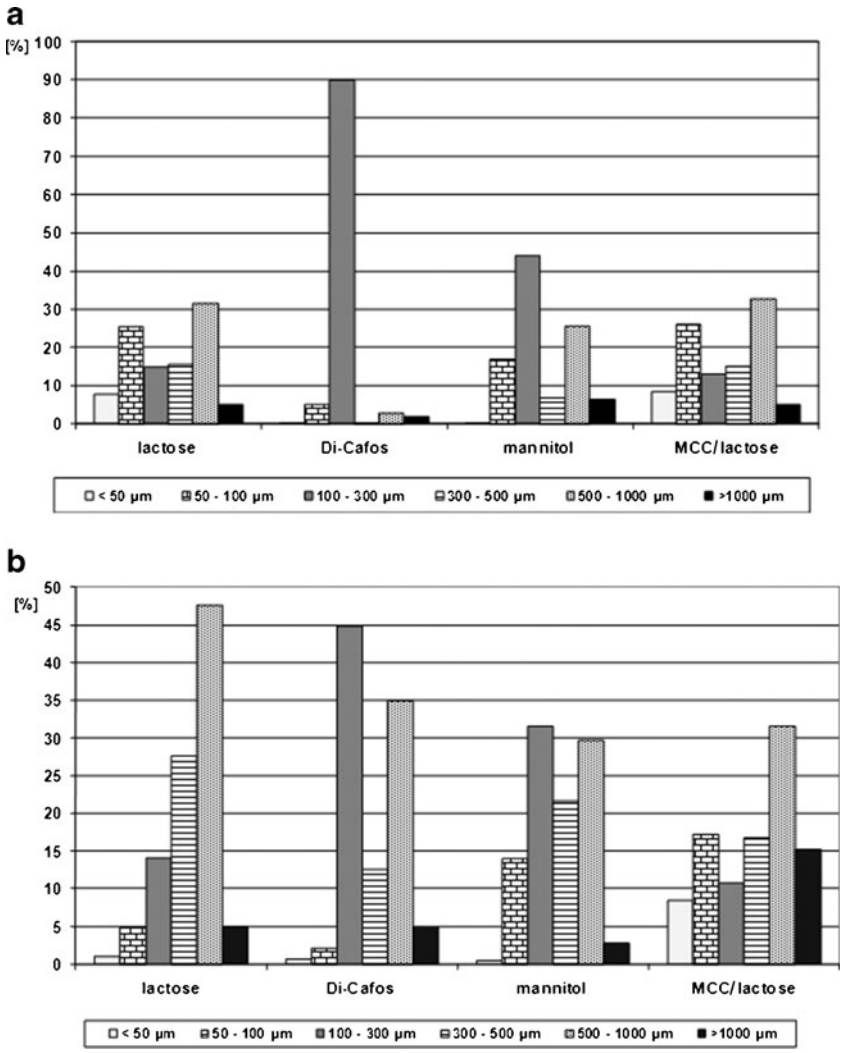

Fig. 1. Particle size distribution in the granules prepared by FMHG with 10% (*w*/*w*) of PEG 6000 and different fillers: **a** placebo granules; **b** with carbamazepine 30% (*w*/*w*)

Table I. Physical Parameters (Mean Values for Two Batches) of Granules Prepared with 10% (*w*/*w*) of PEG 6000 and Different Fillers

Granules filler	Carbamazepine (%)	Flowability[a] (g/s)	Initial density[b] (g/ml)	Tap density[b] (g/ml)	Carr's index[b] (%)
Lactose	0	9.18	0.656	0.732	10.44
	30	22.8	0.602	0.666	9.64
	45	0.19	0.526	0.769	31.58
	70	0.01	0.501	0.695	28.00
Di-Cafos	0	19.49	0.895	1.044	14.29
	30	24.71	0.736	0.894	13.23
	45	0.11	0.669	0.850	21.33
	70	0.06	0.538	0.736	26.88
Mannitol	0	0.35	0.552	0.652	15.38
	30	19.09	0.568	0.657	13.64
	45	18.70	0.577	0.678	14.94
	70	0.07	0.568	0.694	18.18
MCC/lactose	0	3.75	0.536	0.652	17.64
	30	8.67	0.568	0.704	19.32
	45	0.10	0.526	0.735	28.42
	70	0.03	0.439	0.667	34.21

MCC microcrystalline cellulose, *Di-Cafos* calcium hydrogen phosphate
[a] Relative deviation for two batches, <12%
[b] Relative deviation for two batches, <5%

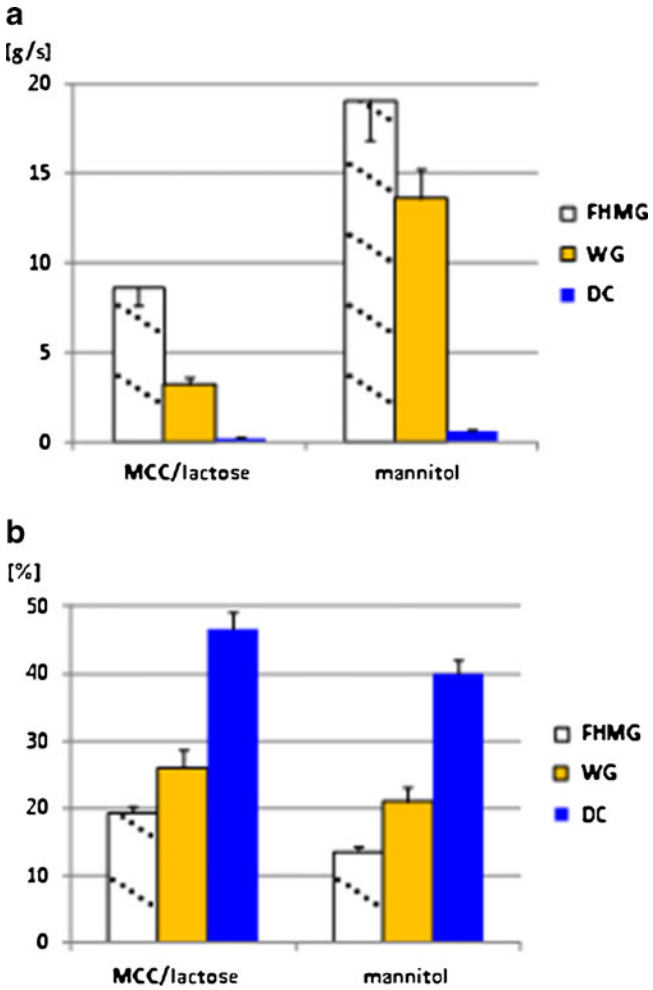

Fig. 2. Comparison of flowability (**a**) and compressibility—Carr's index (**b**) of granules prepared by FHMG process or by wet granulation (*WG*) and powders for direct compression (*DC*). Carbamazepine content, 30% (*w*/*w*)

with mannitol and 45% of carbamazepine, the results are very similar to those for granules with 30% drug content. Carr's index values are the highest for all granules with 45% and 70% carbamazepine content (see Table I).

Flowability and Carr's index were also measured for powders prepared for tabletting by means of a direct compression and for granules obtained by wet granulation. The results for formulations with carbamazepine content of 30% (*w*/*w*), prepared with mannitol or with MCC/lactose filler, are presented in Fig. 2 and compared with the values determined for FHMG granules.

The granules obtained by FHMG process demonstrate the best flowability and the lowest Carr's index, in comparison to the corresponding granules produced by wet granulation or powders. This was observed for both types of fillers.

Tablet Parameters

In a preliminary study, tablets were prepared from placebo granules without disintegrants. They were of good quality but the disintegration time was too long. In order to improve this parameter, 1.0% (*w*/*w*) of colloidal silica and 2.0% (*w*/*w*) of crospovidone were added. These excipients decreased the disintegration time from 30.5 min to less than 5 min on average. In the case of tablets made from granules containing MCC/lactose, the disintegration time decreased even below 1 min. The evaluation results of the physical properties of these tablets are shown in Table II.

Friability was lower than 1.0% for, both, placebo tablets and tablets with carbamazepine (30%, *w*/*w*), with the exception of tablets with lactose and carbamazepine, where friability was very high, i.e., 10.5%. For these tablets, the longest disintegration time, namely 17.7 min, and large deviation in hardness was also observed. The disintegration time for other drug-containing tablets under investigation was lower than 8 min; however, this parameter was significantly higher for each formulation than the one observed for the corresponding placebo tablets.

Tablets obtained from granules prepared by FHMG have lower disintegration time and friability values than the tablets produced from granules prepared by wet granulation (Table III). Faster disintegration corresponded to lower hardness of tablets made from FHMG granules. In spite of the lower hardness, these tablets were more resistant to the mechanical stress as demonstrated in the friability test. The measurements were made 1 week after the preparation of tablets and the hardness of tablets was higher than 70 N as controlled during tabletting, but this effect was much more pronounced for tablets produced with the wet-granulation step indicating that tablet hard-

Table II. The Physical Parameters (Mean Values) Determined for Tablets Prepared with the Granules Obtained in FHMG Process

Granules filler	Carbamazepine (%)	Weight[a] (mg)	Thickness[a] (mm)[a]	Hardness[a] (*N*)	Disintegration time (min)	Friability (%)
Lactose	0	690.9 (±0.3)	6.10 (±0.28)	71.3 (±4.0)	0.8	0.710
	30	571.7 (±1.9)	5.88 (±0.71)	88.1 (±14.2)	17.7	10.5[b]
Di-Cafos	0	918.9 (±1.1)	5.92 (±0.37)	83.5 (±4.4)	3.1	0.475
	30	720.8 (±0.8)	6.00 (±0.21)	90.0 (±7.5)	5.6	0.450
Mannitol	0	587.1 (±0.2)	5.84 (±0.27)	84.2 (±5.7)	2.3	0.375
	30	550.6 (±0.6)	6.07 (±0.32)	94.0 (±4.6)	5.8	0.191
MCC/lactose	0	633.5 (±0.3)	5.87 (±0.30)	85.0 (±5.9)	0.9	0.157
	30	564.4 (±0.7)	5.90 (±0.29)	79.0 (±6.9)	8.7	0.123

FHMG fluidized hot-melt granulation, *Di-Cafos* calcium hydrogen phosphate, *MCC* microcrystalline cellulose
[a] Mean (±RSD); $n=40$
[b] Two tablets broke into halves

Table III. Comparison of Physical Parameters (Mean Values) of Carbamazepine (30%, *w/w*) Tablets Prepared from Granules Produced by FHMG Process and Wet Granulation

Granules filler	Granulation method	Hardness[a] (*N*)	Weight[a] (mg)	Disintegration time (min)	Friability (%)
Mannitol	FHMG	94.0 (±4.6)	550.6 (±0.6)	5.8	0.191
	WG	114.8 (±7.1)	610.0 (±0.8)	21.1	0.410
MCC/lactose	FHMG	79.0 (±6.9)	564.4 (±0.7)	8.7	0.123
	WG	122.3 (±13.2)	646.3 (±1.5)	18.1	0.310

FHMG fluidized hot-melt granulation, *WG* wet granulation
[a] Mean (±RSD); $n=40$

ening occurred and, in consequence, the prolongation of disintegration time ensued.

Dissolution Profile

Dissolution rate of carbamazepine from tablets is presented in Fig. 3. Tablets made of granules prepared by FHMG, with mannitol or with MCC/lactose, exhibit practically 100% of dissolution after 15 min. Corresponding tablets of the same composition, but prepared with granules made by wet granulation, have much worse dissolution profiles; after 45 min, only 67.5% and 18.8% of the drug was released from tablets containing MCC/lactose or mannitol, respectively. Tablets made from granules prepared with lactose using FHMG process released more than 80% of carbamazepine within 30 min. The worse results were achieved for tablets produced from FHMG granules with calcium hydrogen phosphate since the drug release was practically terminated after 15 min, when only half a dose was released.

DISCUSSION

The FHMG process was fast, simple, and generally did not present major technical problems. In contrast to other methods based on the melting process, the amount of PEG used as a binder was low, i.e., only 10% (*w/w*). Kidokoro *et al.* (6) have already found that to obtain a suitable flowability the content of PEG should be approximately at 10% (*w/w*); therefore, the content of the melting material for FHMG method is lower than the content required for the hot-melt granulation (20–30%, *w/w*).

Our preliminary experiments have demonstrated that FHMG was not a suitable method for the preparation of placebo granules with PEG as a binder (10%, *w/w*) and microcrystalline cellulose or pregelatinized starch as fillers. In the first case, poor flowability (only 0.01 g/s) resulted in a very poor filling of the tablet machine. Although flowability parameters were satisfactory for the granules prepared with pregelatinized starch (flowability at 19.2 g/s), the resulting tablets were very fragile and non-resistant to stress.

The FHMG process for placebo granules with lactose, MCC/lactose, mannitol, or Di-Cafos as fillers did not cause problems. In further experiments, granules containing 30%, 45%, or 70% of carbamazepine were prepared using the aforementioned fillers

With the four types of fillers, the granules with satisfactory properties were easily produced when the carbamazepine content was at 30% (*w/w*). Granulation with higher drug content (45% or 70%) was ineffective since the granules adhered to a dryer's wall and the flowability of the product was very poor. This was demonstrated by a high Carr's index (Table I), within the flow range that, according to Ph.Eur., can be classified as only passable or even very poor. The exception are granules containing mannitol, which demonstrate a good or fair flow. In contrast, the flow of granules

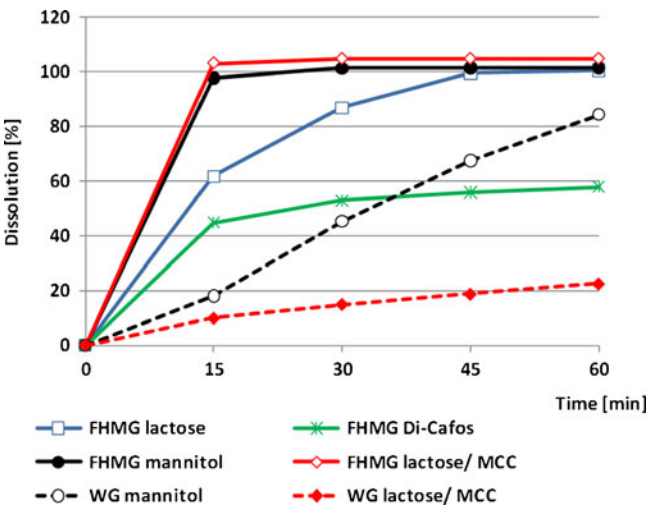

Fig. 3. Dissolution profiles of carbamazepine from tablets prepared from granules (30% of carbamazepine) obtained from FHMG process or by wet granulation (*WG*). Mean values are presented for six tablets (RSD, <5%; for formulation WG lactose/MCC RSD, <20%)

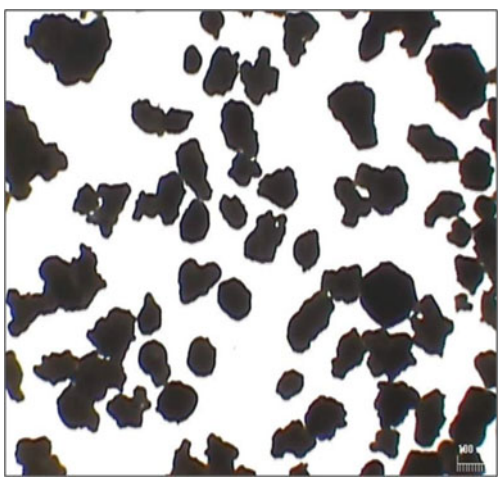

Fig. 4. Carbamazepine (30%, *w/w*) granulated with PEG 6000 (10%, *w/w*) and mannitol in FHMG process

containing 30% of carbamazepine was classified as good (fair for MCC/lactose as a filler). Surprisingly, flowability of drug-loaded granules (30%, *w*/*w*) was even better than placebo granules. Besides, the flowability of granules obtained in FHMG process was significantly improved, not only in comparison to the physical mixture of powders but also to granules prepared by wet granulation (Fig. 2). Finally, tablets were prepared only from granules with the drug content of 30% (*w*/*w*).

In comparison to placebo granules, the distribution of particle size was broader in the carbamazepine-containing product (Fig. 1). The size of granules with 30% (*w*/*w*) drug content was in the range of 100–1,000 μm, with only a very small fraction of fine powder below 100 μm (less than 10%) if lactose or Di-Cafos were used. This indicates that the yield of granulation process was satisfactory, inspite of the fact that FHMG process was not optimized in our study. The size of particles was smaller than the size reported for ketoprofen or ibuprofen granules prepared with PEG 6000 content of 20% (*w*/*w*) (8) since in that study more than 90% of particles were in the size of 500–1,400 μm.

FHMG enabled us to prepare granules with not only better flowability but also with better compressibility (lower Carr's index), as compared with the wet-granulated product or to non-granulated powders of the same composition (Fig. 2). This can be explained by the fact that melted binder makes the particles less porous (6) and more regular in shape (Fig. 4). The plasticizing effect of the melted macrogol is probably also contributing to the observed improvement of the solid material properties.

The tablets prepared from granules obtained in FHMG process had long disintegration time. However, a disintegrant (2% of crospovidone (*w*/*w*)) added externally to granules before tabletting eliminated this problem and, except for tablets with lactose, the disintegration time was shorter than 10 min. Filler type had a strong effect on the friability and disintegration of carbamazepine-containing tablets and, with regard to these parameters, lactose was the least suitable filler. Despite of the same composition, tablets produced from FHMG granules showed significantly faster disintegration and lower friability than tablets from wet-granulated mass (Table III). The friability parameter did not correlate with tablet hardness and that allowed us to obtain tablets with lower hardness still resistant to the mechanical stress, which can occur, for example, during rolling in the coating process. This is probably the result of the better plasticization of the compressed granules by melted PEG which allows for more effective spreading of the binder around particles (6).

The advantage of using FHMG method is also clearly demonstrated by way of a comparison of carbamazepine dissolution profiles for tablets produced either from FHMG granules or from wet-granulated mass (Fig. 3). The application of FHMG method resulted in a fast carbamazepine dissolution, although the drug is poorly soluble in water. This effect might be related to modification of the solid state of the drug (e.g., formation of solid dispersion regions), but such explanation requires more detailed investigation. For example, using DSC and XRD analysis, Passerini *et al.* (8) demonstrated a reduction of drug crystallinity in ketoprofen and ibuprofen granules produced in FHMG process.

The dissolution profile was strongly influenced by the filler type and, in the case of Di-Cafos, a very slow dissolution was observed. However, mannitol and the mixture of lactose and MCC allowed for very fast dissolution of carbamazepine and these fillers should be recommended.

CONCLUSIONS

All granule types prepared with carbamazepine and PEG content of 30% (*w*/*w*) and 10% (*w*/*w*), respectively, have better flowability than the placebo granules with the same filler, and the compressibility of granules produced by FHMG method was better than the compressibility obtained by wet granulation. Tablets produced from granules prepared by FHMG have better physical parameters and significantly faster dissolution of the drug than the tablets produced from granules prepared by wet granulation. Among the investigated fillers, the best results were generally obtained for MCC/lactose and mannitol, although probably lactose can also be successfully used after the optimization of the tabletting stage of production.

REFERENCES

1. Parikh DM, Bonck JA, Maogavero M. Batch fluid bed granulation. In: Parikh DM, editor. Handbook of pharmaceutical granulation technology. New York: Marcel Dekker; 1997. p. 227–302.
2. Tousey MD. The granulation process 101. Basic technologies for tablet making. Pharm Technol. 2002;8–13.
3. Holm P. High Shear Mixer granulators. In: Parikh DM, editor. Handbook of pharmaceutical granulation technology. New York: Marcel Dekker; 1997. p. 194–8.
4. Abberger T, Seo A, Schaefer T. The effect of droplet size and powder particle size on the mechanisms of nucleation and growth in fluid bed melt agglomeration. Int J Pharm. 2002;249:185–97.
5. Walker GM, Holland CR, Ahmad MMN, Craig DQM. Influence of process parameters on fluidized hot-melt granulation and tablet pressing of pharmaceutical powders. Chem Eng Sci. 2005;60:3867–77.
6. Kidokoro M, Haramiishi Y, Sagasaki S, Shimizu T, Yamamoto Y. Application of fluidized hot-melt granulation (FHMG) for the preparation of granules for tableting; properties of granules and tablets prepared by FHMG. Drug Dev Ind Pharm. 2002;28:67–76.
7. Craig DQM. The mechanism of drug release from solid dispersions in water-soluble polymers. Int J Pharm. 2002;231:131–44.
8. Passerini N, Calogera G, Albertini B, Rodriguez L. Melt granulation of pharmaceutical powders: a comparison of high-shear mixer and fluidised bed processes. Int J Pharm. 2010;391:177–86.