

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

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This work describes a melt granulation technique to improve the dissolution characteristics of a poorly water-soluble drug, oxcarbazepine. Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable binder. The advantage of this technique compared to conventional granulation is that no water or organic solvents are needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. In particular, the granules containing oxcarbazepine 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 starch as a dissolution enhancer and a disintegrative agent was also evaluated. After analysis of their solid state was performed by means of x-ray powder diffraction (XRD), the granules were characterized from technological and dissolution point of view. The subsequent step comprised of the preparation and evaluation of the tablets, including the effect of the extragranular introduction of starch. 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 starch. However, the difficult disintegration and bad dissolution performance of the tablets not containing intragranular starch so it is necessary to add disintegrant in the granulating mixture. Moreover, the extragranular addition of a small amount of starch gave rise to further amelioration of the disintegration and dissolution performances.

Key words: *Dissolution enhancement, melt granulation, oxcarbazepine, PEG 4000*

INTRODUCTION

Melt granulation is a process by which pharmaceutical powders gets converted to granules form 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, the apparatus of choice comprises of 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.^[1]

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, a combination of a hydrophobic material, a starch derivative, and stearic acid, among others.^[2-5]

More recently, it has been 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.^[6-7]

In the present work, the feasibility of preparing a fast-release formulation by melt agglomeration has been considered. Oxcarbazepine was chosen as a water-insoluble model drug and lactose as a hydrophilic filler, typically used in both wet and melt agglomeration process. Polyethylene glycol (PEG 4000) was used as a melting binder, in consideration of its favorable solution properties, low melting point, rapid solidification rate, low toxicity, and low cost.

In addition, the potential inclusion of starch as a disintegrative agent and an oxcarbazepine-dissolution enhancer was also considered.

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

The solid-state physical structure was established by X-ray powder diffraction (XRD). Finally, the technological characteristics and the dissolution properties of the

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samples were evaluated, and the release profiles were compared with those of the pure drug.

MATERIALS AND METHODS

Oxcarbazepine (Zydus Cadila, Ahmedabad); polyethylene glycol (PEG 4000), starch (National Chemicals, Baroda); lactose, magnesium stearate (Suvidinath Laboratories, Baroda).

Composition of mixtures

During the formulation study, oxcarbazepine concentration was kept constant at 23% (W/W), while PEG 4000 concentration varied between 7% and 23%. The remaining part of the formulation consisted of lactose and/or starch. Table 1 gives an overview of the formulation compositions evaluated during this study.

Preparation of the granulates

The granulation procedure was standardized on the basis of preliminary trials. Firstly, the mixture of oxcarbazepine, lactose, and/or starch was dry-blended for 10 min at 100 rpm, with the bowl thermostated at 700°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 speed was raised to 400 rpm for 5 min. At the end of granulation process, the granules were allowed to solidify at room temperature by spreading them out in thin layers on trays.

Granule characterization

The granules were evaluated for bulk density (B.D.), tapped density (T.D.), hausner ratio (H.R.), Carr's index (C.I.), and flow properties (angle of repose and flow times).

Dissolution studies of granulates

The United State Pharmacopoeia Paddle (Type-2) method was used for all the *in vitro* dissolution studies. In this method, 0.1 N HCL containing 0.25% SLS was used as dissolution medium at the speed of 50 rpm. The rate of stirring was 100 rpm. An accurately weighed granulate sample, equivalent to 150 mg of oxcarbazepine was placed in 900 mL of dissolution medium maintained at 37°C ± 0.5°C. At appropriate intervals, 5 mL of the samples were taken and filtered through Whatman paper. The dissolution medium was then replaced by 5 mL of fresh dissolution fluid to maintain constant volume. The samples were then analyzed at 256.5 nm by UV/

visible spectrophotometer. The mean of at least three determinations was used to calculate the drug release from each of the formulations.

X-ray diffraction

The powder X-ray diffraction patterns were determined for oxcarbazepine and oxcarbazepine-PEG 4000 melt granules. X-ray diffractograms were obtained using X-ray diffractometer (X'pert Philips, Holland) with Xe-filled counteract, Cu target, voltage 2 kV, current 15 mA, and 2θ over 0°C to 107°C.

Preparation of tablets by melt granulation technique

Prior to compression, 2% (W/W) of magnesium stearate was mixed with each batch of granulates for 10 min. A rotary tableting machine equipped with 10-mm concave punches was employed to prepare tables with an average weight of 650 mg.

Tablet properties

The prepared tablets were then evaluated for weight variation, drug content, and disintegration time according to Indian pharmacopoeia 96; and mechanical tests like those for hardness and friability were carried out.

Dissolution studies of tablets

The United State Pharmacopoeia Paddle (Type-2) method was used for all the *in vitro* dissolution studies. The rate of stirring was 60 rpm. The amount of oxcarbazepine was 150 mg in all formulations. The tablet was placed in 900 mL of dissolution medium maintained at 37°C ± 0.5°C. At appropriate intervals, 5 mL of the samples were taken and filtered through Whatman paper. The dissolution medium was then replaced by 5 mL of fresh dissolution fluid to maintain constant volume. The samples were then analyzed at 256.5 nm by UV/visible spectrophotometer. The mean of at least three determinations was used to calculate the drug release from each of the formulations.

RESULTS AND DISCUSSION

Technological characterization of the granulates

Table 2 reports the results of the characterization of the granulates. According to data from literature, powders with a Carr's index between 5% and 15% and a hausner ratio below 1.25 are suitable for producing tablets. All tested formulations

Table 1: Percentage compositions of the granulates

Ingredients	Batch code				
	A (%)	B (%)	C (%)	D (%)	E (%)
Oxcarbazepine	23	23	23	23	23
Lactose	69.23	61.53	53.84	-	43.84
PEG 4000	7.96	15.38	23.07	23.07	23.07
Starch	-	-	-	53.84	10

Table 2: Technological characterization of granulates
Batch code for granulates of PEG 4000

Parameters	A	B	C	D	E
Bulk density	0.658	0.598	0.620	0.520	0.685
Tapped density	0.696	0.652	0.852	0.456	0.657
Carr's index	5.27	6.12	5.45	8.85	7.69
Hausner ratio	1.039	1.064	1.069	1.059	1.053
Flow time 100 ml/s	25.7	Poor flow	Poor flow	29.54	27.90
Angle of repose	34.59	Poor flow	Poor flow	34.68	34.10

had a Carr's index ranging from 4.47% to 8.69%, while their hausner ratio was below 1.1.

As for the rheological properties, only sample A of the granulates produced with lactose flowed, whereas the granulates containing starch revealed good flowability, confirming the previously reported positive effect of this disintegrant on the rheological properties.

In vitro dissolution of granulates

The *in vitro* dissolution rate of all prepared granulates [Figure 1] was increased compared to the pure drug, because of the higher hydrophilic character of the systems due to carriers and slight reduction of oxcarbazepine crystallinity.

X-ray diffraction

The diffraction patterns of the oxcarbazepine and oxcarbazepine-PEG 4000 melt granules are depicted in Figures 2 and 3 respectively. The diffractograms of the granulates indicated that the polymorphic form of the drug was maintained substantially unchanged after melt granulation process, and reduction in the degree of

crystallinity was detected in comparison to the pure drug.

Preparation and technological characterization of tablets

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

The technical characterization [Table 4] revealed that the tablets were acceptable in terms of uniformity of mass. The hardness was found to diminish with increase in starch content, while friability values were quite homogeneous. However, considering the disintegration time, tablets A (not containing intragranular starch) were found to be not satisfactory. To overcome this problem, 5% of starch was added to samples A, D, and E prior to compression. This

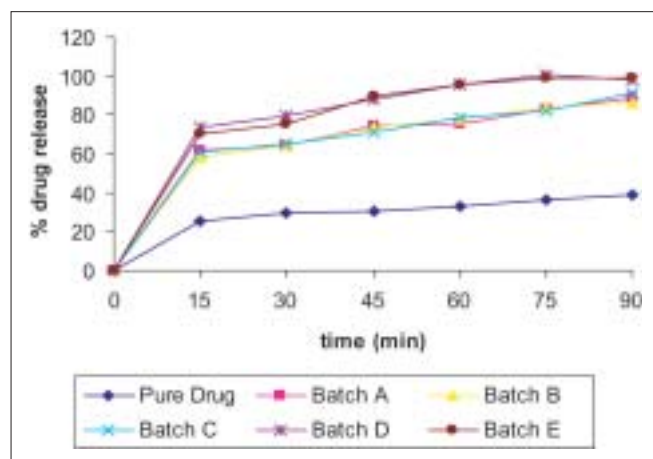


Figure 1: Comparisons of values of percentage drug release of pure drug with those of granulates of PEG 4000

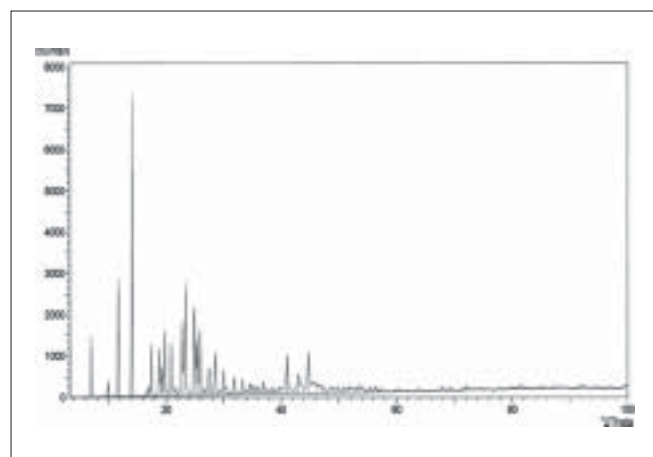


Figure 2: XRD spectra of oxcarbazepine

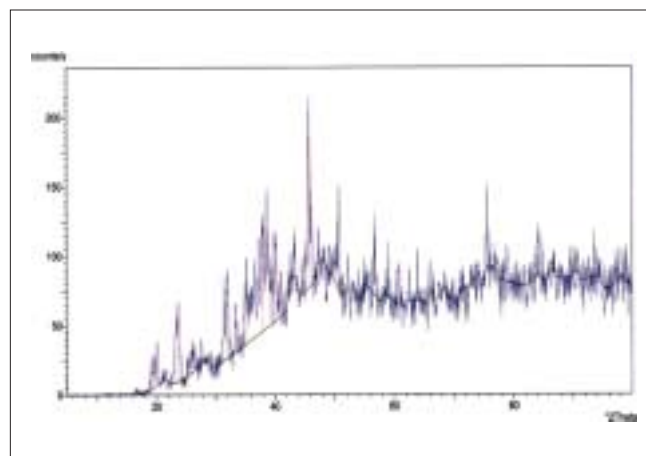


Figure 3: XRD spectra of oxcarbazepine-PEG 4000 melt granules

Table 3: Percentage composition of tablets of oxcarbazepine

Ingredients	A	D	E	F	G	H
Oxcarbazepine	23	23	23	23	23	23
Lactose	61.53	-	46.66	46.67	-	46.67
PEG 4000	7.96	5.98	7.02	8.98	7.96	7.96
Starch ^a	-	66.66	20	-	46.67	10
Starch ^b	-	-	-	20	20	10
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0

Table 4: Technological characterization of the tablets

Batch code for PEG 4000						
Parameters	A	D	E	F	G	H
Mean weight (mg)	658	653	658	642	670	639
Disintegration time (min)	20	6	15	10	5	7.5
Hardness (kg/cm ²)	6.9	5.1	6.2	5.9	6.4	5.7
Friability (%)	0.49	0.12	0.23	0.09	0.83	0.19

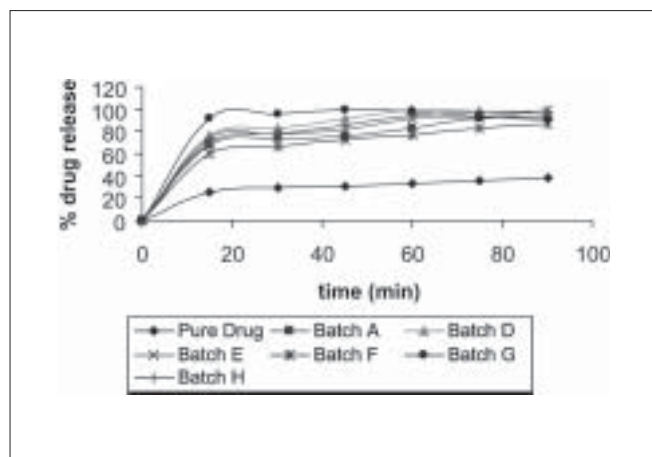


Figure 4: Comparisons of values of percentage drug release of pure drug with those of different formulations of PEG 4000

particularly applies in case of hard granulates, such as those prepared by melt granulation technology. Moreover, the extragranular addition of starch was found to be very useful. Three additional tablet batches were prepared and named F, G, and H respectively. This way, all the tablets were complying pharmacopoeia requirements and obtaining a sensible reduction of the disintegration time. The addition of starch had only a small adverse effect on tablet hardness.

In vitro dissolution of tablets

As reported in the Figure 4, the time necessary for the dissolution of 90% of the drug was reduced to that of the pure drug, with the only exception of the tablets not containing intragranular starch showing a lower concentration of oxcarbazepine dissolution. Hence, the intragranular addition of starch was necessary not only to favor the disintegration of the tablets but also to promote the de-aggregation of the granules, and thereby the dissolution of the drug.

CONCLUSION

In conclusion, melt granulation has been proved to be a viable process to produce a fast-release dosage form for oxcarbazepine, 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 the polymorphic form. The granules containing starch displayed a significant improvement of *in vitro* drug dissolution profiles and were found to be superimposable to those prepared without disintegrant. However, the intragranular addition of starch 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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