RESEARCH ARTICLE

Preparation and evaluation of polymeric carbamazepin spherical crystals by emulsion solvent diffusion technique

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In this study, a significant effect of different polymers on improving the solubility, dissolution rate, and physicochemical properties of carbamazepine (CBZ) has been demonstareted by emulsion solvent diffusion technique, with ethanol–chloroform–water as the solvent system. The hydrophilic polymers like polyethylene glycol, chitosan, and hydrophobic polymer Eudragit RSPO were used in the recrystallization process. The pure drug CBZ and the prepared spherical crystals of CBZ with different polymers were characterized in terms of morphology (microscopical photograph), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), drug contents, solubility, dissolution rate, crushing strength, wettability, flowability, and packability. The FTIR spectra of the prepared spherical crystals showed that changes in the chemical nature occur and do not present great fingerprint difference. The XRD also revealed a characteristic decrease in crystallinity. The solubility and dissolution studies demonstrated a marked increase in solubility and dissolution rate in comparison with the pure drug. The prepared spherical crystals with different polymers exhibited excellent physicochemical properties like flowability, packability, and wettability compared with the pure drug. The spherical crystals with polyethylene glycol and chitosan showed higher crushing strength when compared with the hydrophobic polymer (Eudragit RSPO).

Key words: *Carbamazepine, crushing strength, packability, quasi-emulsion solvent diffusion system, solubility, wettability*

INTRODUCTION

There are many active pharmaceutical ingredients in pharmaceutical market with unfavorable flowability, solubility, and compressibility due to their irregular crystal habit. Poor compressibility of a specific crystal habit of drug can be attributed to the presence of crystal faces that give poor adhesion to each other and absence of the faces that are required for optimal adhesion.

In 1986, Kawashima *et al.* used the spherical crystallization technique for size enlargement of the drug in the field of pharmacy. Spherical crystallization was defined by Kawashima as "an agglomeration process that transfers crystals directly to compact spherical forms during the crystallization process." It also enables coprecipitation of the drug and the encapsulating polymer in the form of a spherical particle.[1]

Spherical crystallization is the novel agglomeration technique that can directly transfer the fine crystals produced in the crystallization or in the reaction process into a spherical shape. It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transfer crystals directly into a compacted spherical form. This technique of particle designing of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size, and particle size distribution) can be modified during the crystallization process. As a consequence of such modifications in the crystal habit, certain micrometric properties (bulk density, flow property, and compactibility) and physicochemical properties (solubility, dissolution rate, bioavailability, and stability) can also be modified. It had been described as a very effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. It has also been applied to improve the flowability and the compression ability of some powders. Moreover, critical steps involved in wet granulation can be avoided.

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DOI: 10.4103/0973-8398.49170

This technique involves selective formation of agglomerates of crystals that are held together by liquid bridges. This technique could enable subsequent processes such as separation, filtration, drying, etc. to be carried out more efficiently. Furthermore, the resultant agglomerated crystals could be easily compounded with other pharmaceutical powders due to their spherical shape.[2] It is a simple process and inexpensive enough for scaling up to a commercial level, which reduces time and cost by involving faster operation, less machinery, and fewer personnel, with great advances in tabletting technology, especially the introduction of a number of directly compressible excipients. Using this technology, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical processing like milling, mixing, and tabletting because of their excellent flowability and packability.[3] The close cooperation of chemists and pharmaceutical technologists can lead to progress in this field. The spherically agglomerated crystals can be prepared in tablet form or compounded directly into a pharmaceutical system without further processing such as granulation. In addition, this technique may enable in converting to a different polymorphic form and thus attain better bioavailability.

Spherical crystallization is carried out by following methods:

1. Spherical agglomeration method.
2. Quasi-emulsion solvent diffusion system (QESDS).
3. Ammonia diffusion system.
4. Neutralization technique.

Out of these techniques, the QESDS is most commonly used. This method employs three solvents:

1. Good solvent: solvent that dissolves API.
2. Poor solvent: solvent in which API is insoluble.
3. Bridging liquid: solvent that partially dissolves API and is immiscible with poor solvent.[4]

Using this method, spherical crystallization can be carried out by using a mixed system of three partially miscible solvents, i.e. good solvent–bridging liquid–poor solvent. When bridging liquid plus good solvent of API are poured into the poor solvent under agitation, quasi-emulsion droplets of bridging liquid or good solvent forms the emulsion droplets in the poor solvent and induces crystallization of the drug followed by agglomeration.

Carbamazepine (CBZ) is an anticonvulsant, also used for the treatment of pain associated with trigeminal neuralgia. It is a white or yellowish white crystalline powder and exists as stone-shaped crystals, having poor flow properties and compressibility. It has limited aqueous solubility as well as a slower dissolution rate, which is absorbed slowly and erratically after oral administration and requires a higher dose for its effect. This agent belongs to BCS class II. Dissolution is the rate limiting step in its bioavailability. In fact, its solubility and dissolution rate are key factors in its bioavailability. Because of its low water solubility (< 200 μg/ml) and the need for a high dose (200 mg), the CBZ pharmacokinetic profile is irregular. After oral administration, it is slowly and irregularly absorbed through the gastrointestinal tract and, generally, the plasmatic peak has a time lag of 4–8 h.[5]

In the present paper, to overcome the problems related to solubility, dissolution rate, flowability, and compressibility, the spherically agglomerated crystals of CBZ were prepared by a QESDS, which is more convenient and is cheaper. In addition, incorporating hydrophilic polymers (polyethylene glycol, chitosan) and pore-forming hydrophobic polymer (Eudragit RSPO) during crystallization imparted better solubility, dissolution rate, compressibility, and strength.

MATERIALS AND METHODS

CBZ IP was obtained as a gift sample from Bajaj Health Care Pvt. Ltd., Mumbai, India. Eudragit RSPO was obtained from Degussa India Pvt. Ltd. Research Center, Mumbai, India, and water-insoluble chitosan from Central Institute of Fisheries Technology, Cochin (degree of deacetylation, 86%). All other chemicals like ethanol and chloroform were obtained from Loba Chemicals, Mumbai, India.

Preparation of CBZ agglomerates

QESDS crystallization technique

CBZ (2.5 g) was dissolved in the mixture of good solvent ethanol (15 ml) and bridging agent chloroform (5 ml) thermally controlled at 40°C so as to form the saturated solution of the drug. The solution was poured into 80 ml of distilled water (poor solvent) with a stirring rate of 1000± 50 rpm using a propeller type of agitator (Remi Motors Ltd., Mumbai, India) at room temperature. After agitating the system for 10 min, the prepared agglomerates were collected by filtration through Whatman filter paper no. 42 under vacuum. The spherical crystals were washed with distilled water and placed at 45°C for drying in a hot air oven for 24 h and then stored in a desiccator.[6,7]

Incorporation of polymers

Eudragit

Eudragit was dissolved along with CBZ in the mixture of ethanol and chloroform in the ratio drug:polymer mass ratio (1:0.05).

Polyethylene glycol 4000

It was dissolved in distilled water rather than CBZ and the mixture of ethanol and chloroform was added to it in the ratio of drug:polymer mass ratio (1:0.05).

Chitosan

One percent solution of Chitosan in acetic acid was first prepared and then this solution was poured into 80 ml of distilled water before starting the procedure. The polymer used was in the ratio drug:polymer mass ratio (1:0.03).

The production yield of all the above agglomerates was found to be between 90 and 95. The codes of the prepared spherical crystals of CBZ are given in Table 1.

Evaluation of spherically agglomerated crystals

Thin layer chromatographic study

The study was carried out using silica gel G as a coating substance with a mixture of 95 ml toluene and 5 ml methanol as the mobile phase. The quantity of the spherical crystals equivalent to 0.20 g of CBZ was dissolved in 10 ml chloroform. The solution was filtered and the filtrate was evaporated to dryness. The residue was dissolved in 10 ml chloroform and 10 µl of this solution was applied to the chromatographic plate. The plate was dried in air for 15 min. Visualization was carried out by sprinkling 0.5% w/v solution of potassium dichromate in a mixture of 1 volume of sulfuric acid and 4 volumes of water. The R_f value of commercial crystals to the prepared spherical agglomerates of CBZ was compared. The method was carried out in triplicate ($n = 3$).

Detection of drug content in spherically agglomerated crystals by a spectrophotometer

Prepared CBZ agglomerates equivalent to 100 mg of CBZ was accurately weighed, crushed, and transferred to a 100 ml standard conical flask. To this, 10 ml of ethanol was added and sonicated for 20–25 min in a sonicator (Model-3.5 l 100, PCI, India) so as to dissolve the drug and the polymer. The volume was made up to 100 ml with 1% SLS and filtered through a Whatman filter paper. From the resulting filtrate, 1 ml solution was taken and diluted to 50 ml so as to form 20 µg/ml and the absorbance was measured at 288 nm against a blank reagent using a UV visible spectrophotometer (Pharma Spec 1700, UV Vis Spectrophotometer; Shimadzu Corporation, Kyoto, Japan). The concentration of the drug present in the formulation was computed from the calibration curve. Each sample was assayed to triplicate ($n = 3$).[8]

Solubility study

Solubility studies were carried out using deionized water as a solvent. Excessive quantity of CBZ and different spherical crystals of CBZ were taken in a series of screw-capped test tubes with a fixed volume (10 ml) of deionized water. The resulting suspension was treated at room temperature with 100 rpm in an incubator shaker. After 24 h, the samples were withdrawn and filtered through 0.2 µ filters. The filtrate was diluted with deionized water and analyzed at 288 nm by UV Vis spectrophotometry (Pharma Spec 1700, UV Vis Spectrophotometer, Shimadzu Corporation).[9] The study was performed in triplicate ($n = 3$).

Table 1: Codes for prepared spherical agglomerated crystals of CBZ

System	Symbol
Commercial CBZ crystals	CBZ
CBZ:granules	GR
CBZ:ethanol:chloroform	ETH
CBZ:ethanol:chloroform:Eudragit RSPO	EUDRSPO
CBZ:ethanol:chloroform:PEG-4000	PEG
CBZ:ethanol:chloroform:chitosan	CTS

Dissolution study

In vitro dissolution was evaluated using a conventional dissolution test. Powder dissolution studies were carried out first on the pure drug and second on the spherical agglomerated crystals. Each test was carried out in 900 ml dissolution medium at 37°C ($n = 6$) and at a stirring speed of 75 rpm with a six-flasks USP type II dissolution apparatus (Lab India Disso 2000, India, digital dissolution testing apparatus). The dissolution medium used was distilled water with 1% SLS. An accurately weighed quantity of each sample equivalent to 200 mg of CBZ was subjected to the test. To avoid the aggregation of powder in contact with dissolution medium, samples were taken at an appropriate time interval. The volume of the dissolution medium was kept constant throughout the run by replacing the removed samples with an equivalent volume of fresh dissolution medium. Samples were filtered through a 0.44 µ filter, suitably diluted and analyzed at 287.5 nm using a UV Vis spectrophotometer (Pharma spec 1700, UV Vis spectrophotometer, Shimadzu Corporation).

Flow property

Flowability of CBZ and its agglomerated crystals were determined in terms of the following parameters: angle of repose, Carr's compressibility index, and Hausnar ratio.[10]

Packability

Packability was assessed by analysis of the tapping process with the Kawakitas (I) and Kunos (II) method and using the parameters a, b, and k in the equation:

$$N/C = 1/(ab) + N/a \quad (1)$$

where, $C = (V_o - V_n)/V_o$, $a = (V_o - V_\infty)/V_o$, N = number of tapping, C = difference in volume (degree of volume reduction), a and b = constant for packability and flowability, V_o = initial volume, V_n = final volume after n^{th} tapping, and V_∞ = powder bed volume at equilibrium.

The slope 1/a and intercept 1/ab of plot *N/C* verses *N* gives the compactibility a, constant of flowability b, and cohesiveness 1/b.

$$\rho_f - \rho_n = (\rho_f - \rho_o) \cdot \exp.(-kn) \quad (2)$$

where ρ_f, ρ_o, ρ_n are apparent densities at equilibrium, initial state, and n^{th} tapped, respectively. The value of k in Kunos equation was determined directly putting the values of the densities.[11,12]

Powder bed hydrophilicity study

CBZ and prepared spherical agglomerates (0.5 g) were

placed on a sintered glass disk forming the bottom of the glass tube. The whole device was brought into contact with water and adjusted at 1 mm under the surface of water. Some methylene blue crystals were put on the surface of the drug. The time taken for the capillary rising of water to the surface was noted. This time was visualized by the dissolution of methylene blue crystals with the color of the powder surface intensively. The shortest rising time would correspond to the most hydrophilic substance, leading to good wettability.[13] The study was performed in triplicate ($n = 3$).

Crushing strength

It was measured using a 50 ml glass hypodermic syringe. The modification includes the removal of the tip of the syringe barrel and the top end of the plunger. The barrel was then used as a hallow support and the guide tube was used with close fitting tolerances to the plunger. The hallow plunger with an open end served as the load cell in which mercury could be added. A window was cut into the barrel to facilitate placement of the granule on the base plate. The plunger acted as a movable plate and was set directly on the granules positioned on the lower plate as the rate of loading may affect the crushing load (g). Mercury was introduced from the reservoir into the upper chamber at the rate of 10 g/s until the single granule crushed. The loading time was <3 min. The total weight of the plunger and the mercury required to fracture a granule was the crushing load. A minimum of 10 granules were tested and the average load in grams was taken as the crushing strength.[14] The study was performed in triplicate ($n = 3$).

Characterization of spherically agglomerated crystals

Microscopic observation

The shape of the CBZ crystals and the agglomerated CBZ crystals were observed under the microscope and photomicrographed at a suitable magnification.[15]

Melting point determination

The melting points of the spherically agglomerated crystals were determined using the capillary tube method.[16]

FTIR

The spectra were collected on a FTIR spectrophotometer (SHIMADZU Fourier transform infrared spectroscopy model) at 4 cm^{-1} resolution for scans. Samples (about 1% w/w) were mixed with KBr powder and compressed to a 12-mm disc by a hydraulic press at 10 tons compression force for 30 s.

X-ray powder diffraction

XRD spectra of CBZ and its agglomerated crystals were obtained using a Philips Analytical X Part PRD/SRS Division, N.B.B.S. and L.U.P, from Nagpur, India. The cavity of the metal sample holder was filled with the sample and then smoothed with the spatula. A scanning rate of 0.04 2θ s^{-1} over the range of 10–60$_{\infty}$ 2θ using CuK$^{\circ}$ as the tube anode having a wavelength 1.5418A$_{\infty}$ was used to produce each spectrum, which is represented in [Figure 1]. For determination of *d*-value and lattice spacing, use the following formula:

$\lambda = 2d \sin(\theta)$

where, λ = wavelength, and N = order of reflection. Lattice spacing = $n \times d$.

RESULTS AND DISCUSSION

Characterization of spherically agglomerated crystals

Microscopic observation [Figure 2] of raw CBZ crystals and the prepared agglomerated crystals showed that the raw crystals were irregular and stone shaped as compared with the agglomerated crystals, which were spherical in shape and were composed of minute needle-like crystals. We can conclude that polymorphism or solvation would have occurred during the agglomeration process.

The spherical agglomerates showed a lower melting point as compared with the raw crystals of CBZ. The lower melting

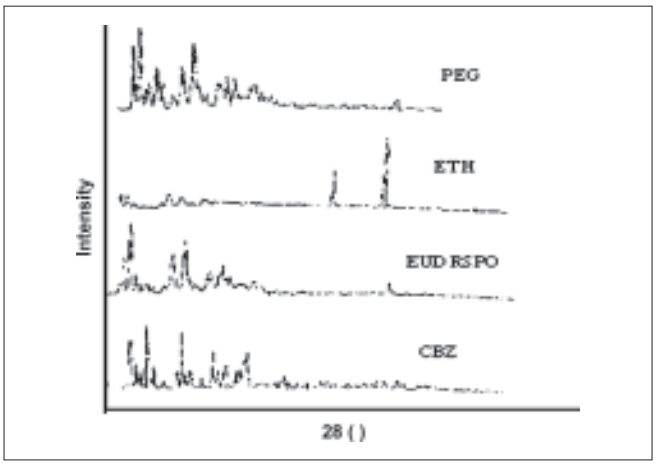

Figure 1: X-ray powder diffractograms of carbamazepine and its spherically agglomerated crystals

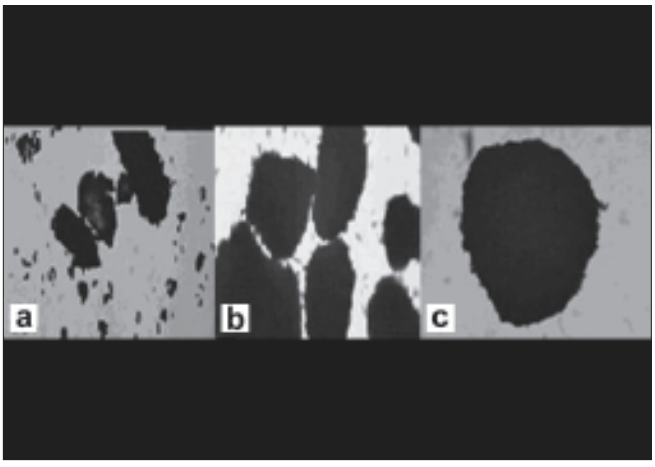

Figure 2: Photographs of raw carbamazepine (CBZ) crystals and its agglomerated crystals. (a) Raw commercial available CBZ crystals, (b) agglomerated crystals of CBZ, and (c) single agglomerated crystals

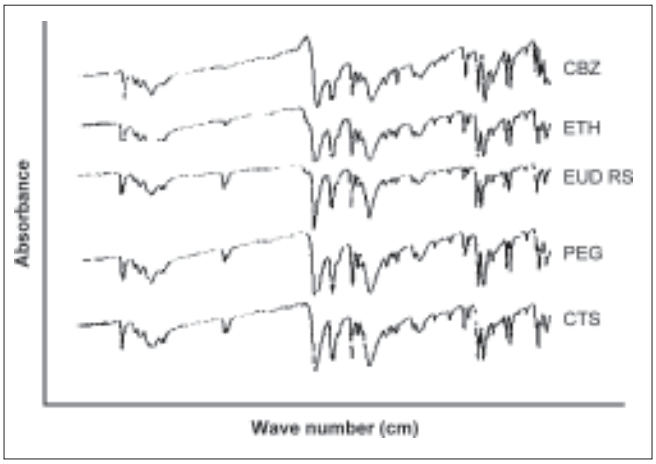

Figure 3: Fourier transform infrared spectroscopy spectra of carbamazepine and its spherically agglomerated crystals

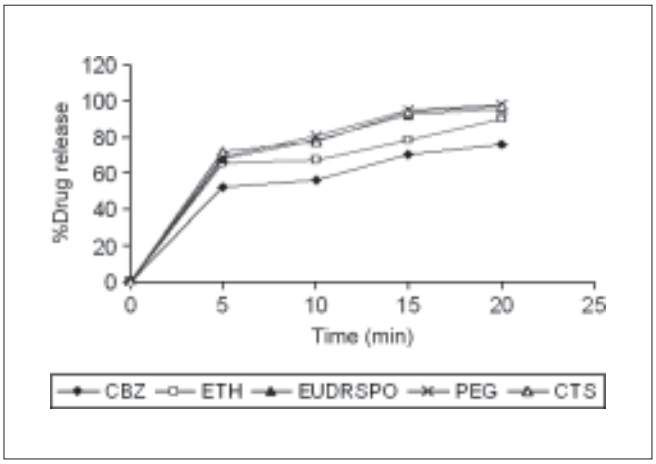

Figure 4: Dissolution study of carbamazepine and its different spherically agglomerated crystals

point observed in the recrystallized samples as compared with the raw crystals may be attributed to the variation in crystallinity due to the alteration in the packing arrangement of the molecules in the crystals and the altered hydrogen bonding.

The IR spectra [Figure 3] of the spherical crystals showed that no changes occurred in the chemical nature and did not present a great fingerprint difference.

Investigation of the X-ray diffractograms [Figure 4] revealed a number of changes in the location of the peaks (appearance and disappearance) of the different crystal forms of agglomerates with respect to CBZ. There is difference in d-spacing between the XRD spectra of CBZ and the agglomerated samples, referring to the habit modification and change in the intensity of the peaks, which indicate a different arrangement of the molecules hence confirming the development of a different polymorphic form. A few diffuse peaks or decrease in crystallinity were observed in the agglomerated crystal chitosan (CTS) in which chitosan polymers were used, which may indicate a slight physical interaction of the drug with the polymers.

Solubility of CBZ in a different solvent

From the solubility study of CBZ in different solvents, the drug showed solubility (mg/ml) in chloroform (98.93), ethanol (49.52), and water (0.161). From the solubility data of CBZ, the good solvent (ethanol), bridging liquid (chloroform), and poor solvent (distilled water) were selected for the spherical crystallization process. Chloroform was chosen as bridging liquid because of its excellent drug wettability and immiscibility with the dispersion medium.

Quantity of the selected solvent was determined using the Scheffe third degree incomplete model.[17] The optimized temperature and agitation speed for drug solution and dispersion medium was 25°C and 1000 ± 50 rpm respectively. Table 2 indicates the optimization of drug:polymer mass ratio. The drug to polymer mass ratio was 1:0.05 for Eudragit and polyethylene glycol and 1:0.03 for chitosan for formulation of spherical crystals.

Quasi-emulsion solvent diffusion method

The method used for the preparation of agglomerated crystals was the Quasi-emulsion solvent diffusion (QESD) method in which droplets of the solvent formed the quasi emulsion. The continuous phase is a liquid in which the drug solution is immiscible and crystallization occurs inside the droplets because of counter diffusion of solvents through the droplets. The average diameter of the agglomerated crystals increased with increasing content of chloroform in the system due to

Table 2: Selection of the drug:polymer ratio for the spherical crystallization process

Name of the polymer	Drug:Polymer mass ratio	Appearance of the agglomerated crystals
Eudragit	1:0.03	Less agglomeration and presence of flocs
	1:0.05	Spherical-shaped agglomerates
	1:0.08	Large irregular-shaped agglomerates
Polyethylene glycol	1:0.03	Less agglomeration
	1:0.05	Perfect spherical agglomerates
	1:0.08	Irregular loosely arranged flocs
Chitosan	1:0.03	Optimized size and spherically agglomerated crystals
	1:0.05	Large agglomerates
	1:0.08	Large irregular-shaped agglomerates

the enhanced agglomeration of powdery crystals. When the amount of ethanol in the system was increased while the amount of chloroform was kept constant, the diffusion rate of ethanol and chloroform from the droplets were enhanced with increasing the content of ethanol in the system. The increase in the diffusion rate of chloroform from the droplets shortens the agglomeration process of the crystals produced in the droplets. Decrease in the chloroform content of the droplets reduces the agglomeration force of the crystal due to an increase in the unwetted part of the crystals with chloroform in the agglomerates resulting in the formation of flocks produced with pendular bridges of water. Thus, diameter and recovery of agglomerates decreased with increasing the ethanol content in the system. The all-agglomerated crystals showed a drug content between 97 and 99%.

Evaluation of different CBZ agglomerated crystals

A thin layer chromatographic study was carried out to confirm the stability of the drug in solvent and the drug polymer interaction. From the R_f value of CBZ and its different agglomerated crystals, it was observed that there is an insignificant difference (ns $P > 0.05$) in R_f values, which indicates that the drug is stable in solvent ethanol and chloroform at 55°C and does not interact with the polymers used in the agglomeration process.

The solubility study was carried out in distilled water. The solubility of CBZ in distilled water was 0.161 mg/ml. There is significant improvement in ($P < 0.01$) the solubility of spherically agglomerated crystal ethanol (ETH) in distilled water, 0.293 mg/ml. This may be due to changes in the crystal forms because of different habit, structure, and surface modification. And, in some instances, solvents included into the crystal forms solvets or clathrates that change the surface properties and the reactivity of the drug particles and the internal energy of the molecules, playing an important role in increasing solubility.

Table 3 indicates the evaluation parameters of different agglomerated crystals.

The solubility of Eudragit RSPO, polyethyleneglycol (PEG), and CTS is also significantly improved ($P < 0.01$) as compared with CBZ raw crystals. The solubility of EUDRSPO, PEG, and CTS in distilled water was found to be 0.307, 0.338, and 0.347 mg/ml, respectively.

The use of the polymer Eudragit showed a decrease in the particle size of the agglomerates, an increase in the sphericity, surface roughness, and intraparticle porosity. Increase in sphericity because of the ability to form micelles due to the presence of a quaternary group in the structure (Eudragit RSPO) is also responsible for increase in the solubility of CBZ. The CBZ accompanied with this polymer showed increased intraparticle porosity, suggesting the absence of polymer deposition in the empty spaces between microcrystals in the agglomerates. The agglomerated crystals prepared by incorporating water-soluble polymers can improve solubility. In the present work, addition of polyethylene glycol water-soluble polymer increased the solubility of CBZ in water as well as in the dissolution medium. The use of hydrophilic bursting polymer in 1% acetic acid solution showed an increase in the solubility of CBZ.[18]

Flowability of the spherically agglomerated crystals was studied in terms of angle of repose, Carr's index, and Hausnar ratio. CBZ crystals have a significantly higher angle of repose ($P < 0.01$) in comparison with the spherical agglomerates, which could be due to the irregular shape of the crystals, which hindered in the uniform flow of crystals from the funnel. The reason for the excellent flowability of spherical crystals is the significant reduction in the interparticle friction because of the perfect spherical shape and the larger size of the crystals. The Carr's index revealed that the flowability of the CBZ was significantly poor ($P < 0.01$) than that of the agglomerated crystals, i.e. these agglomerates had a lower Carr index than CBZ raw crystals. The Hausnar ratio of the agglomerated crystals was found to be less than 1.25, which also indicates improvement in the flowability of the agglomerated crystals.[19]

The packability profile of the agglomerated crystals from

Table 3: Evaluation parameters of CBZ and its spherically agglomerated crystals

Crystal code	CBZ	GR	EUDRSPO	PEG	CTS
Production yield*	100 ± 0.25	97.22 ± 0.21	97.26 ± 0.19	97.11 ± 0.27	97.39 ± 0.22
R_f values in TLC study*	0.29 ± 0.02	0.28 ± 0.03	0.29 ± 0.03	0.29 ± 0.02	0.29 ± 0.02
Solubility (mg/ml)*	0.16 ± 0.03	0.15 ± 0.02	0.31 ± 0.03	0.34 ± 0.02	0.35 ± 0.03
Wettability (h)*	16 ± 0.56	15 ± 0.59	9.5 ± 0.29	6 ± 0.24	6.8 ± 0.38
Angle of repose*	33.69 ± 0.28	20 ± 0.33	22.61 ± 0.22	21.39 ± 0.34	21.52 ± 0.24
Carr's index*	29.93 ± 0.50	18.75 ± 0.98	11.76 ± 0.37	15.62 ± 0.37	17.94 ± 0.79
Hauser ratio*	24.62 ± 0.63	17.14 ± 0.54	1.07 ± 0.29	1.10 ± 0.38	1.11 ± 0.53
Crushing strength* (g)	-	49.28 ± 0.28	45.86 ± 0.26	58.29 ± 0.48	54.73 ± 0.09
a*	0.39 ± 0.28	0.33 ± 0.30	0.13 ± 0.26	0.26 ± 0.16	0.20 ± 0.25
b*	0.016 ± 0.34	0.020 ± 0.27	0.12 ± 0.36	0.021 ± 0.29	0.10 ± 0.35
1/b*	60.60 ± 0.34	49.01 ± 0.27	8.40 ± 0.36	4.85 ± 0.29	9.70 ± 0.35
K*	0.019 ± 0.28	0.023 ± 0.30	0.026 ± 0.26	0.022 ± 0.48	0.027 ± 0.48

*Each value represents mean ± S.D. ($n = 3$)

Kawakitas equation, showed a significantly smaller value ($P < 0.01$) of parameter (a) and a significantly higher value ($P < 0.01$) of parameter (b), (1/b) as compared with raw crystals of CBZ. Kunos equation showed that agglomerates have a significantly larger value ($P < 0.01$) of parameter k. From the values of all these parameters, it is proved that the agglomerated crystals showed a higher packability than that of raw CBZ crystals. The increasing packability of the agglomerated crystals may be due to the lower surface and the wider particle size distribution of the spherical crystals. During the tapping process, smaller particles might have infiltrated into the voids between the larger particles and resulted in improved packability.[20]

The crushing strength of agglomerated crystals is significantly ($P < 0.01$) more than that of the granules. Addition of polymers like polyethylene glycol also slightly improved the mechanical strength of the agglomerates.

Powder bed hydrophilicity study of CBZ and its agglomerates revealed that the agglomerates showed a significantly shorter rising time ($P < 0.01$) of water to its surface as compared with granules and raw CBZ. Agglomerates represent a better wettability as compared with granules (GR) and raw CBZ. The order of wettability was PEG > CTS > ETH > EUDRSPO > GR > CBZ. The reason for the superior wettability of PEG is that at the time of the agglomeration process, PEG in the poor solvent adheres to the agglomerated crystals.

Dissolution study

In the dissolution study, PEG showed 98.14 cumulative% drug releases in 20 min followed by CTS (97.29%), EUDRSPO (95.22), and ETH (89.72) from agglomerates as compared with CBZ (75.72%) [Figure 4] and GR (79.15%). The reason for this faster dissolution was linked to the better wettability of the spherically agglomerated crystals. Incorporating the water-soluble polymer polyethylene glycol into the agglomerates of poorly soluble crystals improved the dissolution rate followed by incorporating the hydrophilic busting polymer chitosan and intraporosity-forming polymer eudragit, which showed an improved dissolution rate as compared with agglomerates without polymers. Agglomerates having a more porous internal structure exhibit a faster drug release rate than those of the less-porous agglomerates. Granules showed a lower dissolution rate because the crystals bounded together through the binding agent and took more time to separate from the granules for dissolution.[21]

CONCLUSION

From the above observations, we can conclude that agglomerated crystals of CBZ with different hydrophilic and hydrophobic polymers prepared by the QESD technique showed an improvement in the solubility, dissolution rate, packability, wettability, flowability, and strength as compared with raw CBZ crystals and granules. PEG was found to be a better polymer in dissolution enhancement of CBZ from agglomerates. Instead of preparation of granules, agglomerates of BCS class II drugs to enhance bioavailability and tabletting properties are a better option for the pharmaceutical industries.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support of AICTE. The authors wish to thank Bajaj Health Care Pvt. Ltd., India, for providing CBZ as a gift sample for this research work. Also, the authors would like to thank Dr. Paul and Mr. A Jadhav for their kind help, respectively, in the XRD studies and in microscopical photography.

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Source of Support: AICTE and Bajaj Health Care Pvt. Ltd., India,
Conflict of Interest: None declared.