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Original Article

An Improvement of Physicomechanical Properties of Carbamazepine Crystals

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Abstract

In order to improve particle properties, new processes combining granulation and crystallization are being developed. This work deals with the spherical crystallization process by the quasi-emulsion mechanism applied to carbamazepine, a pharmaceutical drug. The aim of the present study was to produce of spherical grains made of mall crystals of a drug that have adequate properties for direct compression when manufacturing tablets. Crabamazepine was crystallized under different conditions and the obtained spherical crystals were examined in terms of flow properties, particle size analysis, compression and dissolution behaviors. Physical characteristics of the crystals were studied for the morphology of crystals using scanning electron microscope, for the identification of polymorphism by x-ray powder diffraction and for thermodynamic properties using differential scanning calorimetry. The results showed that the agglomerates produced at 5°C under stirring rate of 300 rpm had superior flow than other agglomerates. Further more the results suggest that agglomerates flow and pack smoothly from the hopper into the die and that tablets formed from agglomerates attain uniformity in weight due to spherical shape of the treated samples. The results showed that, generally, the treated carbamazepine samples (agglomerated forms) possessed superior mechanical and better dissolution rate characteristics to untreated crystals. The results of DSC and x-ray showed that untreated sample and agglomerates were form III and form I of carbamazepine respectively.

Keywords: Carbamazepine crystallization; Dissolution rate; Mechanical properties; Particle size.

Introduction

The direct compression is a modern method in tablet manufacturing. Many processing steps (granulation, drying, etc.) are limited in direct compression, and additionally, wet technology cannot be used with sensitive drugs**.** The direct compression of a powder depends on its particle size and size distribution, and in connection with this, on its flowability, consistent with the production rates of modern compression technology and also on its bulk density. Tablets are the most convenient form of pharmaceutical dosage forms and are widely used in the chemotherapeutic field. Some drug crystals exhibit appropriate flow and compaction properties, but many materials have very poor flowability and compressibility. For tablet making from the latter materials, one of the possible solutions is to generate directly, during the crystallization step, spherical agglomerates of drug crystals with good flowability and compressibility properties. This possible

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solution recently came into forefront of interest because the habit of the particles (form, particle size, size distribution and surface area) can be changed by the crystallization process. The direct tabletting technique has been successfully applied to numerous drugs on the industrial scale. However, when the mechanical properties of the drug particles are inadequate, this process requires formulations with large amounts of fillers. When preliminary granulation is necessary, the spherical crystallization technique appears to be an efficient alternative for obtaining particle destined for direct tabletting, since crystallization and agglomeration are carried out in a single step without any filler. Two types of method have been described in the literature: the spherical agglomeration (SA) method and the quasi–emulsion solvent diffusion (QESD) method also known as the transient emulsion (TE) method. They are essentially distinguished by the miscibility of the drug solvent complex with the non-solvent (1).

SA method proceeds in three steps. The first one is the selection of the crystallization method to precipitate crystals from solution, i.e., thermal method (temperature decrease or evaporation), physicochemical methods (addition of another solvent, salting out) and chemical reaction. The second step is the choice of the wetting agent that will be immiscible with the solvent of crystallization. Finally, the third step is the hardening of the agglomerates (2).

In QEDS method, a quasi emulsion is formed by droplets of solvent containing the drug. The continuous phase is a liquid in which the drug is immiscible. Crystallization occurs inside the droplets because of the counter diffusion of the solvents through the droplets.

It has been shown that flow and compactibility of carbamazepine powders is very poor (3) so that it is impossible to make tablet with good quality. Therefore, the objective of the present study was to develop spherical agglomerates of carbamazpine crystals for direct compression.

Experimental

Materials

Carbamazepine (CBZ) was obtained from Arasto Pharmaceutical Chemical Inc, Iran. Ethanol and isopropyl acetate (Merck, Germany) were of analytical grade.

Methods

Preparation of agglomerates

Carbamazepine was dissolved in ethanol (good solvent) at 60 °C to make quasi-saturated solution. A required amount of the resultant solution (5% w/v) was poured into mixture of water (poor solvent) and isopropyl acetate (wetting agent) thermally controlled at various temperatures (20, 10 and 5 °C) under agitation with a propeller type agitator with four blades. In order to investigate the effect of stirring rate on carbamazepine agglomerates the above solution was stirred at 300, 400 and 500 rpm for 20 min. The agglomerates were separated from the solution through filtration under vacuum and then were placed in a thin layer in an oven at 60 °C for 3 h.

Measurement of powder flow

Flowability of untreated carbamazepine and agglomerates was assessed by determination of angle of repose and Carr's index (CI). Angle of repose was determined by fixed funnel method (4) .The mean of 6 determination was reported. The CI was calculated from the poured and tapped densities. Tapped density was determined by tapping the samples into a 25 ml measuring cylinder using a tapping machine. The CI was calculated according to the following equation (5).

$$CI=[(\text{Tapped density}-\text{Bulk density})/\text{Tapped density}]\times 100 \quad \text{Eq.1}$$

Particle size analysis

A total of 25 g of material was sieved using an Erweka vibration sieve (Erweka, Germany) through a nest of sieves. The vibration rate was set at 200 strokes/min and the sieving time was 10 min. The powder fractions retained by the individual sieves were determined and expressed as mass percentages.

Packability

The packability was evaluated by the tapped density according to Kawakita (6) and Kuno's (7) equation as follows

$$(n/C) = (1/ab)+(n/a) \quad \text{Eq. 2}$$

where n is the tap number, C denotes the volume reduction which can be calculated according to the equation 3, 1/a defines the degree of volume reduction at the limit of tapping, termed compactibility and 1/b is a constant related to cohesion, termed cohesiveness (6).

$$C = (V_0-V_n)/V_0 \quad \text{Eq. 3}$$

where V_0 and V_n are the powder bed volumes at initial and n-th tapped state, respectively.

The plot of n/C versus n is linear and the compactibility 1/a and cohesivity 1/b are obtained from the slope (1/a) and the intercept (1/ab) of the plot of the modified Kawakita equation (6).

The data were also analysed by Kuno (7) equation:

$$\text{Ln}\,(\rho_f-\rho_n) = -kn+\ln\,(\rho_f-\rho_0) \quad \text{Eq. 4}$$

where ρ_f, ρ_n and ρ_0 are the apparent densities at equilibrium, nth tapped and initial state, respectively, and k is the constant.

Scanning electron microscopy (SEM)

The morphology of crystals was examined using a scanning electron microscope (LEO 440i, Cambridge, UK) operating at 15 kV. The samples were sputter-coated with gold before examination.

X -ray diffraction of powder (XRDP)

XRDP data were recorded at room temperature on a Seimens (Model D5000, Germany) x-ray diffractometer at 40 kV, 30 mA and a scanning rate of 0.06º min^{-1} over a range of 2-40 2θ, using $CuK_{\alpha 1}$ radiation of wavelength 1.5405 Å. Samples, round into powders with a mortar and pestle, were measured on a low background quartz plate in an aluminum holder.

Differential Scanning Calorimeter (DSC)

Thermograms of carbamazepine crystals were recorded on a Shimadzu DSC 60 (Japan). Samples (4-5 mg) were placed in aluminum pans and the lids were crimped. The samples were heated ranging from 25-200 °C at the rate of 40 °C min^{-1}. Melting point was automatically calculated. The instrument was calibrated with an indium standard.

Preparation of compacts

The agglomerates and the original crystals (untreated samples) were directly compacted using 8 mm flat-faced punches on a hydraulic press (Riken Seiki Co, Japan). The material for each tablet was weighed (100 mg), introduced into the die and compacted at various compression pressures of 10, 20 and 30 MPa. The compaction surfaces were lubricated with 1% w/w magnesium stearate in ethanol before compaction. The compacts were held under load for 30 s, ejected and stored in screw-capped bottles for 24 h before using, to allow for possible hardening and elastic recovery.

Tablet Crushing Strength

The force required to fracture the compacts on a motorized tablet hardness tester (Erweka, Germany) was measured to determine tablet crushing strength. The results are the mean and standard deviations of a minimum of 5 determinations.

In vitro dissolution

The dissolution tests were performed to the rotating paddle method (USP pharmacopoeia 24). A dissolution apparatus (Erweka, Germany) was employed with a stirring rate of 100 rpm. The dissolution medium was 900 ml containing 1% sodium lauryl sulphate aqueous solution maintained at 37±0.1°C. A suitable amount (18 mg) of CBZ for sink condition was dispersed in 900 ml of the dissolution medium. Samples of the solution were withdrawn at definite time intervals (10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150 and 160 min). The solution was passed through a membrane filter (0.45µm) and then the concentration of carbamazepine in solution was measured with an ultraviolet spectrophotometer (Shimadzu 120A, Japan) at a wavelength of 285 nm

Results and Discussion

Formation of spherical agglomerates

A three-solvent system was utilized to

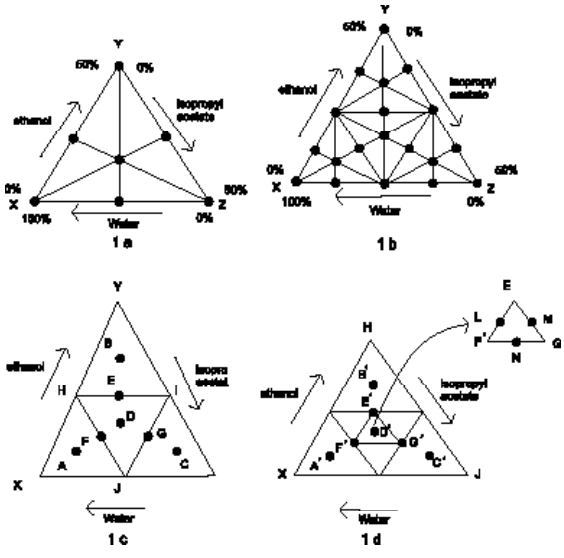

Figure 1. Scheffe ternary diagrams of ethanol-isopropyl acetate-water.

produce the spherical agglomerates. The drug was first dissolved in ethanol (good solvent) at 60 °C. Then the resultant solution was poured into mixture of water (poor solvent) and isopropyl acetate (bridging liquid). The addition of the bridging liquid promotes the transfer of the drug to a third emulsified phase in which crystal agglomerates densify and grow spherically. To optimize carbamazepine spherical crystallization by the ethanol / water / isopropyl acetate system, several parameters were considered. Among these are the difference in temperature between that of ethanolic solution of carbamazepine (T_1) and that of water (T_2) and the stirring rate. To optimize the formation of carbamazepine spherical agglomerates, special attention has to be given to the difference between the solution temperature T_1 and the nonsolvent temperature T_2. The solution temperature was kept constant (60 °C) whereas the nonsolvent temperature was varied (5, 10 and 20 °C) (8). Since the stirring rate during a crystallization procedure could have a profound effect on crystal product, particularly on the crystal size distribution, thus various stirring rates (300, 400 and 500 rpm) were applied.

At first, it must be noted that alcohol is miscible in any proportion with water and isopropyl acetate. On the other hand, isopropyl acetate is miscible with 23 parts of water. Consequently, if a ternary diagram is envisaged, water and isopropyl acetate make an emulsion in a large area of this diagram. We have demonstrated that a very concentrated carbamazepine solution in alcohol must be used to obtain sufficient consolidation of spherical agglomerates. This was the reason why we chose to use a quasi-saturated solution of carbamazepine.

To find the best proportion of the three liquids for the formation of crystal agglomerates, a ternary diagram was built. The chosen model was an experimental design according to the Scheffe design. According to this model, seven experiments were still to be carried out (Figure 1a). If the parallels to the three sides of the triangle are drawn through the middle of the sides, four new triangles are traced on which seven points are determined in the same way as far for the first triangle. As some points are common to both triangles, 19 points can be identified (Figure 1b).

The points on the vertex corresponded to the mixture of only two liquids. Since the presence of three liquids is compulsory, these points must be excluded, seven points remain for the experiments: A, B, C, D, E, F, and G (Figure 1c). The observations for these 7 points are

Table 1. Results of the experiments corresponding to the seven points of the Scheffe Ternary diagram in Figure 1c.

sample	Ethanol (%)	Water (%)	Isopropyl acetate (%)	comment
C	8	59	33	Two liquid phases
G	12.5	62.5	25	Two phases, crystals at the interface
D	17	66	17	Two phases, flocs at the interface
E	25	62.5	12.5	Same as C
B	33	59	8	Crystals in one phase medium
F	12.5	75	12.5	Round agglomerates+crystals
A	8	84	8	Agglomerates in one phase medium

Table 2. Results of the experiments corresponding to the seven points of the Scheffe ternary diagram in Figure 1d.

[illegible]	Ethanol (%)	Water (%)	Isopropyl acetate (%)	[illegible]
A'	5	91.25	3.75	Very dense suspension
F'	6.25	87.5	6.25	Agglomerates in a cos plasma medium
G'	6.25	81.25	12.5	Flocs
C'	5	78.75	16.25	Two phases, flocs at the interface
D'	8.75	83.75	7.5	Flocs
E'	12.5	81.25	6.25	Agglomerates in a cos plasma medium
B'	17.5	78.75	3.75	Very dense suspension

reported in Table 1. For the thorough study, triangle XHJ was more closely investigated after division into four triangles in the same way as previously described. The new points were A',B',C',D',E',F',and G'(Figure 1d). The resulting observations for these 7 new points are stated in Table 2. The last investigation of some points in the F', E', G' zone (L, M, N) enable us to find the best proportion for spherical crystal formation (Figure 1d). The observations for L, M and N are reported in Table 3. The results showed that the optimal ratio for spherical crystal formation is found on the L zone; and these proportion for alcohol / water / isopropyl acetate were then finally selected to investigate the effects of stirring rate, and the difference in temperature between the carbamazepine solution (T_1) and nonsolvent (T_2) during crystallization on the physicomechanical properties of spherical agglomerates (Table 4).

Micromeretics properties of agglomerated crystals

In order to achieve uniformity in tablet weight, the feed crystals must flow and pack smoothly into the die cavity of the tabletting machine. Therefore, it is an essential purpose of particle design for direct compression to improve the flow and packing properties of pharmaceutical powders. The results of the effect of temperature and stirring rate on micromeritics properties of the agglomerated carbamazepine are shown in Table 6. The Table shows that the flowability that represented in terms of the angle of repose and Carr's index in most of agglomerates was much improved compared to those of the original powders (untreated carbamazepine). Two way analysis of variance showed that there were significant differences ($p<0.05$) between the angle of repose and Carr's index of the agglomerated samples.

The results showed that the agglomerates produced at 5 °C under stirring rate of 300 rpm (F1) had superior flow than other agglomerates (low angle of repose and Carr index). The agglomerates were easily packed by tapping, the process of which was described by Kawakita's and Kuno's equations (6, 7). As shown in Table 5 the smaller values of parameter a in Kawakita's equation for the agglomerates indicated their higher packability than the original powder. The apparent packing velocity by tapping, represented by parameter b, for agglomerates was slower than that for conventional crystals, since agglomerates were packed closely even without tapping due to their excellent flowability and packability. The large values of parameter k in Kuno's equation for the agglomerates indicated that the rate of their packing process was much higher than that of the original crystals. These findings suggest

Table 3. Results of the experiments corresponding to the three points of the Scheffe ternary diagram in Figure 1d.

[illegible]	Ethanol (%)	Water (%)	Isopropyl acetate (%)	[illegible]
L	10	83.75	6.25	Spherical crystals
M	10	81.25	8.75	Two phases, flocs at the interface
N	6.3	83.75	8.75	flocs

Table 4. Different crystallization conditions for L-zone (ethanol 10%, Isopropyl acetate 6.25%, water 83.75%).

Sample	nonsolvent temperature (°C)	stirring rate (rpm)
F1	5	300
F2	5	400
F3	5	500
F4	10	300
F5	10	400
F6	10	500
F7	20	300
F8	20	400
F9	20	500

Table 5. Parameters of packability of conventional carbamazepine crystals and agglomerated samples.

Materials	a[a]	b[b]	1/b
Conventional crystal	0.312	0.133	7.519
F1	0.093	0.034	29.412
F2	0.109	0.072	13.826
F3	0.109	0.032	31.348
F4	0.061	0.037	27.019
F5	0.243	0.040	25.013
F6	0.230	0.084	11.914
F7	0.387	0.105	9.518
F8	0.130	0.074	13.516
F9	0.376	0.119	8.418

[a] parameter in Eq.2.
[b] parameter in Eq. 4

that agglomerates flow and pack smoothly from the hopper into the die and that tablets formed from agglomerates attain uniformity in weight.

SEM of original crystals and agglomerated are shown in Figure 2. It is clear from the micrographs that the agglomerate of carbamazepine has larger particle size. This could be one of the reasons for the excellent flowability and packability of the agglomerates. Figure 2 also shows that the agglomerates are spherical in shape compared to conventional crystals. On the basis of these findings, it could be concluded that good flowability and packability for agglomerates were attributable to the spherical shape and smooth surface, since the area of contacts in the powder bed for spherical agglomerates was smaller than that for plate shaped conventional crystals. The micrographs show that agglomerated particles are in spherical shape, whereas the untreated carbamazepine has irregular shape. The spherical single particle is formed by very small needle-shaped crystals, which are closely compacted into a spherical form, as is clearly evident when the crystal surface is enlarged (Figure 2c).

The results in Table 5 show that bulk density in general increases with ΔT (T_1-T_2) and bulk density assumes a maximum value with the high ΔT. Results show that stirring exerts no significant effect on the bulk density in the case of high ΔT but in the case of intermediate ΔT bulk density decreases with stirring rate. While in the case of slow cooling bulk density shows maximum value with the intermediate stirring

Table 6. Micromeritics properties of untreated carbamazepine powders and the agglomerates.

Samples	Bulk density (g/cm³) (n=3)	Tapped density (g/cm³) (n=3)	Angle of repose (°) (n=6)	Carr's Index (%) (n=3)
Conventional crystals	0.583±0.000	0.847±0.012	41.0±1.0	31.1±0.9
F1	0.719±0.001	0.239±0.003	16.4±0.1	8.4±0.7
F2	0.728±0.002	0.254±0.005	19.1±2.0	10.6±0.8
F3	0.728±0.002	0.251±0.002	17.4±0.3	11.4±1.2
F4	0.717±0.001	0.225±0.000	20.6±1.1	5.3±0.6
F5	0.783±0.001	0.282±0.002	29.0±0.3	22.6±1.0
F6	0.781±0.001	0.257±0.002	13.3±0.9	22.1±0.9
F7	0.163±0.002	0.282±0.005	28.3±0.3	38.3±1.1
F8	0.784±0.002	0.236±0.002	16.3±2.0	13.5±1.3
F9	0.184±0.001	0.288±0.005	28.3±0.8	36.3±0.9

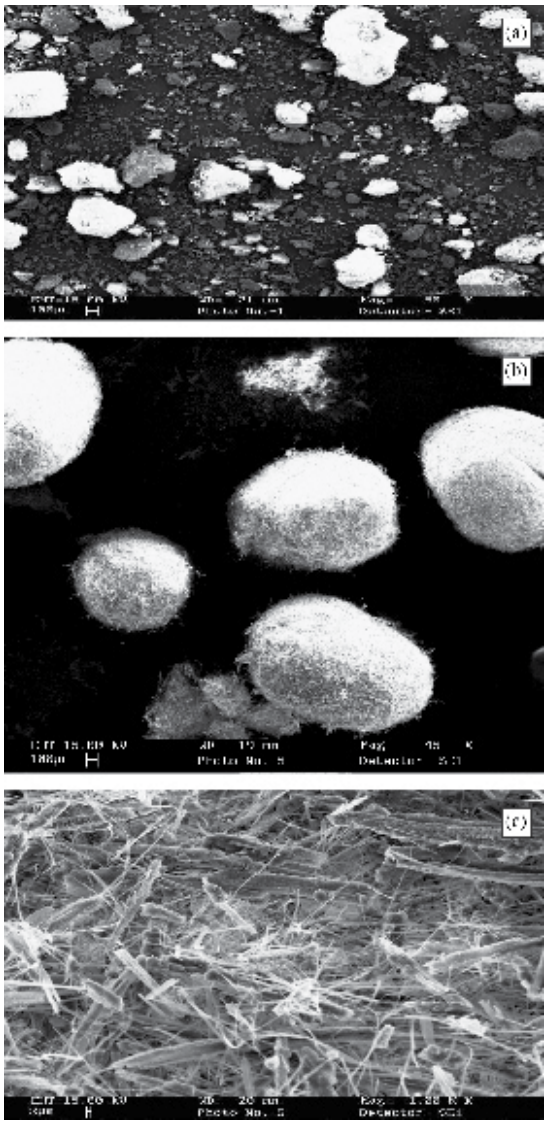

Figure 2. Micrographs of carbamazepine samples: (a) untreated×50 ; (b) agglomerates×45; (c) agglomerates×1000.

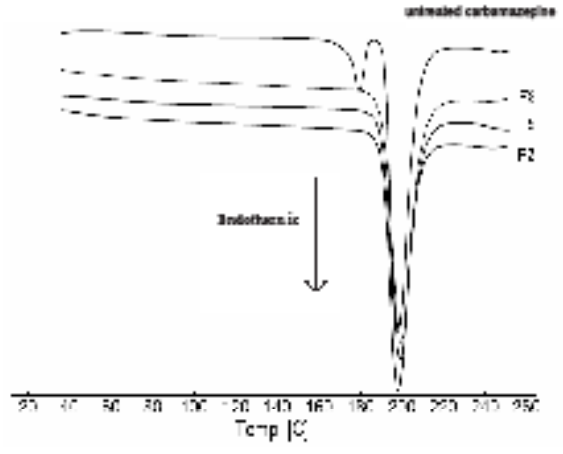

Figure 3. Thermograms of different carbamazepine crystals (for clarification of the legends, please refer to Table 4).

rate (400 rpm). Theses changes of bulk and tapped densities should be related to size, shape, surface roughness and density (compactity) of the agglomerates. Smaller, less spherical, rougher and less compact agglomerates contribute to looser packing and smaller bulk and tapped density due to greater interparticle contact area and friction (9).

In order to better analyse the effect of stirring rate and ΔT on particle size of carbamazepine agglomerates, the resultant particle size distribution for each sample was listed in Table 7. The particle size distribution for the samples produced under different conditions was found to be different. The commercial (control) carbamazepine has smaller particle sizes (the mean particle size was 15 μm). The size of 94% of the crystals is less than 20 μm, whereas, most of the agglomerated samples fall between 500-1180 μm. Table 7 also shows the effect of crystallization conditions on the particle size distribution of agglomerated samples. The results of stirring rate and ΔT on the size of carbamazepine agglomerates are also listed in Table 7. It can be seen from the table stirring rate has significant effect on particle size distribution. As the stirring rate was increased the particle size of agglomerates was decreased. For example when the stirring rate was increased from 300 (F1) to 500 rpm (F3) at a constant ΔT, about 90 and 37% of particles fell in larger than 1180 μm respectively. Similar results were obtained for particle size distribution of agglomerated samples at other ΔT. As shown in Table 7, an increase in stirring rate resulted in a reduction in the mean particle size of carbamazepine agglomerates. During the preparation of agglomerates the increased mechanical shear force, produced by increasing the stirring rate, rapidly broke up the solution of drug into finer droplets, leading to finer agglomerates. However, agglomerates were not formed well at low stirring rates (10). This table also shows that a reduction in the ΔT resulted in a decrease in particle size. For example when the ΔT was decreased from 55 (F1) to 40°C (F7) at a constant stirring rate of 300 rpm, the

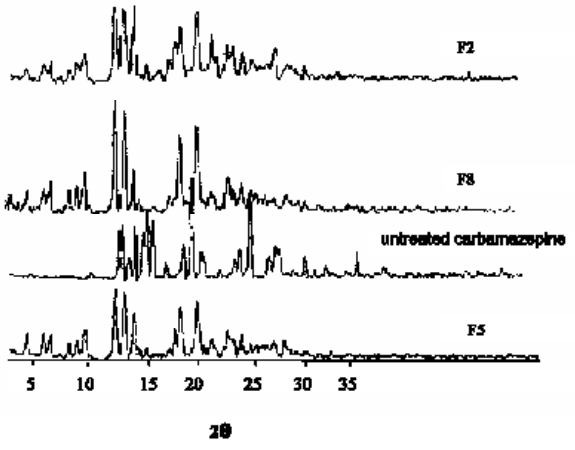

Figure 4. X-ray diffraction patterns of different carbamazepine crystals (for clarification of the legends, please refer to Table 4).

percentages of particle size of treated samples less than 1180 were 90 to 29.7 respectively. Similar results were obtained at stirring rates of 400 and 500 rpm. In fact, a high ΔT and slower stirring rate are very favourable in the building-up of crystal agglomerates with larger particle sizes.

Solid-state characterization

Differential scanning calorimetry curves of agglomerates and untreated carbamazepine are illustrated in Figure 3. DSC thermograms at 40°C/min of untreated carbamazepine showed two endotherms of fusion. The first peak corresponded to the melting of form III (179°C), followed by exothermic crystallization as polymorph I (185°C), which subsequently melted at 197°C (10). It has been shown that the DSC traces of carbamazepine samples particularly for form IV depend on the analytical heating rate, and it was possible to observe different pattern at different heating rates due to differences in the rate of transformation of form IV or III to form I (11). The DSC curve of agglomerated carbamazepine samples (F2, F5 and F8) exhibited only one sharp endotherm at 190°C. These findings showed that untreated sample and agglomerates were form III and form I, respectively (12).

X-ray powder diffractometry (XRPD) is a powerful technique to identify the various polymorphs of carbamazepine. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. Commercial carbamazepine showed a pattern identical to carbamazepine USP reference standard (Figure 4) and the data obtained in the present study were in good agreement with those published for polymorph III by Lowes et al (13). Characteristic high-intensity diffraction peaks were detected at 2°θ =14.9, 15.2, 15.8, 27.2, 27.5 and 32.0. Further, the most providing identification is the absence of peaks from 2 to 10°2θ. X-ray powder diffractograms of prepared samples (Figure 4) were in good agreement to those published for form I by Kala, Krahn and coworkers (14, 15) in which typical signals were recorded at 2°θ=6.1, 9.4, 12.25, 19.8, 19.9 and 22.8.

Table 7. The effect of ΔT and stirring rate on the particle size distribution of agglomerated carbamazepine (n=3).

Samples	% frequency						Mean particle size ± σ (μm)
	<500 (μm)	500-710 (μm)	710-850 (μm)	850-1000 (μm)	1000-1180 (μm)	>1180 (μm)	
Untreated	100	-	-	-	-	-	15±4
F1	-	-	2	2	6	90	1150±330
F2	-	2	5.3	7.4	23.3	63	1100±300
F3	-	7	11	15	30	37	1030±260
F4	-	0.97	1.9	4.8	6.8	85.63	1142±240
F5	-	2.5	3.4	10.1	48	36	1083±230
F6	1	4.1	7.1	11.2	30.6	46	1065±240
F7	1	3.2	8.5	22.3	35.3	29.7	1020±260
F8	2	6.8	14.8	17.6	34.3	24.5	991±220
F9	10.4	7.8	20	25.2	27.8	8.8	853±260

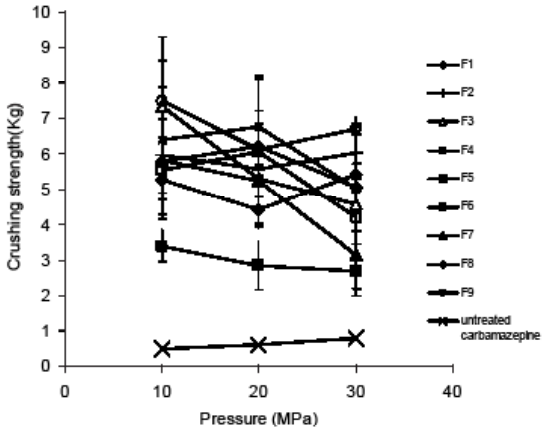

Figure 5. The crushing strength of the tablets made from untreated and agglomerated carbamazepine samples (for clarification of the legends, please refer to Table 4).

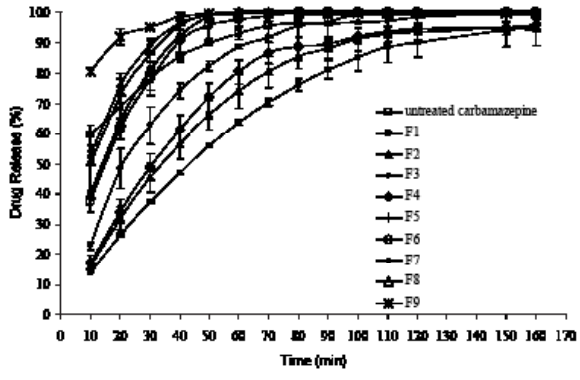

Figure 6. Dissolution profiles of agglomerates and untreated carbamazepine powders (for clarification of the legends, please refer to Table 4).

Compression

Good compactibility and compressibility are essential properties of directly compressible crystals. Compactibility of samples was evaluated based on the crushing strengths of the compact compressed at different compaction pressures. The influence of compression pressure on the crushing strength of tablets made from different carbamazepine particles is shown in Figure 5. It can be seen from the Figure that the crushing strength of untreated carbamazepine tablets are close to zero. This is due to high capping tendency of these tablets under compression. The results showed that all treated carbamazepine samples (agglomerated forms) possessed superior mechanical characteristic to untreated crystals. Agglomerates were compressed into compacts having considerable hardness without capping up to 30 MPa. The crushing strength of some agglomerates decreased at 30 MPa because some capping occurred. In particular, untreated carbamazepine in spite of small particle size, could not be transformed to tablets and produced weak compacts with a high tendency to capping at all compaction pressures and slugging was required to make a coherent tablet from untreated carbamazepine, whereas spherical crystals formed a coherent tablet under direct compression. Thus, the spherical crystals are directly compressible, which could be a result of the new clear surface formed during compression. The high crushing strengths of the tablets are indicative of stronger interparticulate bondings between the agglomerates compared to the untreated carbamazepine. The improved compactibility of agglomerates may be attributed to their structural characteristics (Figure 2c). It has been shown that a reduction in bulk density results in an increase in the crushing strength of tablets (16). Similar results were obtained in this study. Results showed that there were no significant difference between the crushing strengths of tablets made from the agglomerates at 10 and 20 MPa ($p>0.05$).

Dissolution

Dissolution of a drug depends on the physicochemical and physicotechnical properties of drug particles. These crystal attributes directly affect the absorption kinetics of a drug and thereby bioavailability of dosage forms. This assumes greater importance for drugs exhibiting low solubility that makes absorption to be dissolution rate-limited. It is established that the modification of the polymorphic state of a compound can bring an increase in solubility. But the influence on other attributes such as stability, biological efficacy, metabolism, etc. as a result of change in polymorphic state demands a thorough investigation while using this approach. Results of the dissolution study for different carbamazepine crystals are shown in Figure 6. They are expressed as a percentage of dissolved drug without considering the shape and particle size or in relation to the original sample surface. The drug dissolution profiles of

agglomerates are comparable with the untreated carbamazepine. However, it must be recalled that the particle size of the untreated carbamazepine is much finer than that of agglomerates (See Table 7). Therefore the dissolution will be faster from agglomerates than from untreated, when it is expressed more realistically as a function of the surface area before dissolution. This could be explained by flat shape of carbamazepine, which can produce very dense aggregates. In deed, the flat faces of the crystals adhere to each other during the dissolution (17). The time required for 75% of drug dissolution from the agglomerated samples were significantly different. The slower drug release from samples F1, F2, F3 and F4, may be attributed to the higher crushing strength of these agglomerates. Because agglomerates did not break due to lack of intragranular disintegrant the slower drug release can be predicted from stronger agglomerates (18).

Conclusion

The spherically agglomerated crystals of carbamazepine were successfully prepared for direct tabletting by the spherical crystallization technique. The micromeretic properties of agglomerates, such as flowability, packability and compactibility were dramatically improved, resulting in successful direct tabletting without capping .The main factor in the improvement of flowability and packability was a significant reduction in interparticle friction, due to their spherical shapes and smooth surfaces. Compressibility of the agglomerates was much improved, due to the increased interparticle bonding of agglomerates fractured during compression. The speed of agitation and ΔT significantly affect the micromeretic and compression properties of the agglomerates. The effect of varing ΔT is probably due to their influence on the amount of drug solubilization. The agglomerates have shown in vitro drug release performance comparable with untreated carbamazepine. Therefore, this technique can be exploited to obtain agglomerates for tabletting.

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