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International Journal of Pharmaceutics 256 (2003) 53–63
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique

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Received 25 July 2002; received in revised form 29 November 2002; accepted 19 December 2002

Abstract

This work describes a new approach to prepare a fast-release dosage form for carbamazepine (CBZ), involving the use of melt granulation process in high shear mixer for the production of tablets. In particular, the granules containing CBZ were prepared using polyethylene glycol (PEG) 4000 as a melting binder and lactose monohydrate as a hydrophilic filler. The potential of the intragranular addition of crospovidone as a dissolution enhancer and a disintegrant agent was also evaluated. After the analysis of their solid state performed by means of X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC), the granules were characterised from the technological and dissolution point of view. The subsequent step encompassed the preparation and the evaluation of the tablets, including the effect of the extragranular introduction of crospovidone. Besides the remarkable enhancement of drug dissolution rate of the granulates in comparison to physical mixtures and pure drug, no significant differences were found between the dissolution profiles of the granulates containing lactose or crospovidone. However, the difficult disintegration and bad dissolution performance of the tablets not containing intragranular crospovidone highlight the necessity of this disintegrant in the granulating mixture. Moreover, the extragranular addition of a small amount of crospovidone gave rise to a further amelioration of the disintegration and dissolution performances.

Keywords: Carbamazepine; Melt granulation technique; Dissolution enhancement; Tablets; PEG 4000; Crospovidone

1. Introduction

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, apparatus of choice are the high shear mixers, where the product temperature is raised above the melting point of the binder either by a heating jacket or, when the impeller speed is high enough, by the heat of friction generated by the impeller blades (Schaefer, 1997).

In the last few years, melt agglomeration technique in the high shear mixer has been successfully applied to develop sustained release formulations using lipophilic melting binders, such as glycerol monostearate (Thies and Kleinebudde, 1999), a combination of a hydrophobic material, a starch derivative (Zhou et al., 1996) and stearic acid (Voinovich et al., 2000; Perissutti et al., 2002b) among others.

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doi:10.1016/S0378-5173(03)00062-0

More recently, Passerini et al. (2002) proved that melt granulation can be a viable means to enhance the in vitro dissolution rate of ibuprofen, employing poloxamer 188 as a melting binder.

In the present work, the feasibility of a fast-release rate formulation by melt agglomeration has been considered. Carbamazepine (CBZ) was chosen as a water-insoluble model drug (Levy et al., 1975) and lactose as a hydrophilic filler, typically used in both wet and melt agglomeration processes (Schaefer, 1997). Polyethylene glycol (PEG) 4000 was employed as a melting binder, in consideration of its favourable solution properties, low melting point, rapid solidification rate, low toxicity and low cost (Craig, 1990). Further, this melting binder resulted to be a viable dissolution enhancer for CBZ in solid dispersions (Doshi et al., 1997) and in extrudates prepared by hot-melt extrusion (Perissutti et al., 2002a).

In addition, the potential inclusion of crospovidone as a disintegrant agent (Bühler, 1993) and CBZ dissolution enhancer (Moneghini et al., 2002) was also considered.

Thereafter, the second part of the research project encompassed the preparation of tablets to evaluate the potential of compressing granulates prepared by melt agglomeration.

The solid-state physical structure was established by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD). Finally, the technological characteristics and the dissolution properties of the samples were evaluated and the release profiles were compared to that of pure drug and the corresponding physical mixtures.

2. Materials and methods

2.1. Materials

CBZ reagent grade was obtained from Sintofarm (Guastalla, Reggio Emilia, Italy); PEG 4000 reagent grade was purchased from ACEF (Fiorenzuola d'Arda, Piacenza, Italy); monohydrate lactose E.P. grade (Pharmatose 200 mesh) was obtained from Meggle (Wasserburg, Germany); crospovidone (PVP-CL) was obtained from GAF (Milano, Italy). Magnesium stearate, which acted as a lubricant during tabletting procedure, was purchased from Agrar (Roma, Italy).

Table 1
Percent compositions of the granulates

Samples	A	B	C	D	E
CBZ	25	25	25	25	25
Lactose	60	57	55	–	45
PEG	15	18	20	20	20
PVP-CL	–	–	–	55	10

2.2. Methods

2.2.1. Composition of the mixtures

During the formulation study the CBZ concentration was kept constant at 25% (w/w), while the PEG concentration varied between 15 and 20%. The remaining part of the formulation consisted of lactose and/or PVP-CL. Table 1 gives an overview of the formulation compositions evaluated during this study.

2.2.2. Preparation of the granulates

The granules were prepared in the 10-l laboratory scale Zanchetta Roto J high shear mixer equipped with an electrically heated jacket (maximum temperature 100 °C), already described by Vojnovic et al. (1993). The granulation procedure was standardised on the basis of preliminary trials, and the temperature of the powders inside the bowl were continuously recorded by a thermo-resistance probe fixed on the bowl lid and dipped in the powder mass. Firstly, the mixture of CBZ, lactose and/or PVP-CL was dry blended for 10 min at 100 rpm with the bowl thermostated at 70 °C. Then, the appropriate amount of PEG flakes was added under stirring, and the mixing phase was continued for further 5 min at 100 rpm. During the subsequent massing phase the impeller speed was raised to 400 rpm for 5 min. At the end of the granulation process the granules were allowed to solidify at room temperature by spreading them out in thin layers on trays. The cooled granules were stored in sealed bags for 10 days.

2.2.3. Granule characterisation

A vibrating apparatus (Octagon 200, Endecotts, London, UK) and a set of sieves with increasingly smaller openings (2000, 1250, 800, 630, 500, 400, 3150 and 250 μm) were used for size distribution determinations. After removal of lumps larger than 2 mm the particle size distribution of the granules was characterised through the determination of the

mean geometric diameter ($D_{50\%}$) and the geometric standard deviation (ρ_g). Both were calculated by a computer program (Sapra, 1990). The granulate size fraction $\leq$1250 μm was selected for further characterisations and processing.

The bulk density (d_{10}) and tap density (d_{2000}) were determined with a volume presser (Giuliani IG/4, Torino, Italy) that dropped 10 and 2000 times, respectively. The compactability index or Carr index (CI) was derived as previously reported (Moneghini et al., 2000).

The flow properties were evaluated using a flow tester (model PTG-1, Pharma Test, Hainburg, Germany). Each granulate was placed in a 100-ml funnel (with an orifice of 6 mm) and the product was allowed to flow only under the force of gravity. The instrument automatically evaluated the flow time and the angle of repose of the granulates.

2.2.4. Dissolution studies of granulates

The dissolution test was performed according to the rotating paddle method (USP 23). A dissolution apparatus (model DT-1, Erweka, Eusenstamm, Germany) was employed with a stirring rate of 100 rpm and was maintained at 37 ± 0.1 °C. The dissolution media was 900 ml of freshly demineralised water.

An accurately weighed granulate sample, containing a suitable amount (18 mg) of CBZ for sink conditions ($C \ll C_s$), was dissolved in 900 ml of dissolution medium. The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer (model 552, Perkin-Elmer, Padova, Italy) and absorbance values were recorded at the maximum wavelength of the drug (285 nm). The excipients did not interfere with the UV analysis. The results were the average of triplicate experiments, and standard deviations did not exceed 5% of mean value. The same procedure was followed for physical mixtures and samples containing the same amount of pure drug as a powder.

2.2.5. Preparation of the tablets

Prior to compression 2% (w/w) of magnesium stearate was mixed with each batch of granulates in a biconic mixer (IG/MS/B, Giuliani, Torino, Italy) for 10 min. A rotary tabletting machine (Ronchi AM 13, Milano, Italy), equipped with 10-mm concave punches, was employed to prepare tablets with an average weight of 400 mg. The maximum pressure was 3030 kg/cm^2 and the tabletting speed was 75 tablets/min.

2.2.6. Tablets properties

The friability of 20 tablets from each lot was determined using a friabilator (model Ta-UZ, Erweka), rotating 100 times.

The crushing strength was measured with a hardness tester (model TBH 30, Erweka). Ten tablets from each lot were analysed.

The disintegration time was tested using the disintegration test apparatus (model ZT 3, Erweka). Water kept at 37 °C was used as a medium and the basket was raised and lowered at a constant frequency of 30 cycles/min. Six tablets from each lot were evaluated.

2.2.7. Dissolution studies of tablets

In order to maintain sink conditions also in this case, the dissolution test was performed according to Giunchedi et al. (1993) in a cylindrical vessel with a nominal capacity of 5000 ml (instead of 1000 ml). A rotating basket was employed with a stirring rate of 100 rpm in order to overcome the problems due to sticking of the tablets to the wall of the container or to floating of the tablets on the surface. The distance between the bottom of the basket and the bottom of the vessel was 50 mm. The dissolution medium was 5000 ml of freshly demineralised water, maintained at 37 ± 0.1 °C.

Samples of tablets corresponding to 100 mg of drug were placed into the basket. The same procedure was followed for samples of the pure drug as a powder, to compare the samples in the same hydro-dynamic conditions.

The aqueous solution was filtered and continuously pumped to a flow cell in the spectrophotometer. Also in this case, the results were the average of triplicate experiments and standard deviations did not exceed 5% of mean value.

2.2.8. Analysis of solid state

DSC analysis was carried out using a differential scanning calorimeter (model TA 4000, equipped with a measuring cell DSC 20 Mettler). Samples of granulates, containing about 2.5 mg of CBZ, were placed in pierced aluminium pans and heated at a scanning rate

of 10 °C/min from 25 to 210 °C. The same procedure was followed for the pure drug, the carriers, the physical mixtures (PMs) of the components (prepared in the same percentage to that of the granulates) and for the samples of tablets gently milled in a frozen mortar.

Further, the granulates, their corresponding physical mixtures and the starting materials were studied by means of XRD technique using an STOE D500 diffractometer with Cu Kα radiation ($\lambda = 1.5418$ Å), monochromatised by a secondary flat graphite crystal. The scanning angle ranged from 5 to 35° of 2θ, steps were of 0.1° of 2θ and the counting time was 1 s/step. The voltage was 40 kV and the current 20 mA.

3. Results and discussion

3.1. Solid-state analysis of the granulates

The physical characterisation was firstly carried out by means of XRD analysis. The diffraction patterns of the granulates and the PMs compared to the starting materials are depicted in Figs. 1 and 2, respectively. The XRD patterns of starting CBZ indicated that the sample consisted of a mixture of polymorphs III and I, the latter being evident by the signals at 6.1, 9.4, 19.9 and 22.8° 2θ (Lowes et al., 1987). Monohydrate lactose presented very intense signals at 19 and 22° 2θ and a low intensity signal at 12.6° (Chidavaenzi et al., 2001). PEG showed two peaks at 19.2 and 23.4° 2θ, as previously reported for crystalline PEG 4000 (Lin and Cham, 1995; Corrigan et al., 2002), and some more peaks of minor intensity. In the XRD pattern of PVP-CL, a lack of well-defined peaks was noticed, whereas an intense scattering phenomenon was detected, typical of amorphous materials (Mura et al., 1999).

The diffractograms of the granulates indicated that the polymorphic form of the drug was maintained substantially unchanged after melt granulation process, and only a little reduction of the degree of crystallinity was detected in comparison with the corresponding PMs.

Fig. 3 reports the DSC scans of the raw materials. Thermal analysis completely reconfirmed the previously reported XRD findings. The thermogram of CBZ conducted at 10 °C/min, revealed only but one endotherm at 189.7 °C. Yet, by repeating the DSC run at higher scanning rate, as suggested by several authors (Lowes et al., 1987; Rustichelli et al., 2000; Moneghini et al., 2001), an additional endotherm (172.8 °C) can be detected, confirming that the CBZ sample

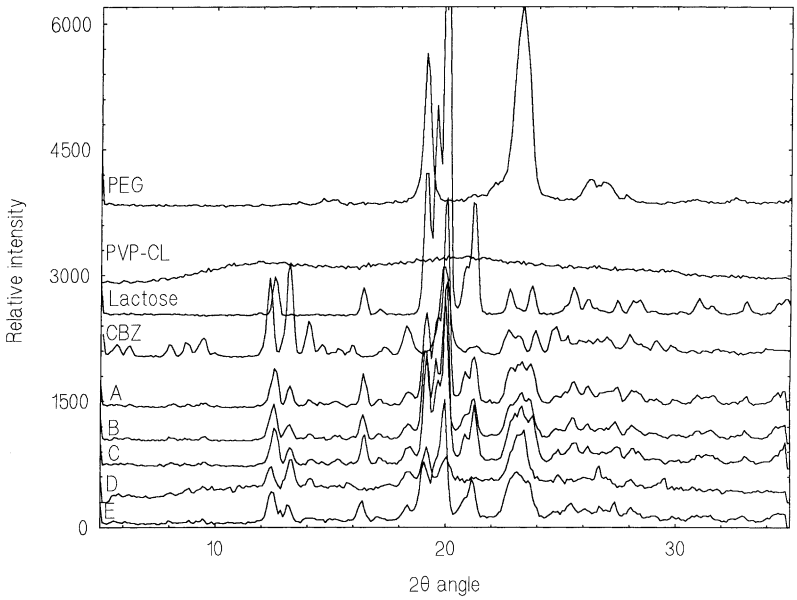

Fig. 1. XRD patterns of granulates compared to raw materials.

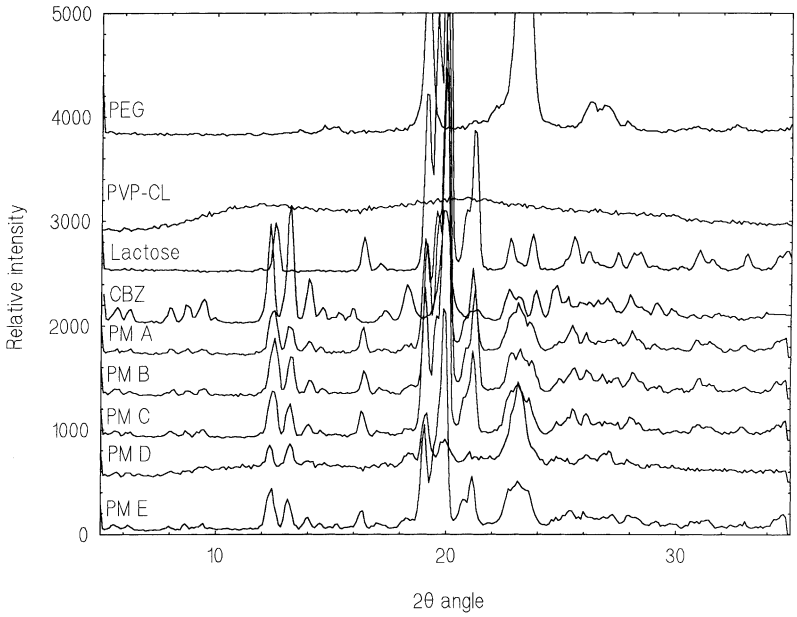

Fig. 2. XRD patterns of physical mixtures compared to raw materials.

consisted of a mixture of I and III anhydrous forms. The DSC scan of PEG 4000 showed a large melting peak at 62.3 °C and a weak exothermal inflection at about 150 °C, due to its instability on heating, similarly to that reported by Moneghini et al. (2001). In the considered range of temperatures, the DSC curve of lactose monohydrate showed only the dehydration endotherm in the 140 °C region. PVP-CL scan showed

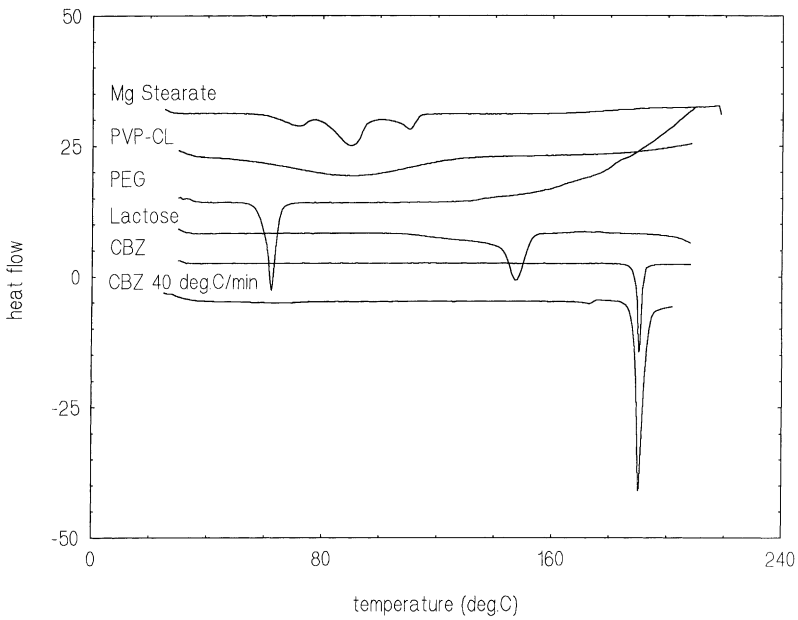

Fig. 3. DSC curves of raw materials.

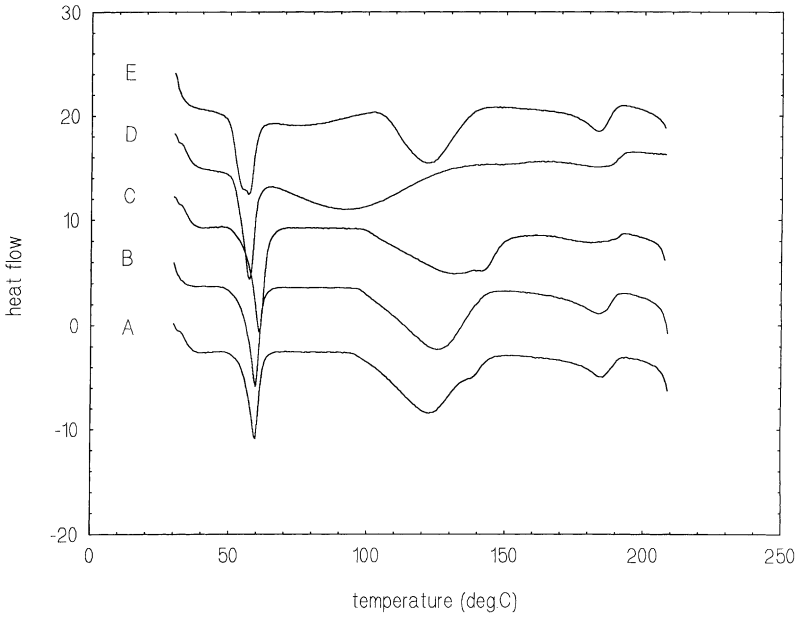

Fig. 4. DSC curves of granulates.

a broad endotherm with a maximum at 90.3 °C, due to the water absorbed by the hygroscopic cross-linked polymer.

In the DSC curves of the granulates (Fig. 4), three thermal events were detected: the fusion of the PEG, the dehydration of the lactose and finally the melting of the drug. In particular, the monohydrate lactose was slightly disrupted since its dehydration did not appear as the usual sharp peak and it shifted to a lower temperature, similarly to that reported by Chidavaenzi et al. (2001). As expected, among the granulates, the only exception was represented by the sample D (not containing lactose) that revealed the dehydration of the PVP-CL at about 100 °C. In comparison to the granulates, the PMs (Fig. 5) showed a scarce reduction of drug fusion enthalpy and a remarkable increase of the dehydration enthalpy of lactose and PVP-CL. This fact was probably due to the water contained in the granulates which had partially evaporated during the melt granulation process, as already noticed by other authors (Schaefer and Mathiesen, 1996; Wong et al., 2000).

3.2. Technological characterisation of the granulates

Table 2 reports the results of the characterisation of the granulates. As it can be seen, the mean

Table 2
Technological characterisation of the granulates

	A	B	C	D	E
d_{10} (g/ml)	0.620	0.574	0.720	0.460	0.630
d_{2000} (g/ml)	0.649	0.605	0.765	0.500	0.690
CI	4.47	5.12	5.88	8.00	8.69
Hausner ratio	1.047	1.054	1.063	1.087	1.095
Flow time 100 ml/s	26.7	No flow	No flow	28.24	26.20
Angle of repose (°)	33.9	No flow	No flow	33.8	33.20
$D_{50\%}$ (μm)	436	1010	1500	400	980
ρ_g	2.25	6.5	7.85	2.50	3.74

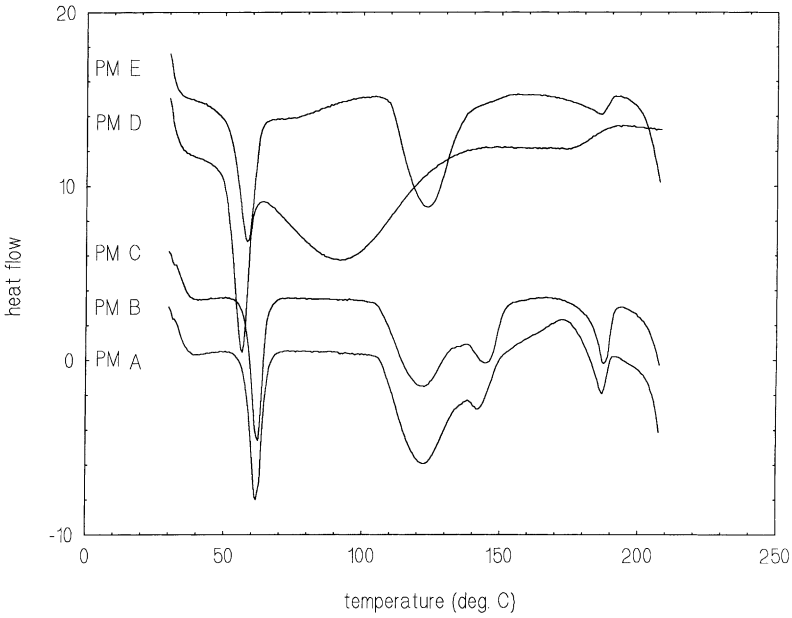

Fig. 5. DSC curves of physical mixtures.

geometric diameter increased as the PEG content increased, whereas a dramatic decrease of the mean diameter was noticed when replacing lactose by PVP-CL. According to the literature data, powders with a CI between 5 and 15% and a Hausner ratio below 1.25 are suitable for producing tablets (Wells, 1997). All tested formulations had a CI ranging between 4.47 and 8.69 whilst their Hausner ratio was below 1.1.

As for the rheological properties, only the sample A of the granulates produced with lactose flowed, whereas the granulates containing PVP-CL revealed a good flowability, confirming the previously reported positive effect of this disintegrant on the rheological properties (Bühler, 1993).

3.3. *In vitro dissolution of the granulates*

The in vitro dissolution rate of all prepared granulates (Fig. 6) was increased compared to the corresponding physical mixtures (Fig. 7) and the drug

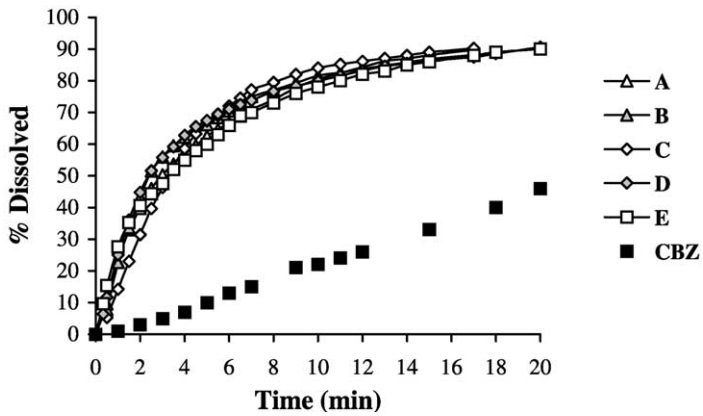

Fig. 6. In vitro dissolution profiles of granulates compared to pure CBZ.

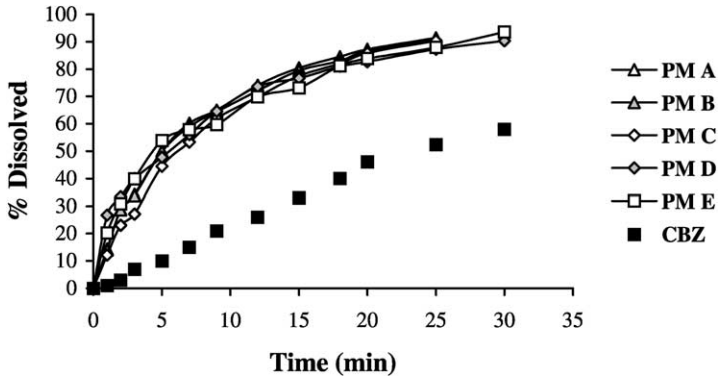

Fig. 7. In vitro dissolution profiles of physical mixtures compared to pure CBZ.

alone, because of the higher hydrophilic character of the systems due to the carriers and the slight reduction of CBZ crystallinity. No significant differences were attested by the analysis of variance ($P = 0.05$) between the samples with different amount of PEG, nor with the incorporation of 55 or 10% of PVP-CL into the formulation.

3.4. Preparation and technological characterisation of the tablets

The subsequent step consisted in the preparation of the tablets. Due to the superimposable dissolution profiles of granulates A, B and C, only the first sample was subjected to compression because of its favourable flow properties. Hence, after addition of 2% magnesium stearate following the procedure reported earlier, granulates A, D and E were tabletted. The composition of the resulting tablets is reported in Table 3.

The technical characterisation (Table 4) revealed that the tablets were acceptable in terms of uniformity of mass. The hardness was diminishing as the PVP-CL content increased, whilst friability values were quite homogeneous. However, considering the disintegration time, tablets A (not containing PVP-CL intragranular) were found to be not satisfactory for the requisites of European Pharmacopoeia (2001). To overcome this problem, 5% of PVP-CL was added to samples A, D and E prior to compression. This procedure particularly applies in case of hard granulates (Bühler, 1993), such as those prepared by melt granulation technique. Moreover, the extragranular addition of PVP-CL was previously found to be very useful in a formulation design study of atenolol fast-release tablets (Moneghini et al., 2000). Three additional tablet batches were prepared and named F, G and H, respectively. This way,

Table 3
Percent composition of the tablets

Samples	A	D	E	F	G	H
CBZ	24.5	24.5	24.5	23.3	23.3	23.3
Lactose	58.7	–	44.2	55.8	–	41.8
PEG	14.8	9.6	19.6	13.9	18.5	18.6
PVP-CL[a]	–	53.8	9.7	–	51.2	9.3
PVP-CL[b]	–	–	–	5.0	5.0	5.0
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0

[a] Intragranular PVP-CL.
[b] Extragranular PVP-CL.

Table 4
Technological characterisation of the tablets

	A	D	E	F	G	H
Mean weight (mg)	403	402	405	422	430	423
Friability (%)	0.50	0.09	0.15	0.11	0.78	0.10
Hardness (N)	123.7	48.4	86.3	90.4	48.0	70.0
Disintegration time (min)	18	4	10	12	3.5	8
$t_{90\%}$ (min)	–	78	80	115	75	78

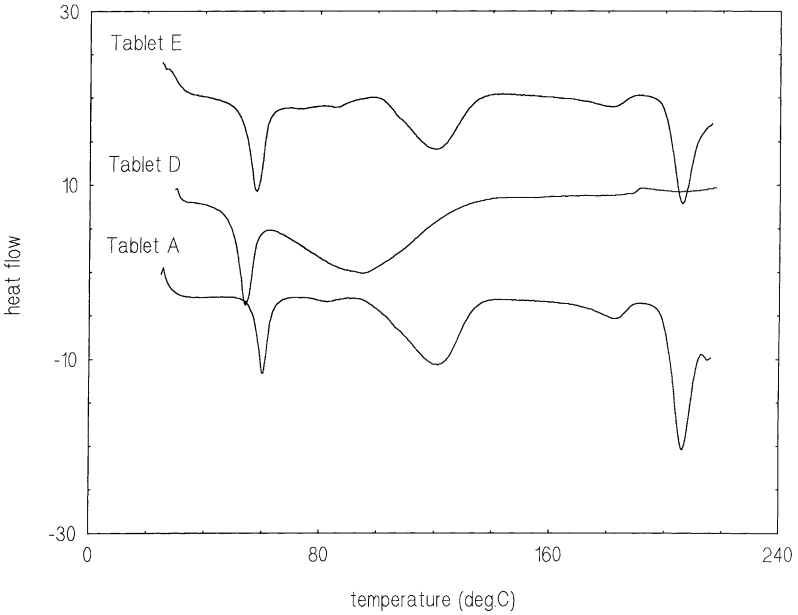

Fig. 8. DSC curves of tablets.

all the tablets were conforming to the requisites of the Italian Pharmacopoeia (see Table 4), obtaining a sensible reduction of the disintegration time. The addition of PVP-CL had only a small adverse effect on tablet hardness, which remained anyway acceptable.

3.5. Solid-state analysis of the tablets

The assessment of the possible changes in the solid state of components due to compression process was performed by DSC. The results of this analysis, depicted in Fig. 8, indicated that there was no change in CBZ thermal behaviour, but revealed a remarkable downward shift of the lactose melting peak in comparison to granulates and PMs, indicative of solid–solid interactions. For an overview of PEG and lactose melting points registered at the DSC after melt granulation phase and compression stage, the thermal data are reported in Table 5. As it can be seen, the melting point of PEG increased after compaction, indicating an effect of the compression procedure on the solid state of the material, as already reported by Adolfsson and Nyström (1996). It must also be pointed out that these differences on solid state between granulates and tablets could be due to the thermo-mechanical properties of PEG 4000. It melts at a temperature of approximately 55 °C that is often reached during the compression process (Adolfsson and Nyström, 1996). The melting of PEG was also noticed by other authors when using pressures higher than 120 MN/m^2 (Fassihi, 1991). In particular, Lin and Cham (1995) noticed a similar behaviour using PEGs preheated at 80 °C, likewise the PEG used in this research. Therefore, it is a reasonable supposition that lactose should partially dissolve during the compression stage in the molten PEG, thus, justifying the shift in lactose melting point.

This phenomenon may also explain the difficult disintegration of the tablets not containing PVP-CL intragranular. In fact, the liquid-surface film theory attributes bonding to the presence of a thin liquid film,

Table 5
Comparison between thermal data of melt granulates and tablets

Sample	PEG, m.p. (°C)	Lactose, m.p. (°C)
Granules A	59.0	213.7
Tablets A	60.4	206.3
Granules D	54.1	–
Tablets D	54.2	–
Granules E	57.1	213.8
Tablets E	57.5	206.0

Table 6
In vitro dissolution parameters of tablets and CBZ

Tablet	$t_{50\%}$ (min)	$t_{90\%}$ (min)
A	25	135
D	9.5	78
E	19	80
F	28	115
G	5	75
H	14	78
CBZ (powder)	25	145

which can be the consequence of fusion or solution at the surface of the particles induced by the energy of compression (Parrot, 1990). Upon release of the tabletting pressure, the solidification of the fused material would form solid bridges between the particles.

As reported in Table 6, the time necessary for the dissolution of 90% of the drug ($t_{90\%}$) was reduced to half of that of the pure drug ($t_{90\%} = 145$ min), with the only exception of the tablet F (not containing PVP-CL intragranular) showing a lower enhancement of CBZ dissolution. Hence, not only the intragranular addition of PVP-CL was necessary to favour the disintegration of the tablets, but also to promote the de-aggregation of the granulates, thus, the dissolution of the drug. In fact, as described by Ford and Rubinstein (1980), tablets compressed from granules prepared by in situ fusion processes of PEG 6000 did not disintegrate but gradually eroded. According to Ford (1983) this was explained by the fact that the break up of the tablets was not governed by the disintegration, but it depended on the rate at which the binder dissolved, since the latter was distributed across the particle surface. Similar behaviour was also noticed by Abberger and Henck (2000) and Abberger (2001) in tablets compressed from fluid-bed melt granulates containing lactose and PEG 4000, who attributed this performance to the formation of a binder matrix which could not be destroyed by the extragranular disintegrant.

4. Conclusions

In conclusion, melt granulation has been proved to be a viable means process to produce a fast-release dosage form for CBZ, using PEG 4000 as a melt binder, without using solvents or water. Solid-state analysis indicated only a scarce reduction of the crystallinity of the drug and no changes in its polymorphic form. The granulates displayed a significant improvement of in vitro drug dissolution behaviour. The dissolution profiles of granulates containing PVP-CL were found to be superimposable to those prepared without the disintegrant. However, the intragranular addition of PVP-CL was found to be necessary to produce tablets with a satisfactory disintegration time and a remarkable increase of the drug dissolution rate.

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