Original Research Article

Influence of excipients and processing conditions on the development of agglomerates of racecadotril by crystallo-co-agglomeration

Kevin Garala, Jaydeep Patel, Anjali Patel, Mihir Raval[1], Abhay Dharamsi[2]

Department of Pharmaceutics, Atmiya Institute of Pharmacy, Kalawad Road, [1]Department of Pharmaceutical Sciences, Saurashtra University, Rajkot, Gujarat, [2]Department of Pharmaceutics, Swift School of Pharmacy, Rajpura, Punjab, India

Abstract

Purpose: The purpose of the present investigation was to improve the flow and mechanical properties of racecadotril by a crystallo-co-agglomeration (CCA) technique. Direct tableting is a requirement of pharmaceutical industries. Poor mechanical properties of crystalline drug particles require wet granulation which is uneconomical, laborious, and tedious. **Materials and Methods:** The objective of this work was to study the influence of various polymers/excipients and processing conditions on the formation of directly compressible agglomerates of the water-insoluble drug, racecadotril, an antidiarrheal agent. The agglomerates of racecadotril were prepared using dichloromethane (DCM)—water as the crystallization system. DCM acted as a good solvent for racecadotril as well as a bridging liquid for the agglomeration of the crystallized drug and water as the nonsolvent. The prepared agglomerates were tested for micromeritic and mechanical properties. **Results:** The process yielded ~90 to 96% wt/ wt spherical agglomerates containing racecadotril with the diameter between 299 and 521 μ. A higher rotational speed of crystallization system reduces the size of the agglomerates and disturbs the sphericity. Spherical agglomerates were generated with a uniform dispersion of the crystallized drug. CCA showed excellent flowability and crushing strength. **Conclusion:** Excipients and processing conditions can play a key role in preparing spherical agglomerates of racecadotril by CCA, an excellent alternative to the wet granulation process to prepare intermediates for direct compression.

Key words: Crystallo-co-agglomeration, crushing strength, flowability, racecadotril

INTRODUCTION

A large number of drugs are crystalline in nature and also exhibit different crystal habits. Different habits of crystals affect the compression and tableting behavior.[1] These crystal habits play an important role in influencing the flowability, compactability, compression characteristics, packing, and dissolution.[2] When the mechanical properties of a drug are inadequate, a preliminary wet granulation with or without excipients is necessary which is a very tedious technique and has many inconveniences like additional labor, selection of binder and solvent, and is also uneconomical, time consuming, and so on.[3] Nowadays, direct compression for tableting is required to make the process of tablet production economical. This process is again influenced by the particle properties of the drug.[4,5]

Nonconventional enlargement techniques of particle size employed in the field of pharmacy include extrusion spheronization,[6] melt solidification,[7] melt granulation,[8] melt extrusion,[9] and spherical crystallization (SC).[10] Among them, SC developed by *Kawashima et al.*, in the early 1990s has been considered effective in modification of the crystal nature and preparation of directly compressible agglomerates.[11] Moreover, apart from modifications in the primary and secondary properties of the particles, these techniques also offer advantages in terms of reduction in the number of unit operations and, in turn, processing cost. The suitability of these techniques relies on the desired properties of the enlarged particle and the physicochemical properties of the drug and excipients used. To overcome the limitations of SC in obtaining directly compressible agglomerates of low-dose and poorly compressible drugs and combination of drugs, *Kadam et al.* advocated the

Address for correspondence:
Mr. Kevin Garala,
Department of Pharmaceutics,
Atmiya Institute of Pharmacy, Yogidham Gurukul,
Kalawad Road, Rajkot – 360 005, Gujarat, India.
E-mail: kevincgarala@gmail.com

Access this article online

Quick Response Code:

Website: www.jpionline.org

DOI: 10.4103/2230-973X.106996

crystallo-co-agglomeration (CCA) technique.[12] CCA is a modification of an SC technique in which a drug is crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system.

CCA is a novel particle-engineering technique, which aggregates crystals of drugs in the form of small spherical particles using excipients and solvents to develop an intermediate material with improved micromeritic and mechanical properties, solubility, and dissolution.[13] The rate of dissolution of the drug from the agglomerates or compacts thereof can be improved and modified by using suitable excipients during the process of preparation of agglomeration.[14,15] Moreover, the agglomerates obtained by this technique can be employed as directly compressible tablet intermediates and/or spheres to be encapsulated. Various studies have been done for the drugs which have low aqueous solubility with poor physicochemical and physicomechanical properties like ibuprofen,[13] a combination of ibuprofen and paracetamol,[16] ketoprofen,[17] naproxen,[14] bromhexidine hydrochloride,[18] and aceclofenac.[19]

The present work reports a CCA technique used to prepare agglomerates of racecadotril, an antidiarrheal drug, the crystalline form consisting of long needles, which otherwise has low bulk density, very poor flow property as well as compressibility, and very low solubility in water which makes direct compression difficult. Therefore, racecadotril seems particularly unacceptable for the preparation of tablets. Moreover, large quantities of racecadotril are necessary, whereas it is generally desirable to obtain a tablet of a small size (between 10 and 15 mm in diameter at the most) to increase patient compliance. Furthermore, racecadotril is insoluble in water and this makes a rapid release of molecules by disintegration of the tablet more difficult.[20] This work mainly focuses on the study of the influence of the processing conditions, that is, temperature of the crystallization system and rotational speed, and the various excipients either alone or in combination on the formation of CCA of racecadotril and its mechanical properties to obtain excellent flow, compaction, and highly efficient and improved material in terms of processability as well as for direct compression to tablets.

An excipient to be incorporated in the formation of agglomerates should have an affinity toward the bridging liquid. Talc, due to its hydrophobicity, undergoes preferential wetting with bridging liquids and is a suitable excipient for incorporation in agglomerates. Apart from talc, various hydrophilic and hydrophobic polymers have been used to study their effect on physicochemical and physicomechanical properties.

MATERIALS AND METHODS

Materials

Racecadotril was procured from Ogene Systems (I) Pvt Ltd., Hyderabad, India. Lactose monohydrate and carbopol were purchased from Merck Pvt. Ltd., Mumbai, India. Talc, chitosan, hydroxypropyl methylcellulose (HPMC) E50 LV, hydroxypropyl cellulose (HPC), methylcellulose (MC), ethylcellulose (EC), polyvinylpyrrolidone (PVP) K30, and polyethylene glycol (PEG) 400 and PEG 6000 were purchased from Hi-Media Ltd., Mumbai, India. Eudragit RS 100, Eudragit S 100, and Eudragit L 100 were gifted by the Evonik Degussa Incorporation, Mumbai, India. Carbopol was obtained from Noveon Corporation, Mumbai, India. All other solvents and chemicals used were of analytical grade (Hi-Media Ltd., Mumbai, India).

Methods

Selection of the solvent system

The solubility study of racecadotril was performed to select good solvents and poor solvents for the drug. Various solvents ranging from highly polar to nonpolar were tried for this study. About 2 mL of each solvent was taken and an excess quantity of the drug was added in it. These saturated solutions were then kept for 24 hours in a cryostatic constant temperature reciprocating shaker bath at a temperature of 25 ± 1°C with constant shaking at 120 rpm (rpm: Revolutions per minute). The saturated solutions were then filtered and the concentration of drug in the solution was measured at 231 nm using an ultraviolet (UV)-visible spectrophotometer (Shimadzu, Japan). The solubility study was repeated three times in the same manner to obtain reproducible results.

Preparation of agglomerates

On the basis of the solubility data, good and poor solvents were identified and selected for preparing CCA of racecadotril. A crystallization protocol was designed in which the drug was dissolved in good and poor solvent dropwise, which was stirred using a four-blade mechanical stirrer in Morishima vessel. The stirring was continued for about 15 minutes. The stirring was stopped when the overall mixture appeared clear at the top and the particles settled down. The agglomerates generated were filtered and dried at room temperature. Various excipients were used either alone or in combination by dissolving in either good or poor solvent before the experiment was started, to study its effect on the formation of CCA and optimization of their concentrations to obtain agglomerates of desired properties.

Design of the experiment

After a preliminary optimization of polymers, a 3^2 full factorial design was used in this study for the effect of two independent variables (concentration of PEG 6000 and speed), each at three levels; experimental batches were performed at all nine possible combinations. The mean geometric diameter (mm), circularity factor and crushing strength (g) were selected as dependent variables. The data were subjected to surface methodology to determine the effect of concentration of PEG 6000 (X_1) and speed (X_2) on the various dependent variables. Three dependent variables were selected, that is, mean geometric diameter (Y_1), circularity factor (Y_2), and crushing strength (Y_3). The values of variables in a 3^2 factorial design are indicated in Table 1. A statistical model incorporating interactive and polynomial terms was used to calculate the responses.

Table 1: The 3^2 full factorial experimental design

Variable level in coded form	
X_1	X_2
-1	-1
0	-1
+1	-1
-1	0
0	0
+1	0
-1	+1
0	+1
+1	+1

Translation of coded levels in actual units			
Coded level	-1	0	+1
X_1: PEG 6000 (%)	0.25	0.38	0.5
X_2: Speed (rpm)	600	800	1000

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} \times_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the nine trials, and b_i (b_1, b_2, b_{12}, b_{11}, and b_{22}) is the estimated coefficient for the corresponding factor X_i (X_1, X_2, X_1 X_2, X_{12}, and X_{22}), which represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1 X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate the nonlinearity.

Micromeritic study

The size and size distribution of prepared agglomerates was analyzed using an optical microscopy method. The size of 100 randomly selected agglomerates was measured and appropriate geometric mean diameter (d_g) was calculated.[21]

Sphericity determination

Photomicrographs of the prepared agglomerates were taken using a charge-coupled device camera at a fixed magnification. The photomicrographs of the agglomerates were observed for sphericity determination. Shape factor (P) and circularity factor (CF) for the agglomerates were obtained from the area (A) and perimeter (P').[22] The tracings of enlarged photomicrographs of agglomerates were used for the measurement of area and perimeter.

$$P = P''/P'$$

where $P'' = 2\pi (A/\pi)^{1/2}$

Circularity factor (CF) = $(P')^2/4\pi A$

Crushing strength

The crushing strength of the prepared agglomerates (n = 5) was determined by mercury loaded cell method described by Jarosz and Parrot.[23] The total weight of the tube with mercury, at the stage where the agglomerate broke was the crushing strength of the agglomerate.

Drug content and percentage yield

Drug content is the experimentally measured and racecadotril content is expressed as percentage (%).[17] The accurately weighed agglomerates of racecadotril were dissolved in methanol in a 50 mL volumetric flask. These solutions were appropriately diluted with the same medium and the racecadotril content was measured by a UV spectrophotometer at 231 nm. The experimental racecadotril content was calculated using calibration equation.

% yield of agglomerates was calculated using the formula:

$$\%\ \text{Yield} = \frac{\text{Total weight of Drug}}{\text{Total weight of drug and polymer}} \times 100$$

Flowability

In this study, the angle of repose, compressibility index, and Hausner ratio (HR) were determined to evaluate the flow behavior of the prepared agglomerates.

Angle of repose

Angle of repose is the internal angle between the surface of a pile of powder and the horizontal axis.[24] This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.[25] It is the easiest and most commonly used test for powder flowability.[26] The angle of repose was measured by a fixed funnel method described by Pilpel.[27] According to the flow properties of the material to be tested, funnels with or without stem, with different angles and orifice diameters are used. The end of a funnel was placed 2 cm above a flat base. The powder or agglomerate was released from the funnel. From the height of the cone (h) and the radius of the base (r), the angle of repose (α) was determined by using the following equation:

$$\alpha = \tan^{-1}(h / r)$$

Carr's compressibility index and HR

The bulk and tapped densities were used to calculate the compressibility index (Carr's compressibility index, CI) and HR. The CI is a measure of the propensity of a powder to consolidate.[28] The preliminary results showed that after 1,250 taps, the volume change was negligible for all the samples. So, the samples were tapped 1,250 times in this experiment. Changes occurring in the packing arrangement during the tapping procedure are expressed as the CI. The CI of the samples can be computed from the bulk and tapped densities by the following equation:[29]

$$CI\ (\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

The greater the compressibility of a bulk solid, the less flowable it will be. Compressibility can therefore be used to indirectly assess properties such as uniformity in size and shape, deformability, surface area, cohesion, and moisture content of the material.[29]

Alternatively, HR was calculated using the measured values of bulk density and tapped density as follows:[30]

$$HR = \frac{P_t}{P_b}$$

Moisture content

Moisture content of the prepared agglomerates was determined by infrared (IR) moisture balance; 5 g of agglomerates was used for the determination of moisture content. The agglomerates were separately placed in a heating pan and heated at a temperature of 105°C for four hours. The percentage reduction in the weight of the agglomerates due to loss of moisture was measured for the determination of moisture content. The average of three determinations was considered as the percentage of moisture content.

In vitro dissolution study

In vitro dissolution studies for pure drug and prepared agglomerates were performed using United States Pharmacopeia (USP) type I dissolution apparatus (paddle type) to measure the drug release from agglomerates; 900 mL of acetate buffer pH 4.5 containing 1% sodium lauryl sulfate was used as a dissolution medium at 37 ± 0.5°C and 100 rpm [as per Indian Pharmacopoeia (IP) 2007]. Aliquots of 5 mL were withdrawn at predetermined time intervals and replaced with the same amount of dissolution medium. After suitable dilution with the dissolution medium, the samples were analyzed spectrophotometrically at 231 nm and the cumulative percentage drug released was calculated.

Characterization of optimized agglomerates

Surface topography

Photomicrographs of the prepared agglomerates were taken using a charge-coupled device camera at a fixed magnification. The photomicrographs of the agglomerates were observed for surface morphology and sphericity.[14]

Measurement of packability

Kawakita analysis

The packing ability of the samples was investigated by tapping them into a measuring cylinder using a tapping machine. Initially, 10 g of optimized agglomerates was weighed and then gently poured into a measuring cylinder. The volume of the 10 g sample was recorded. The poured density (minimum density) was calculated from the powder mass (10 g) and the volume. Then the cylinder was tapped and the volume was recorded after 10, 20, 30, 50, and 100, followed by an increment of 100 taps until the volume remained significantly unchanged. The packability was calculated by the Kawakita equation:[31]

$$\frac{n}{c} = \frac{1}{ab} + \frac{n}{a}$$

where *a* and *b* are the constants, *n* is the tap number, and *C* denotes the volume reduction which can be calculated according to the following equation:

$$C = \frac{Vo - Vn}{Vo}$$

where *Vo* and *Vn* are the bed volumes of the powder or agglomerate at the initial and n^{th} tapped states, respectively. The value of *a* indicates total volume reduction due to tapping of powder or agglomerates and *b* is inversely proportional to the yield strength of the agglomerates. The values of *a* and *b* were used to study the flow and compression behavior of the agglomerates. The combination of Kawakita parameters *a* and b^{-1} may thus be indicative of the incidence of particle rearrangement during compression, that is, the relative importance of the initial stage for the overall compression behavior.[32]

Kuno's analysis

The relationship between the change in apparent density and the number of tappings described by Kuno in 1979[33] is

$$ln(Pt - Pn) = -Kn + ln\,(Pt - Po)$$

where ρ_t is the apparent density at equilibrium, ρ_n the apparent density at the nth tapped state, ρ_o the apparent density at the initial cascade state, and the constant *K* represents the rate of packing process under tapping.[34]

Heckel plot analysis

The accurately weighed quantity of samples was compressed by a hydraulic press (Technosearch Instruments, Mumbai, India) at a constant compression at different pressures for one minute of dwell time.[15] Lubrication of dies and punches was carried out by 1% w/v dispersion of magnesium stearate in acetone. The compacts were allowed to relax for 24 hours in a vacuum at an ambient temperature and the data obtained was subject to the Heckel plot using the following equation:

$$ln\frac{1}{1-D} = kp + A$$

where *D* is relative density of the compacts, that is, the ratio of compact density to true density of powder, *P* is the applied compression pressure, and *k* and *A* are constants.[35] The reported mean yield pressure, *Py*, is the reciprocal of the slope *k*, which was calculated using linear regression in a pressure range determined separately for each material. The constant *A* expresses the densification at low pressure. *k* is equal to $1/3\sigma_0$ where σ_o is yield strength and $3\sigma_0$ is mean yield pressure (*Py*). Here, density of the prepared compacts for the Heckel parameter was calculated from the volume of compacts and mass of compacts.

Elastic recovery

The elastic recovery (ER) was determined by filling a specific quantity of optimized agglomerated and drug crystals in a die-specific diameter, the surface of which was coated with magnesium stearate in advance; then, the universal tensile compression tester was used to compress the samples at a constant speed.[14] The thickness of the compacts was measured immediately after ejection (Hc) and after the 24-hour relaxation period (He). The following equation was used to calculate the elastic recovery;[36]

$$\%\ \mathrm{ER} = [(\mathrm{He} - \mathrm{Hc}) / \mathrm{Hc}] \times 100$$

Stability study

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or

commercial product. The United States Food and Drug Administration (US FDA) and International Conference on Harmonization (ICH) specifies the guidelines for the stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. According to the guidelines of the ICH, the optimized agglomerates were stored at 40 ± 0.5°C and 75 ± 5% relative humidity (RH) for six months.[36,37] The samples were withdrawn at different intervals and analyzed. If a significant change had occurred under these stress conditions, then the formulation would have had to be tested at an intermediate condition, that is, 30°C and 75% RH. In the present work, stability studies were carried out for the selected formulations at 40 ± 0.5°C and 75 ± 5 % RH for six months using a programmable environmental test chamber (Remi, India). The optimized formulation was evaluated for drug content and all dependent variables.

RESULTS AND DISCUSSION

Selection of the solvent system

The selection of the solvent system for the agglomeration process depends on solubility and stability of the drug in the solvent system. Water has been reported as a processing (bad solvent/external phase) medium, and organic solvents (relatively nontoxic) as good solvents (internal phase) and/or bridging liquids in the system design. This sort of solvent selection has been suggested due to scarce requirement of organic solvent (as a good solvent as well as bridging liquid) than that of bad solvent (aqueous external phase) requirement. The bridging liquid should carry out preferential wetting of crystals and form liquid bridges during the process of agglomeration. Simultaneously, the bridging liquid should be immiscible with a bad solvent. If the bridging liquid acts as a good solvent, it means that it performs the dual role of acting as a good solvent and a bridging liquid. Then the good solvent used should be immiscible with the bad solvent to avoid drug loss due to cosolvency.

The amount of bridging liquid required can be decided by trial and error. It has been observed that the addition of an inadequate amount of bridging liquid shows underwetting of crystals resulting in the generation of smaller sized agglomerates with more number of fines and excess addition of bridging liquid generates bigger sized agglomerates requiring more processing time for completion of the agglomeration process. For selection of a good solvent, the rotary shake flask method was used. The solubility study was carried out using a number of solvents [i.e., water, ethanol, dichloromethane (DCM), acetone, methanol, benzene, chloroform, dimethylformamide, ethyl acetate, hexane, and toluene]. Solubility of the drug was determined in various solvent systems and the result is depicted in Figure 1. From Figure 1, it is seen that the drug has the highest solubility in DCM and lowest in water. So, it was concluded that DCM would be considered as a good solvent and water would be a poor solvent.

Preliminary optimization

Plain drug agglomerates (without excipients) have shown poor resistance to breaking, poor compressibility, and low compactibility due to inherent poor cohesiveness of the drug. Therefore, it has been suggested to improve these properties by the addition of various polymers like HPMC, PEG, EC, Eudragit, chitosan, and so on. It has been reported that agglomerates obtained by the optimum addition of Eudragit RS 100 imparts sufficient mechanical strength and sphericity to the agglomerates, whereas its excess addition leads to the deformation of agglomerates. PEG causes a reduction in the interfacial tension between water and the bridging liquid resulting in a reduction in the force of cohesion between particles. This leads to the generation of spherical agglomerates with a smaller size. PEG, due to its soft and plastic nature, undergoes plastic deformation and gives better compressibility to the agglomerates during the process of compression. The EC being hard and tough in nature increases the strength of agglomerates. However, due to its solubility in the bridging liquid (organic solvent), it imparts higher viscosity to the internal phase resulting in increased interfacial tension. The increased viscosity retards the diffusion of the bridging liquid, hampers nucleation and crystal formation, and increases the time for completion of the agglomeration process. The details of all preliminary batches have been summarized in Table 2. Promising results were observed with the combination of Eudragit RS100 and PEG 6000.

On the basis of preliminary trials, Eudragit RS 100 (0.4%) was selected as the optimum polymer and its amount was kept constant in all the batches. Due to its solubility in acetone, it was solubilized in a small amount of acetone and then mixed with good solvent, that is, DCM. The second polymer PEG 6000 gave promising results as shown in Table 2. Due to good aqueous solubility, PEG 6000 was added in a poor solvent, that is, water, of the system. Further, the effect of speed and concentration of PEG 6000 on the properties of prepared formulations were also analyzed by using the design of the experiment.

Experimental design (3^2 full factorial design)

Preliminary investigations of the process parameters revealed that factors such as concentration of PEG 6000 (X_1) and rotational speed (X_2) exhibited a significant influence on the mean geometric

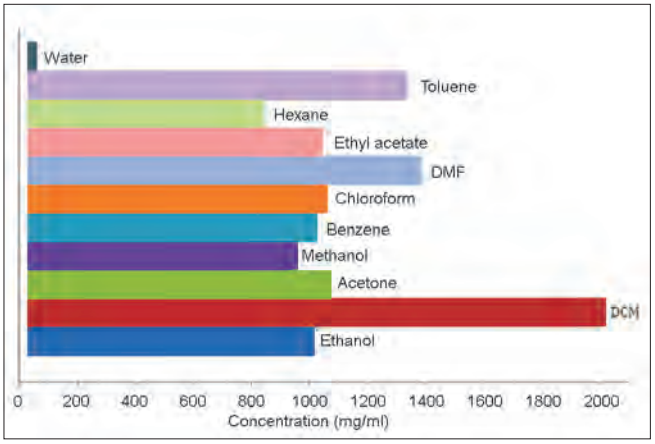

Figure 1: Solubility profile of racecadotril in solvent systems

diameter (mm), circularity factor, and crushing strength (g); hence, they were utilized for further systematic studies. All the three selected dependent variables, mean geometric diameter (d_g), circularity factor (CF), and crushing strength (CS) for all the nine batches showed a wide variation of 0.229-0.521 mm, 0.792-1.123, and 27.89-48.23 g, respectively [Table 3]. The data clearly indicate the strong influence of X_1 and X_2 on selected responses (d_g, CF, and CS). The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficients and the mathematical sign carried, positive or negative. For d_g, coefficients b_{11}, b_{22}, and b_{12} were found to be insignificant, as *P* values were more than 0.05 and hence removed from the full model. Similarly, for CF and CS, values of b_{11}, b_{22}, and b_{12} were insignificant and hence removed from the full model [Table 4]. Table 5 shows the results of analysis of variance (ANOVA) performed to justify the removal of insignificant factors. The high values of correlation coefficients for d_g, CF, and CS indicate a good fit. The critical values of *F* for d_g, CF, and CS were found to be 9.28 (DF =3, 3) at $\propto$ =0.05 Moreover, the calculated *F* value for dg, CF, and CS, was found to be 0.4575, 1.8252, and 2.4537, respectively, less than the critical value, which suggests no significant difference between the full and reduced model. The data of all the nine batches of factorial design were used to generate interpolated values using the Design Expert® version 8 software.

Influence of formulation composition factor on geometric mean diameter

The major aim of the present investigation was to improve the micromeritics, flowability, and mechanical properties of racecadotril. The particle size of the pure drug was sufficiently increased and the results are shown in Table 3. The contour plot for the geometric mean diameter [Figure 2] illustrates the strong influence of two factors (concentration of PEG 6000 and speed). The d_g of 0.521 mm was observed with PEG 6000 at 0.50% and speed at 600 rpm. From the regression analysis, it was clearly observed that the concentration of PEG has a positive effect and speed has a negative effect on d_g. Increase in the diameter of the agglomerates with increase in PEG concentration might be attributed to the ability of PEG to bind the growing crystals during the process. As seen in Figure 2, the d_g reduces with increase in the rotational speed.

Influence of formulation composition factor on circularity factor

The circularity factor of each optimized batch was calculated using the area and perimeter of the agglomerates and the average was considered. Area (A) and perimeter (P') of the agglomerates was calculated using traced photomicrographs of the agglomerates. The results revealed in the shape and circularity factors near unity (1) showed that the agglomerates possess perfect spherical shape. The contour plot for the circularity factor [Figure 3] illustrated a strong influence of both the factors (concentration of PEG 6000 and speed). The CF of 1.056 was observed with PEG 6000 at 0.50% and speed at 1000 rpm. From the regression analysis, it was clearly observed that the concentration of PEG and speed have a positive effect on CS. The encouraging results of flow

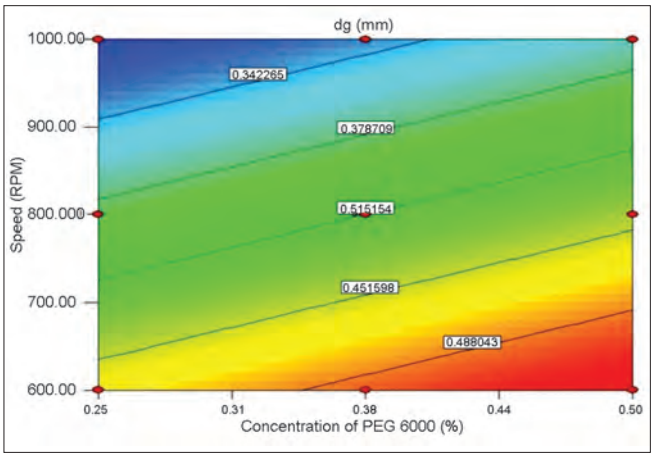

Figure 2: Effect of independent variables on geometric mean diameter (d_g)

Table 2: Preliminary trials

Excipient 1 (%)	Excipient 2 (%)	Angle of repose	Carr's index	Hausner ratio	Crushing strength
Pure drug		45.63	39.48	1.61	-
-	-	41.63	35	1.56	20
Talc (0.2-0.5)	-	36-40	21-30	1.3-1.4	22.12-25
Lactose (0.2-0.5)		35-40	30-35	1.4-1.45	25-29
Eudragit RS 100 (0.2-0.5)	-	32-35	20-27	1.3-1.35	40-43
Eudragit S 100 (0.2-0.5)	-	34-38	25-30	1.3-1.4	32-35
Eudragit L 100 (0.2-0.5)	-	35-40	25-30	1.35-1.4	30-35
Chitosan (0.5-2)	-	35-38	28-32	1.32-1.38	38-42
HPC (0.2-0.5)	-	32-36	25-30	1.34-1.4	27-34
MC (0.2-0.5)	-	35-40	30-33	1.43-1.48	30-35
Carbopol (0.2-0.5)	-	36-40	26-30	1.35-1.4	25-30
EC (0.2-0.5)	-	35-40	27-31	1.32-1.39	25-30
Eudragit RS 100 (0.4)	PVP K30 (0.2-0.5)	30-34	18-20	1.24-1.35	39-43
Eudragit RS 100 (0.4)	HPMC E50 LV (0.2-0.5)	32-36	15-19	1.25-1.28	35-40
Eudragit RS 100 (0.4)	PEG 400 (0.2-0.5)	36-39	22-27	1.30-1.32	40.7-43
Eudragit RS 100 (0.4)	PEG 6000 (0.2-0.5)	31-35	20-22	1.27-1.32	42-48

HPC: Hydroxypropyl cellulose, MC: Methylcellulose, EC: Ethylcellulose, PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropyl methylcellulose, PEG: Polyethylene glycol

properties and compressibility parameters were mainly because of improving sphericity of prepared crystal-co-agglomerates. Thus, the presence of suitable additives was required to produce agglomerates with spherical shape and smooth surface to provide excellent flow and compaction.

Influence of formulation composition factor on crushing strength

Randomly selected agglomerates from each batch were tested for the determination of CS. The total weight of mercury and weight of the plunger to fracture/deform the agglomerate was considered as CS. The contour plot for crushing strength [Figure 4] illustrated the strong influence of two factors (concentration of PEG 6000 and speed). The CS of 48.23 g was observed with PEG 6000 at 0.50% and speed at 600 rpm. From the regression analysis, it is clearly observed that the concentration of PEG has a positive effect and speed has a negative effect on CS but the magnitude of X_1 was reasonably higher than the X_2. CS of the prepared agglomerates was increased with PEG concentration. As seen in Figure 4, the CS reduces with increase in the rotational speed. It might be due to the formation followed by entrapment of air bubbles within the matrix of agglomerates. The results of crushing strength of CCA showed that the presence of excipients improved the strength of the agglomerates. This could be attributed to the increased agglomeration of crystals with good bridging due to the presence of suitable additives. Improved crushing strength of the agglomerates revealed the improvement in mechanical and handling properties. Increased cohesive interaction between particles caused better binding and close packing between crystals.[16]

Table 3: Results of experimental design batches*

Batch	X_1	X_2	d_g	CF	CS
1	0.25	600	0.468±0.009	0.792±0.021	35.44±0.97
2	0.38	600	0.486±0.012	1.123±0.011	39.56±1.02
3	0.50	600	0.521±0.011	1.102±0.014	48.23±0.89
4	0.25	800	0.382±0.021	0.865±0.016	31.41±00.83
5	0.38	800	0.422±0.017	0.901±0.009	37.89±1.05
6	0.50	800	0.444±0.008	1.089±0.013	44.56±1.12
7	0.25	1000	0.299±0.025	1.082±0.021	27.89±0.64
8	0.38	1000	0.336±0.023	1.067±0.011	33.33±0.78
9	0.50	1000	0.361±0.014	1.056±0.012	42.22±1.03

* Results are the average of three determinations±standard deviation (SD), CF: Circularity factor, CS: Crushing strength, dg: Mean geometry diameter, X1: PEG 6000 (%); X2: Speed (rpm)

Agitation of the crystallization system is required to aid the process of dispersion from internal phase to external phase. It has been reported that the speed of the agitation affects size, sphericity, and strength of crystal agglomerates. A higher speed of agitation increases the sphericity of the agglomerates but reduces the strength. The time required for the completion of agglomeration process gets diminished with a higher speed of agitation.

Optimization of CCA

From the overlay plot [Figure 5], the optimized batch was prepared at $X_1 = 0.495$ and $X_2 = 815$ and performed practically.

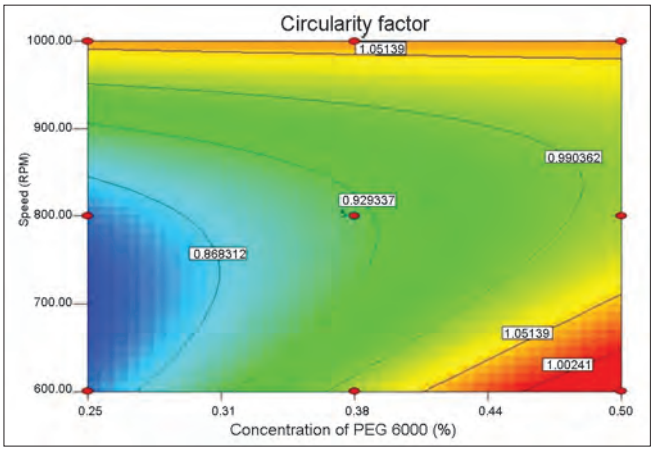

Figure 3: Effect of independent variables on circularity factor (CF)

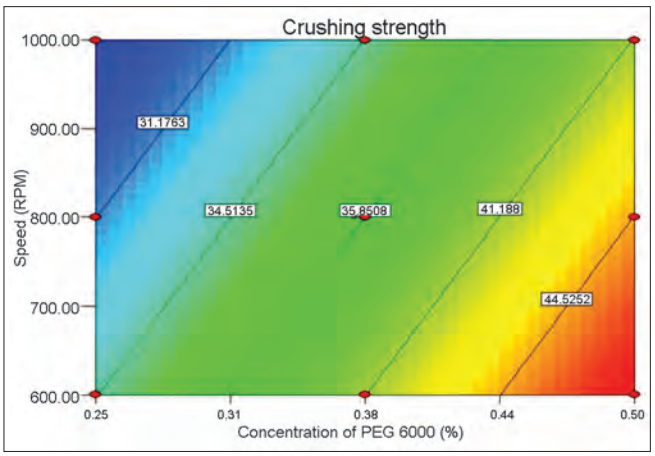

Figure 4: Effect of independent variables on crushing strength (CS)

Table 4: Summary of regression analysis*

Coefficients	b_0	b_1	b_2	b_{11}[a]	b_{22}[a]	b_{12}[a]
d_g						
FM	0.4163	0.0295	−0.0798	−0.0015	−0.0035	0.0022
RM	0.4132	0.0295	−0.0798	–	–	–
CF						
FM	0.9734	0.0846	0.0313	−0.0326	0.0853	−0.0840
RM	1.0085	0.0846	0.0313	–	–	–
CS						
FM	37.0433	6.7100	−3.3016	1.3600	−0.1750	0.3800
RM	37.0433	6.7100	−3.3016	–	–	–

*FM: Full model, RM: Reduced model, dg: Mean geometry diameter, CF: Circularity factor, CS: Crushing strength, [a]Response is insignificant at P=0.05

It was determined by the Design Expert® software. On the basis of the criteria for the desired response, the following batch was formulated to evaluate the reliability of the evolved equations. The experimental values and predicted values of each response are presented in Table 6. The percentage relative error of each response was estimated using the following equation:

$$\% \text{ Relative error} = \frac{|\text{Predicted value} - \text{Experimental value}|}{\text{Predicted value}} \times 100$$

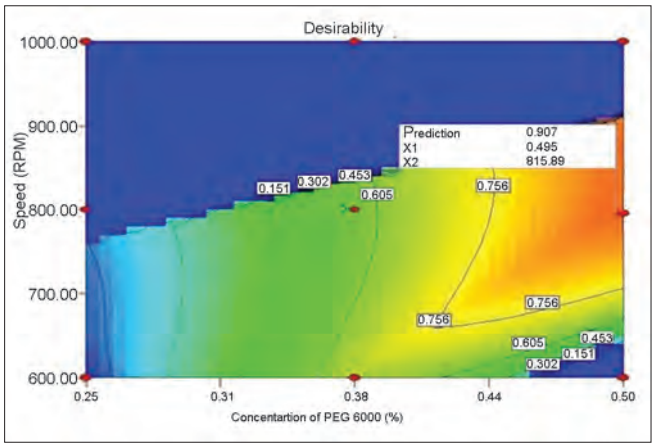

Figure 5: Overlay plot of desirability of all dependent variables

Table 5: Calculation of testing the model in portions*

	DF	SS	MS	R^2
d_g				
Regression				
FM	5	0.043511	0.008702	0.9975
RM	2	0.043462	0.021731	0.9964
Error				
FM	3	0.000107	3.57E-05	
RM	6	0.000156	2.61E-05	
CF				
Regression				
FM	5	0.093823	0.018765	0.9921
RM	2	0.048901	0.024451	0.9128
Error				
FM	3	0.024611	0.008204	
RM	6	0.069533	0.011589	
CS				
Regression				
FM	5	339.8887	67.97773	0.9948
RM	2	335.5506	167.7753	0.9821
Error				
FM	3	1.7681	0.5893	
RM	6	6.1061	1.0176	

*DF: Degree of freedom, SS: Sum of squares, MS: Mean of squares, R: Regression coefficient

The percentage relative errors for all responses of check point batch were in the range of acceptance. It was concluded that the experimental values were in excellent agreement with theoretical values. This proved the validity of the equations and selected experimental design.

Figure 5 shows the overlay plot of desirability in terms of high d_g and CS as well as optimum CF of all prepared batches. From Figure 5, it is seen that X_1 at 0.495% and X_2 at 815 rpm required increased circularity and crushing strength with optimum mean geometric diameter.

The percentage relative error obtained from the optimized batch was in the range of 3.0215-6.9414. It can be seen that in all the cases, there was a reasonable agreement of predicted values and experimental values, as low values of relative error were found. This confirmed the role of a derived reduced polynomial equation, proved the validity of the model, and ascertained the effects of PEG and speed on dependent variables. Furthermore, the optimized batch was characterized by various evaluation methods.

Percentage yield and drug content

The total yield of agglomerates was determined by dividing the measured weight with the weight of the total amount of nonvolatile compound. In the process of CCA, simultaneous crystallization and agglomeration of particles took place leading to the formation of matrix agglomerates having a uniform dispersion of the crystallized drug. The percentage yield of the agglomerates was in the range of 90-96% w/w and almost all the batches showed drug loading >95% [Table 7]. It revealed that the drug and polymer (s)/excipient (s) were recrystallized at the greater extent to form agglomerates without any considerable wastage of drug.

Micromeritics study

The formed agglomerates of all batches were very good in shape and circularity. According to the literature, materials with CI values between 5 and 15% have very good flowability. A statistically insignificant difference was observed in the values of CI for different batches of CCA [Table 8] suggesting that the agglomerates of all batches have an excellent flowability as compared to the pure drug. Moreover, the angle of repose of all batches was below 30, indicating a very good flow. Furthermore, small values of Hausner ratio in the agglomerates compared to the pure drug suggest an improvement in the flow property of agglomerates and ease of handling. This helps in producing a uniform batch of agglomerates for oral delivery. The shape of the particles of the pure drug resulted in more electrostatic charges which ultimately lead to very poor flowability.[38] The prepared

Table 6: Comparison between predicted and experimental results of optimized batch

Responses	Predicted value	Observed value	Relative error (%)
dg	0.493	0.461	6.9414
CF	0.999	0.944	5.8385
CS	43.33	44.68	3.0215

dg: Mean geometry diameter, CF: Circularity factor, CS: Crushing strength

agglomerates showed a fluffy texture which might hinder its flow. The agglomerates prepared in the presence of polymers/excipients showed improvements in flow due to reduced interparticulate friction.[39]

Moisture content

Moisture content of the agglomerates is an important parameter in deciding the stability of the moisture-sensitive actives. Methods like IR moisture balance have been recommended for the determination of moisture, which gives a direct indication of the weight loss relative to the percentage of moisture. Moisture content of the agglomerates depends upon the amount and type of polymer (s)/excipients (s) employed in the formulation. Moisture content of the prepared agglomerates was found to be between 1.05 and 2.13 %. These findings suggest that it was not extreme enough to affect the stability of the agglomerates.

In vitro dissolution study

All the batches of the agglomerates showed >95% drug release within two hours [Figure 6]. The drug release profile [Figure 6] showed an improvement in the percentage of drug dissolved from the agglomerates compared to the pure drug. Improvement in dissolution might be due to the presence of hydrophilic polymer in agglomerates.

Surface topography

Photomicrographs of the optimized agglomerates showed a marked improvement in the surface morphology and sphericity compared to pure drug [Figure 7]. As shown in [Figure 7a], the pure drug crystals were morphologically needles and rods with more aspect ratio, whereas the optimized agglomerates [Figure 7b] showed encouraging results in terms of improved sphericity as well as surface smoothness. The results revealed shape and circularity factors near unity (1.0) [Tables 3 and 8].

Packability and compressibility parameters

As shown in Table 9, increased values of *a* (compressibility or extent of densification due to tapping) and decreased value of b^{-1} (cohesiveness or how fast/easily the final packing state was achieved) compared with the values of the pure drug in the Kawakita equation is an indication of the improvement in packability of the agglomerates compared with the pure drug. Increased values of *K* (Kuno's constant) compared with the pure

Table 7: Percentage yield and drug content of experimental design batches*

Batch	% yield	Drug content (%)
1	94.56±1.201	96.24±1.075
2	92.12±0.986	98.67±2.124
3	90.36±1.024	99.62±2.475
4	91.31±1.237	100.21±2.15
5	90.89±1.543	95.55±2.654
6	94.57±2.451	98.63±1.896
7	95.69±2.035	97.14±1.761
8	95.85±1.844	99.76±2.054
9	92.57±1.512	100.35±2.09
10	95.45±1.025	99.04±1.945

*Results are the average of three determinations±ΣD

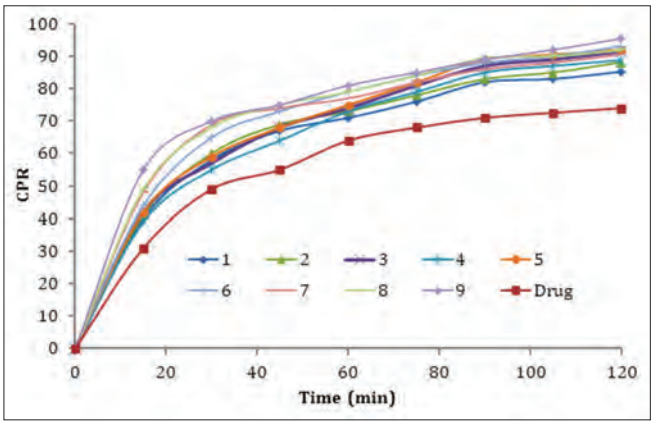

Figure 6: Dissolution profiles of pure drug and prepared agglomerates

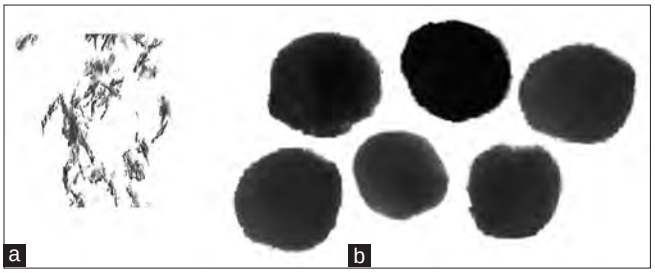

Figure 7: Photomicrograph of (a) pure drug and (b) optimized agglomerates

Table 8: Results of micromeritic properties of design experiment batches*

Batch	Angle of repose±SD	Carr's index±SD	Hausner ratio±SD	Shape factor±SD
Drug	45.63±3.65	39.48±2.05	1.613±0.132	-
1	26.73±1.22	25.81±1.16	1.38±0.01	0.953±0.014
2	26.56±2.35	18.92±1.41	1.22±0.02	0.942±0.021
3	24.91±1.84	14.73±1.98	1.18±0.01	0.975±0.018
4	24.74±1.56	16.31±1.81	1.18±0.01	0.983±0.032
5	23.49±1.39	8.58±0.99	1.09±0.01	0.889±0.026
6	24.94±1.49	13.32±1.12	1.14±0.01	0.916±0.085
7	23.46±2.85	16.61±1.92	1.20±0.02	0.894±0.091
8	27.14±1.24	19.63±1.05	1.22±0.02	0.905±0.063
9	26.03±2.73	20.64±1.05	1.24±0.02	0.987±0.047

SD: Standard deviation; * Results are the average of three determinations±SD

drug revealed marked improvements in compressibility and packability of the agglomerates obtained with the use of additives.

Heckel plot analysis

In the Heckel analysis, the true density of tablets was considered when the highest pressure (60 MPa for agglomerates and 40 MPa for crystals of drug) was applied on the powder/agglomerates.[40] The optimized agglomerates exhibited a significant improvement in the packability compared to the pure drug [Figure 8]. The improvement in true density in the agglomerates compared to the pure drug was also an indication of enhanced compaction. The evaluated constants of the Heckel plot of the pure drug and optimized agglomerates are depicted in Table 10. It was further confirmed that the elastic recoveries of the agglomerated crystals were smaller than those of the original drug crystals [Table 10].

The slope of the Heckel plot *k* indicates the plastic behavior of the material [Figure 8]. The larger the value of *k*, the more superior the plasticity of the material. The linearity in the Heckel plot was an indication of plastic deformation during compression. Furthermore, *A* value of the optimized agglomerates was less than of the pure drug. This result suggested that a low compression pressure was required to attain the closest packing of the agglomerates, fracturing of the texture, and densifying of the fractured particles.[41] The low value of yield strength was again an indication of low resistance to pressure, good densification, and uncomplicated compaction.[42] Thus, the Heckel plot data suggested that the agglomerated crystals were fractured easily and the new surface of crystals generated might contribute to promote plastic deformation under compression.[43] Again, smaller elastic recoveries in the case of the agglomerated crystals proved the above findings.

Table 9: Packability parameters of drug and optimized agglomerates

Batch	Kawakita's constant		Kuno's constant
	a	b^{-1}	*K*
Drug	0.424	17.455	0.0795
Optimized formulation	0.0661	1.2393	0.1247

Table 10: Compressional and elastic recovery study

Batch	Heckel plot parameters		Yield strength (σ_o)	Elastic recovery (%)
	k	*A*		
Drug	0.079	1.375	9.746	4.453
Optimized formulation	0.0931	0.0143	0.8879	0.371

In vitro dissolution study of optimized agglomerates

The optimized agglomerates showed higher dissolution as compared to the pure drug [Figure 9]. The improvement in dissolution might be due to the reduction of crystallinity which is under further investigation.

Similarity factor (f_2)

The similarity factor (f_2) as defined by the FDA is logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percentage (%) dissolution between the two curves. It is calculated by following equation:

$$f_2 = 50 \times \log\left[\left\{1+\frac{1}{n}\sum_{r=1}^{n} wt\ (Rt - Tt)\right\}^{-0.5} \times 100\right]$$

where, n = number of time points

R_t = % dissolved at time t of reference product (pre change)

T_t = % dissolved at time t of test product (post change).

Similarity factor f_2 is used to check the similarity between release profile of the reference standard and the test formulation. It is adopted by the FDA Center for Drug Evaluation and Research (CDER) as an assessment criterion of similarity between different *in vitro* profiles, and its value ranges from 50 to 100; a value larger than 50 shows similarities.[44,45] Therefore, the pure drug were taken as a reference standard. The calculated value for f_2 was 45.85, which was found to be less than 50, which shows difference between the release profiles of the pure drug and optimized agglomerates.

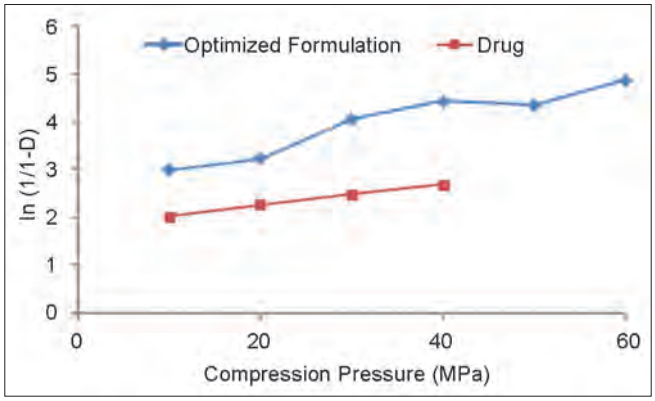

Figure 8: Heckel plots of drug and optimized agglomerates

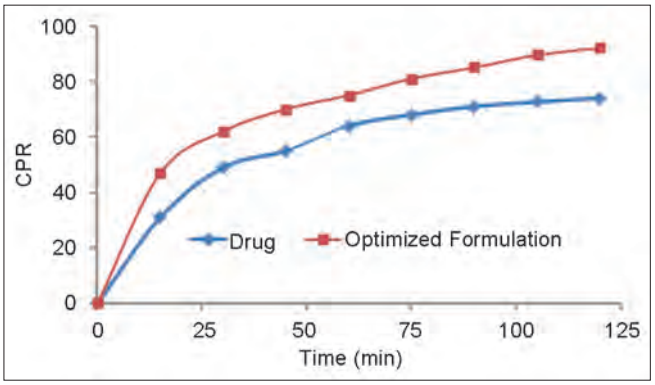

Figure 9: *In vitro* dissolution profile of optimized batch and pure drug

Table 11: Results of stability testing*

Test parameters	At initial time	After stability period
Drug content	99.04±1.945	98.46±2.053
d_g	0.461±0.011	0.448±0.009
CF	0.944±0.023	0.958±0.017
CS	44.68±0.985	43.64±1.104

*All the values are expressed as mean±S.D. (n=3), d_g: Mean geometry diameter, CF: Circularity factor, CS: Crushing strength

Stability study

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specification. Drug decomposition or degradation occurs during stability, because of the chemical alteration of the active ingredients or due to product instability, lowering the concentration of the drug in the dosage form. The results after the stability period are given in Table 11. Results of the stability study show no remarkable change in the all selected responses.

CONCLUSION

The CCA technique can be successfully employed as an alternate to conventional wet granulation. The agglomerates of racecadotril were obtained with excellent physicomechanical properties. They possessed increased particle size, sphericity, and crushing strength resulting in excellent flowability and packability due to reduced interparticulate friction. The dissolution study of the prepared agglomerates showed slight enhancement in the rate of drug release compared to the pure drug. The presence of suitable excipients is important, and again, optimization of excipient concentration is essential to obtain agglomerates with desired properties. The systematic approach enables us to obtain ready-to-compress agglomerates of active pharmaceutical ingredients by using the novel CCA technique and avoiding the time-consuming traditional wet granulation method.

ACKNOWLEDGMENT

The authors are grateful to the Gujarat Council on Science and Technology (GUJCOST), Gandhinagar, Gujarat for providing financial assistance in this work (MRP-2015538). They also express their gratitude to the Evonic Degussa Incorporation, Mumbai, India for providing samples of Eudragit as a gift.

REFERENCES

1. Rasenack N, Müller BW. Crystal habit and tableting behavior. Int J Pharm 2002;244:45-57.
2. Tiwari AK. Modification of crystal habit and its role in dosage form performance. Drug Dev Ind Pharm 2001;27:699-709.
3. Joshi A, Shah SP, Mishra AN. Preparation and evaluation of directly compressible form of rifampicin and ibuprofen. Ind J Pharm Sci 2003;65:232-8.
4. Usha AN, Mutalik S, Reddy MS, Ranjith AK, Kushtagi P, Udupa N. Preparation and *in vitro*, preclinical and clinical studies of aceclofenac spherical agglomerates. Eur J Pharm Biopharm 2008;70:674-83.
5. Paradkar AR, Pawar AP, Jadav NR. Crystallo-co-agglomeration: A novel particle engineering technique. Asian J Pharm 2010;4:4-10.
6. Gokonda SR, Hileman GA, Upadrastha SM. Development of matrix controlled release beads by extrusion-spheronization techniques technology using a statistical screening design. Drug Dev Ind Pharm 1994;20:279-92.
7. Paradkar AR, Maheshwari M, Ketkar AR, Chauhan B. Preparation and evaluation of ibuprofen beads by melt solidification technique. Int J Pharm 2003;255:33-42.
8. Johansen A, Schaefer T, Kristensen HG. Evaluation of melt agglomeration properties of polyethylene glycols using a mixer torque rheometer. Int J Pharm 1999;183:155-64.
9. Sprockel OL, Sen M, Shivanand P, Prapaitrakul W. A melt extrusion process for manufacturing matrix drug delivery systems. Int J Pharm 1997;155:191-9.
10. Kawashima Y, Lin SY, Naito M, Takenama H. Direct agglomeration of sodium theophylline crystals produced by salting out in liquid. Chem Pharm Bull 1982;30:1837-43.
11. Kawashima Y, Okumura M, Takenama H. Spherical crystallization: Direct spherical agglomeration of salicylic acid during crystallization. Science 1982;216:1127-8.
12. Kadam SS, Mahadik KR, Paradkar AR. A process for making agglomerates for use as or in a drug delivery system. Indian Patent 1997;183036.
13. Pawar A, Paradkar A, Kadam S, Mahadik K. Agglomeration of Ibuprofen with talc by novel crystallo-co-agglomeration technique. AAPS PharmSciTech 2004;5:E55.
14. Maghsoodi M, Taghizadeh O, Martin GP, Nokhodchi A. Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. Int J Pharm 2008;351:45-54.
15. Jadhav N, Pawar A, Paradkar A. Design and evaluation of deformable talc agglomerates prepared by crystallo-coagglomeration technique for generating heterogeneous matrix. AAPS PharmSciTech 2007;8:E59.
16. Pawar A, Paradkar A, Kadam S, Mahadik K. Crystallo-coagglomeration: A novel process to obtain ibuprofen-paracetamol agglomerates. AAPS PharmSciTech 2004;5:E44.
17. Chavda V, Maheshwari R. Tailoring of ketoprofen particle morphology via novel crystallocoaglomeration technique to obtain direct compressible material. Asian J Pharm 2008;2:61-7.
18. Jadhav N, Pawar A, Paradkar A. Effect of drug content and agglomerate size on tablet ability and drug release characteristics of bromhexine hydrochloride-talc agglomerates prepared by crystallo-co-agglomeration. Acta Pharm 2010;60:25-38.
19. Sarfaraz M, Khan K, Doddayya H, Reddy S, Udupi R. Particle design of aceclofenac-disintegrant agglomerates for direct compression by crystallo-co-agglomeration technique. Asian J Pharm Tech 2011;1:40-8.
20. Schwartz JC, Lecomte JM, Form of administration of racecadotril. US Patent 20090186084A1, 2009.
21. Martin A, Swarbrick J, Cammarata A. Physical pharmacy: Physical chemical principles in the pharmaceutical sciences. Bombay, India; Varghese Publishing House; 1991. p. 423-52.
22. Raval MK, Sorathiya KR, Chauhan NP, Patel JM, Parikh RK, Sheth NR. Influence of polymers/excipients on development of agglomerated crystals of secnidazole by crystallo-co-agglomeration technique to improve processability. Drug Dev Ind Pharm 2012 [Epub ahead of print].

23. Jaroz PJ, Parrott EL. Comparison of granule strength and tablet tensile strength. J Pharm Sci 1983;72:530-5.
24. Gold GR. Devall N, Palermo BT, Slater JG. Powder flow studies II. Effect of glidants on flow rate and angle of repose. J Pharm Sci 1966;55:1291-5.
25. Train D. Some aspects of the property of angle of repose of powders. J Pharm Pharmacol 1958;10:127-35.
26. Jallo LJ, Ghoroi C, Gurumurthy L, Patel U, Dave RN. Improvement of flow and bulk density of pharmaceutical powders using surface modification, Int J Pharm 2012;423:213-25.
27. Pilpel N. The flow properties of magnesia. J Pharm Pharmacol 1964;16:705-16.
28. Carr RL. Evaluating flow properties of solids. Chem Eng 1965;72:163-8.
29. Schüssele A, Bauer-Brandl A. Note on the measurement of flowability according to the European Pharmacopoeia. Int J Pharm 2003;257:301-4.
30. Hausner HH. Friction conditions in a mass of metal powder. Int J Powder Metall 1967;3:7-13.
31. Kawakita K, Tsutsumi Y. A comparison of equations for powder compression. Bull Chem Soc Jpn 1966;39:1364-8.
32. Nordstrom J, Klevan I, Alderborn G. A particle rearrangement index based on the Kawakita powder compression equation. J Pharm Sci 2009;98:1053-63.
33. Kuno H. Funtai (powder theory and application). In: Iinoya K, Beddow JK, Jimbo G, editor. Tokyo: Maruzen; 1979. p. 342.
34. Mallick S, Pradhan SK, Chandran M, Acharya M, Digdarsini T, Mohapatra R. Study of particle rearrangement, compression behavior and dissolution properties after melt dispersion of ibuprofen, Avicel and Aerosil. Results Pharma Sci 2011;1:1-10.
35. Heckel RW. An analysis of powder compaction phenomena. Trans Mettall Soc AIME 1961;221:1001-8.
36. Armstrong NA, Haines-Nutt RF. Elastic recovery and surface area changes in compacted powder systems. Powder Technol 1974;9:287-90.
37. Garala KC, Shah PH. Influence of crosslinking agent on the release of drug from the matrix transdermal patches of HPMC/ Eudragit RL 100 polymer blends. J Macromolecular Sci Part A 2010;47:273-81.
38. Kumar S, Chawla G, Bansal AK. Spherical crystallization of mebendazole to improve processability. Pharm Dev Technol 2008;13:559-68.
39. Yadav VB, Yadav AV. Comparative tabletting behavior of Carbamazepine granules with spherical agglomerated crystals prepared by spherical crystallization technique. Int J Chem Tech Res 2009;1:476-82.
40. Barot BS, Parejiya PB, Patel TM, Parikh RK, Gohel MC. Development of directly compressible metformin hydrochloride by the spray-drying technique. Acta Pharm 2010;60:165-75.
41. Kawashima Y, Cui F, Takeuchi H, Niwa T, Hino T, Kiuchi K. Improvement in flowability and compressibility of pharmaceutical crystals for direct tabletting by spherical crystallization with a two solvent system. Powder Technol 1994;78:151-6.
42. Patra NC, Singh SP, Pandit HK, Vimla M. A systematic study on micromeritic properties and consolidation behaviour of Terminalia Arjuna bark powder for processing into tablet dosage form. Int J Pharma Exp 2007;6:6-10.
43. Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya K, Hino T. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tabletting designed by spherical crystallization process. Powder Technol 2003;130:283-9.
44. US Department of Health and Human Services, Food And Drug Administration, Centre for Drug Evaluation and Research (1997). Guidance for Industry: Dissolution Testing of Immediate Release Solid Dosage Forms. Available from: http://www.fda.gov/Drugs/ Guidance compliance Regulatory Information/Guidance/ ucm070 246.pdf [Last accessed on 2011 Jun 19].
45. EMEA: Committee for Proprietary Products, London, UK (1999). Note for Guidance on Quality of Modified Release Product: A Oral Dosage form. Available from: http://www.ema.europa.eu/pdfs/ human/qwp/060496en.pdf. [Last accessed on 2011 Jun 19].

How to cite this article: Garala K, Patel J, Patel A, Raval M, Dharamsi A. Influence of excipients and processing conditions on the development of agglomerates of racecadotril by crystallo-co-agglomeration. Int J Pharma Investig 2012;2:189-200.
Source of Support: Nil. **Conflict of Interest:** None declared.