ORIGINAL ARTICLE

Sustained Release Spherical Agglomerates of Tiaprofenic Acid Prepared by Quasi-emulsion Solvent Diffusion Method

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Abstract

Purpose: The purpose of this study was to prepare sustained release (SR) spherical agglomerates with improved flow and compression properties using spherical crystallization technique. **Methods:** The spherical agglomerates of tiaprofenic acid were prepared by using quasi-emulsion solvent diffusion technique. Acetone and 0.1 N HCl were used as good solvent and poor solvent, respectively, while Eudragit RS100 and RL100 were used as release retardant polymers. The prepared agglomerates were evaluated for micromeritic, mechanical, and compression properties. Morphology and release characteristic of agglomerates was evaluated by scanning electron microscopy (SEM) analysis and *in-vitro* dissolution study, respectively. Differential scanning calorimetry (DSC) and Fourier transform-infrared (FT-IR) were performed to determine the presence of any drug-polymer interaction. **Results:** Spherical agglomerates were generated with uniform dispersion of drug within the matrix of polymer having size in the range of 100-500 µm. Due to spherical shape, agglomerates showed excellent flow, packability, compatibility, and mechanical properties. Good mechanical strength was indicated through higher crushing strength of agglomerates. Improved compressibility of agglomerates was indicated by lower σ_0 value in Heckel plot analysis, higher tensile strength, and lower elastic recovery compared to pure drug crystals. Sphericity and surface smoothness of agglomerates were revealed in SEM photos. *In-vitro* dissolution study indicated SR of drug for prolonged period. DSC and FT-IR indicated the absence of drug-polymer interaction and no change in molecular structure of drug due to agglomeration in the presence of polymers. **Conclusion:** Quasi-emulsion solvent diffusion technique has been successfully utilized for the development of directly compressible SR spherical agglomerates of poorly soluble drugs like tiaprofenic acid.

Key words: Direct compression, quasi-emulsion solvent diffusion, spherical agglomerates, sustained release, tiaprofenic acid

INTRODUCTION

Spherical crystallization techniques are the novel innovation in particle engineering in which crystallized drug particles are tailored to spherical agglomerates, which can be utilized for direct compression to save money and time for tableting. As a nonconventional particle size enlargement technique, spherical crystallization directly transforms crystals into a compacted spherical form during crystallization.[1,2] The method is widely used to improve flowability, packability, and compactibility of crystalline drugs making them suitable for direct compression.[3-5] The technique is in addition found to be valuable for enhancement in wetting, solution, and dissolution properties of a variety of APIs.[6-8] This technique has been further extended to be used with the polymers for producing modified release drug delivery systems such as microspheres,[9] microballoons,[10] biodegradable nanospheres,[11] and microcapsules.[12] Taste masking of bitter drugs can also be done by utilizing spherical crystallization technique.[13,14]

Among the several techniques available for spherical crystallization, quasi-emulsion solvent diffusion technique

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is promising for the preparation of agglomerates of poorly soluble drugs. This process involves the formation of quasi-emulsion of drug solution in good solvent with a poor solvent (nonsolvent) followed by counter diffusion of good solvent and poor solvent resulting in crystallization and agglomeration of the drug. A suitable polymer is required to stabilize emulsion. Residual good solvent present in dispersed globules/droplets acts as a bridging liquid to induce agglomeration of the generated crystals.[15] It could provide significant advantages over conventional techniques for preparation of microspheres. This process involves the coprecipitation of drug and polymers to produce functional drug devices depending on the polymer properties such as sustained release (SR) microspheres,[16,17] microballoons,[10] microcapsules,[12] and biodegradable nanospheres.[11] Quasi-emulsion solvent diffusion method could simplify the traditional manufacturing processes for SR preparations having solid dispersion structure and is suitable for preparing the sustained-release microspheres for poorly water-soluble drug.[18]

Tiaprofenic acid (5-benzoyl-alpha-methyl-2-thiophene-aceticacid) is a member of the 2-arylpropionic acid (2-APA) class of nonsteroidal anti-inflammatory drugs and is effective in rheumatoid arthritis, osteoarthritis, musculoskeletal disorder, soft tissue injuries, and a variety of inflammatory conditions. It is an inhibitor of prostaglandin synthetase enzymes which are known to be associated with inflammation and pain. The drug possesses very poor flow and compaction properties which make it unsuitable for direct compression. The drug has a relatively short elimination half-life of only 1.5-2.5 h, which is independent of dose,[19,20] and therefore, it is required to be formulated as a SR delivery system which modifies the release rate of a drug and prolongs its duration of action.

This study was performed to prepare SR spherical agglomerates of poorly soluble drug Tiaprofenic acid by quasi-emulsion solvent diffusion technique of spherical crystallization to improve tableting properties to make it suitable for direct compression. The prepared agglomerates were subjected to evaluate for improvement in micromeritic, mechanical, and compression properties as well as dissolution behavior.

MATERIALS AND METHODS

Materials

Tiaprofenic acid was procured from Ningbo Pharma, China. Eudragit RS100 and Eudragit RL100 were procured from Corel Pharma-Chem, Ahmedabad, India. Acetone and HCl were purchased from Merck Pvt. Ltd., Mumbai, India. All other solvents and chemicals used were of analytical grade and purchased from Loba Chemie Pvt. Ltd., Mumbai, India.

Preparation of agglomerates

The spherical agglomerates of TPA were prepared by quasi-emulsion solvent diffusion method of spherical crystallization using various types and concentration of polymers as shown in [Table 1]. The drug and polymer were dissolved in acetone which served as a good solvent and binding liquid and crystallization was carried out by adding the solution of drug and polymer to a beaker filled with poor solvent 0.1 N hydrochloric acid solution which was kept under stirring at the rate of around 500 RPM using magnetic stirrer. It is stirred continuously for about 1 h and then the agglomerates generated were allowed to settle down before removed by filtration and dried for 24 h at ambient temperature. Various parameters such as rate and duration of stirring and quantity of polymer were optimized to prepare agglomerates with desired characteristics.

Drug loading and % yield of agglomerates

Drug loading efficiency is expressed as percentage (%) and is calculated as the ratio of experimental drug content to theoretical one.

Drug loading was determined by dissolving accurately weighed quantity of agglomerates (containing drug equivalent to 50 mg) into 50 ml of phosphate buffer pH 7.4 in a volumetric flask. After appropriate dilution with the same solution, absorbance of diluted solution was measured using ultraviolet-visible (UV) spectrophotometer at 316.0 nm. A calibration equation was used to calculate the experimental drug content. The % drug loading was calculated using formula:

$$\% \text{ drug loading} = \frac{\text{Experimental drug content}}{\text{Theoretical content}} \times 100 \quad (1)$$

To determine % yield of agglomerates, weight of drug and polymer utilized and weight of agglomerates after drying

Table 1: Formulation of agglomerates

Batch code	Polymer	Polymer: Drug ratio	Polymer %
A1	Eudragit RS100	1:3	25.00
A2	Eudragit RS100	1:2.5	28.57
A3	Eudragit RS100	1:2	33.33
A4	Eudragit RS100	1:1.5	40.00
A5	Eudragit RS100	1:1	50.00
B1	Eudragit RL100	1:3	25.00
B2	Eudragit RL100	1:2.5	28.57
B3	Eudragit RL100	1:2	33.33
B4	Eudragit RL100	1:1.5	40.00
B5	Eudragit RL100	1:1	50.00

was determined. The % yield of agglomerates was calculated using formula:

$$\% \text{ yield} = \frac{\text{Total weight of agglomerates formed}}{\text{Total weight of drug and polymer used}} \times 100 \quad (2)$$

Micromeritic parameters

The untreated drug crystals and agglomerates were subjected to determine micromeritic parameters. Optical microscopy method was utilized to determine particle size and size distribution. Particle size analysis was performed using eye piece micrometer which was calibrated using stage micrometer. To determine size and size distribution, the size of randomly selected 50 agglomerates were measured and mean diameter was calculated.

Flow property of the prepared agglomerates was studied by determination of angle of repose, Carr's compressibility index and Hausner's ratio. Fixed funnel method was utilized to measure angle of repose. The agglomerates were allowed to flow under the gravitational force through a funnel fixed at a constant height (h) and the mean radius (r) of the heap of powder cone was measured when the apex of the conical pile so formed touched the tip of funnel. The angle of repose was calculated using following equation:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right) \quad (3)$$

Poured bulk density (ρ_0) and tapped bulk density (ρ_t) were used to calculate Carr's index and Hausner's ratio which reflect compressibility of the agglomerates and also have correlation with flowability. For the determination of poured and tapped bulk densities of untreated drug and agglomerates electro lab tap density tester was utilized. Following equations were used to calculate Carr's index and Hausner's ratio.

$$\text{Carr's index (\%)} = \frac{\rho_t - \rho_0}{\rho_t} \times 100 \quad (4)$$

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_0} \quad (5)$$

Packability and compactibility parameters

Packability and compactibility of agglomerates were evaluated by analysis of the tapping process and determining the parameter a, b, 1/b, and k in the Kawakita's and Kuno's equations. Constant a describes the degree of densification due to tapping and called as compactibility while 1/b is a constant related to cohesion called cohesiveness and describes how fast or easily the ultimate packing state was achieved. The compactibility a and cohesiveness 1/b can be determined using the slope and intercept obtained from straight line curve of n/C Vs. n/a using Kawakita's equation.[21,22] Parameter (k) calculated using Kuno's equation gives idea about the rate of packing of powder/granules.[23]

Kawakita's equation: $n/C = 1/(ab) + n/a$ (6)

Kuno's equation: $\ln(q_t - q_n) = -Kn + \ln(q_t - q_0)$ (7)

Where, $C = (V_0 - V_n)/V_0$; n is number of tapping; V_0 is initial volume and V_n is volume after n number of tap; q_0 is the initial density, q_n is density at n tap, and q_t density at infinite tap; constants a, b, and K represents compactibility, cohesiveness, and packability of powder under mechanical stress.

Heckel plot analysis

Heckle plot analysis was performed to determine compression behavior of prepared agglomerates. The prepared agglomerates were compressed using a 6 mm flat-faced punch at the constant compression speed at different pressures (10, 20, 30, and 40 MPa).[24] The lubrication of punch and die were done using 1% w/v magnesium stearate dispersion in acetone before compression. The compression characteristics of the agglomerates were evaluated using parameters of Heckel equation.[25,26]

$$\ln [1/E] = KP + A \quad (8)$$

Where, E is the % porosity of the tablet at applied pressure P, the reciprocal of the slope of Heckel plot K is the mean yield pressure P_y. The constant A indicates densification at low pressure.

The value of E can be calculated using following equation.

$$E = 100\left(1 - \frac{4W}{P\ D\ H}\right) \quad (9)$$

Where, W: Weight of tablet mass, P_t: True density, H: Thickness and D: Diameter

Mechanical handling properties

For mechanical handling properties, elastic recovery, and tensile strength of compacts of agglomerates were determined while crushing strength of agglomerates was evaluated to determine mechanical strength. Elastic recovery of compacts was measured using the compacts prepared from untreated drug and prepared agglomerates. After determination of thickness of compacts instantaneously after ejection (H_c), the compacts were subjected for the relaxation for 24 h and thickness was again measured after relaxation (H_e). Elastic recovery, expressed as percentage (%), was calculated using the following equation.[27]

$$\%ER=[(H_e-H_c)/H_c] \times 100 \quad (10)$$

After determination of elastic recovery, compacts of agglomerates were utilized to determine tensile strength. For measurement of tensile strength, the force required to fracture the compacts (F) was measured using hardness tester.[28] The following equation was used to calculate tensile strengths of the compacts.[29,30]

$$T=\frac{2F}{\pi D t} \quad (11)$$

Where, D is diameter and t is thickness of the compacts of agglomerates, respectively.

Mercury load cell method utilizing 10 ml hypodermic glass syringe was used to determine crushing strength of the prepared agglomerates.[31] The single agglomerate was positioned inside the syringe and the mercury was added at constant rate via hollow syringe tube until agglomerate broke. The total mass in g of the tube along with mercury was measured at the point when agglomerate breaks. This total weight gave the value of crushing strength for the agglomerate undergone test.

Surface topography and sphericity determination

Photomicrographs of the drug and prepared agglomerates were taken using an optical microscope and observed for surface morphology. Sphericity determination of agglomerates was performed by calculating shape factor (P) and circularity factor (S). Shape factor (P) and circularity factor (S) for the prepared agglomerates were obtained from the area (A) and perimeter (P') of the agglomerates using equations 12 and 13.[32] The photomicrographs of the agglomerates were taken, and tracings of the enlarged photomicrographs were used for the measurement of area and perimeter.

$$\text{Shape factor } (P)=P''/P' \quad (12)$$

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

$$\text{Circularity Factor } (S) = (P')^2/4\pi A \quad (13)$$

Differential scanning calorimetry (DSC)

To determine the drug-polymer compatibility and molecular interaction of drug during crystallization and agglomeration, DSC of the agglomerates were performed. DSC of the pure drug crystals and prepared agglomerates were carried out using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of drug within agglomerates. The samples were kept in hermetically sealed aluminum pans under air atmosphere and heated in the temperature range of 45°C to 300°C at a constant heating rate of 10°C/min. Empty aluminum pan was used as a reference.

Fourier transform-infrared (FT-IR) spectroscopy

FT-IR spectra of pure drug and prepared agglomerates were recorded to determine the drug-polymer compatibility and evaluate any structural modification of drug during crystallization and agglomeration. FT-IR was performed using Infrared spectrophotometer (FT-IR 8400 spectrophotometer, Shimadzu, Japan). The samples dispersed in KBr disc/pellet were placed in the light path for recording the IR Spectra.

In vitro dissolution study

In vitro dissolution studies for prepared agglomerates were performed using USP Apparatus I (Basket type) to evaluate the influence of agglomeration process and polymers on drug release. 900 ml of phosphate buffer pH 7.4 was used as a dissolution medium at 37°C±0.5°C and 50 RPM. Samples of 5 ml were withdrawn at a predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 h) and each time the same amount of dissolution medium was added to replace the withdrawn samples. After suitable dilution with medium samples was analyzed for drug content by UV-visible spectroscopy (Shimadzu UV-1700) at 316 nm, and the cumulative percentage drug released was calculated.

RESULTS AND DISCUSSION

The spherical agglomerates of the drug with polymer was prepared by quasi-emulsion solvent diffusion technique of spherical crystallization utilizing two solvent system including acetone as a good solvent and 0.1 N HCl as a bad solvent. Speed (500 RPM) and duration of stirring (1 Hr), and other processing variables were optimized through preliminary trials for good agglomeration. Mechanism of formation of spherical agglomerates involve the formation of quasi-emulsion droplets and then counter diffusion of solvents resulting in crystallization and simultaneous agglomeration of particles resulting into formation of spherical agglomerates with homogeneous dispersion of crystallized drug. Acetone also worked as bridging liquid which in the presence of polymer formed liquid bridges between crystallized particles to form agglomerates. As shown in Table 2, the percentage yield for all batches (≥80%) and drug loading efficiency of agglomerates (≥87%) found satisfactory. It indicated that the drug and polymer were recrystallized at the highest amount to form agglomerates without any substantial loss of drug and polymer. As the concentration of polymer increased, yield, and drug loading also increased which may be attributed to more agglomeration in the presence of polymer. These further confirmed by increase in the mean size of agglomerates with increase in polymer concentration.

The agglomerates prepared were of the size in the range of 100-500 µm [Figures 1 and 2] with average size about 300 µm [Table 3] indicating good agglomeration after

crystallization. Increase in mean diameter of agglomerates was about 10-20 times compared to pure drug crystals [Figure 3]. This finding indicated that drug crystals were agglomerated simultaneously after crystallization to form spherical agglomerates in the presence of polymer. Particle size of the agglomerates in Batch A1 and B1 were smaller compared to other batches which may be due to a lower concentration of polymer. As the concentration of polymer increased, the size distribution shifted to higher size range [Figures 1 and 2] indicated more agglomeration at higher polymer concentration. There was considerable improvement in flow and packing properties of agglomerates indicated by remarkable reduction in Carr's index, Hausner's ratio, and angle of repose of agglomerates compared to pure drug. This can be attributed to spherical shape and smooth surface of the agglomerates formed due to simultaneous agglomeration of drug crystals.[33] Thus, agglomerates prepared in the presence of polymer possessed improved micromeritic properties compared to pure drug crystals.

As revealed in [Table 4], values of parameter a (compactibility) and parameter 1/b (cohesiveness) for agglomerates were smaller compared to that of pure drug crystals in Kawakita's equation. This indicated improvement in packability of agglomerates compared to pure drug crystals. These also indicated slower apparent packing velocity obtained by tapping for the agglomerates than that for the drug crystals, as the agglomerates were packed more closely, even without tapping, due to improved flowability, and packability, and there were not significant changes in the volume due to tapping. Results also confirmed by increased values of K (Kuno's constant) for agglomerates compared to pure drug crystals, calculated by means of Kuno's equation. Higher values of parameter "K" obtained from Kuno's equation for agglomerates were an indication of higher packing rate. Again it was also concluded that lower concentration of polymer was not sufficient to produce drastic improvement in packability. These findings suggested remarkable improvements in compactibility and packability of spherical agglomerates prepared with polymers due to improved micromeritic properties.[34]

Table 2: % yield and drug loading efficiency of agglomerates

Batch	Drug loading efficiency	% yield
A1	87.23%	80.25%
A2	90.00%	89.43%
A3	90.46%	94.00%
A4	90.31%	95.20%
A5	91.08%	96.00%
B1	88.92%	81.50%
B2	90.15%	90.57%
B3	90.62%	95.33%
B4	89.69%	94.80%
B5	91.23%	96.50%

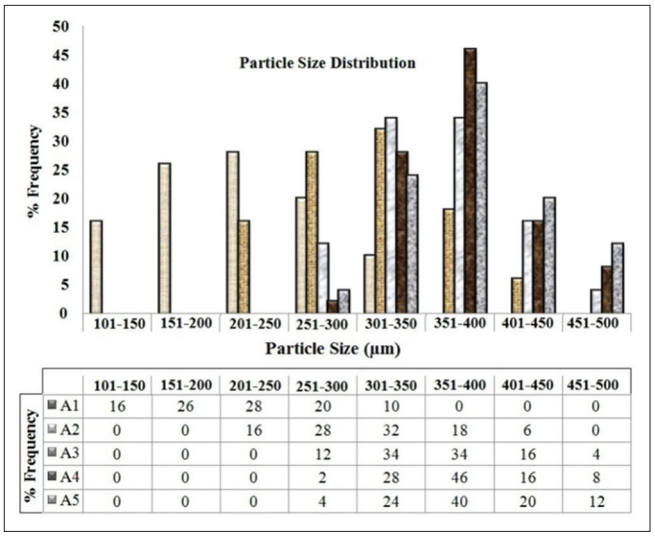

Figure 1: Particle size distribution of agglomerates prepared with Eudragit RS100 (A1 to A5)

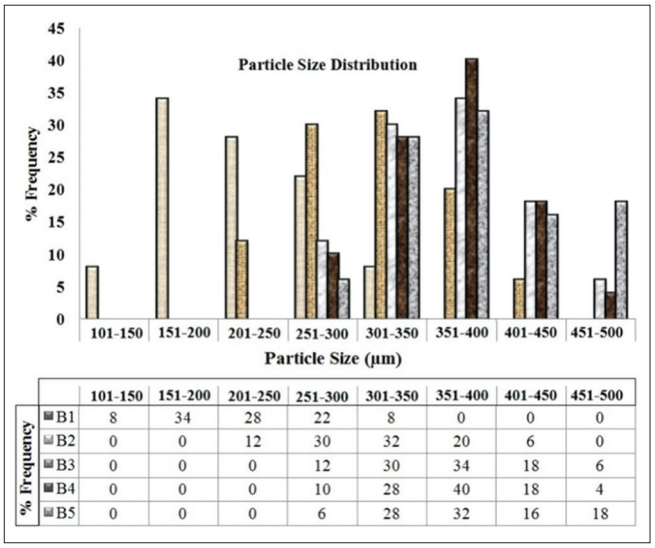

Figure 2: Particle size distribution of agglomerates prepared with Eudragit RL100 (B1 to B5)

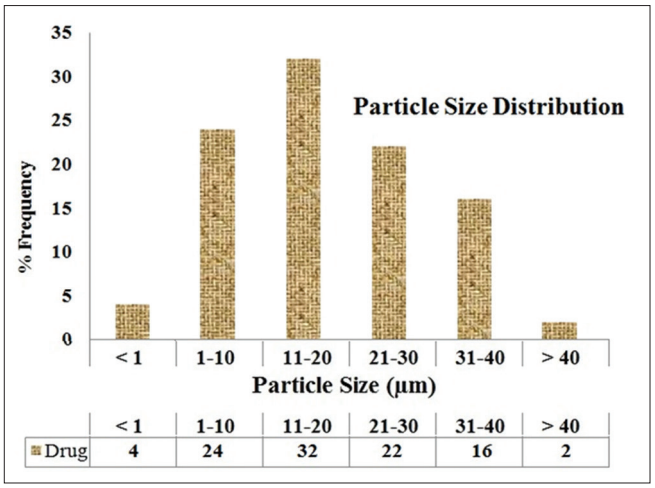

Figure 3: Particle size distribution of pure drug crystals

Table 3: Micromeritic properties of drug and agglomerates

Batch	Arithmetic mean diameter (μm)	Angle of repose* (°θ)	Carr's index* (%)	Hausner's ratio*
Drug	19.73	45.49±0.970	34.76±0.82	1.53±0.019
A1	217.86	27.35±0.405	23.18±1.05	1.30±0.018
A2	311.46	23.91±0.239	12.59±1.23	1.14±0.016
A3	361.32	22.90±0.311	12.50±1.07	1.14±0.014
A4	378.39	22.86±0.303	11.19±1.21	1.13±0.015
A5	383.72	22.91±0.290	9.27±1.10	1.10±0.013
B1	221.33	27.09±0.412	23.19±1.40	1.30±0.024
B2	315.46	23.55±0.239	15.23±1.08	1.18±0.015
B3	364.79	23.45±0.229	15.33±1.15	1.88±0.016
B4	366.92	23.05±0.150	13.24±1.08	1.15±0.014
B5	383.46	22.95±0.225	11.91±1.86	1.44±0.024

*Results are mean±standard deviation of n=3 observations

Table 4: Packability parameters of drug and agglomerates

Batch	Kawakita's constants		Kuno's constants
	A	1/b	K
Drug	0.3557	3.3086	0.0684
A1	0.2245	1.9028	0.1087
A2	0.1593	1.5770	0.0966
A3	0.1395	1.5845	0.1161
A4	0.1192	1.3459	0.1095
A5	0.1014	1.3801	0.1215
B1	0.2443	1.6996	0.1118
B2	0.1591	1.3452	0.1217
B3	0.1623	1.3452	0.1215
B4	0.1418	1.2243	0.1360
B5	0.1395	1.5845	0.1161

Table 5: Heckel plot parameters

Batch	Heckel plot constants		Yield strength (σ_0)
	Constant (A*)	Yield pressure (P_y)	
Drug	0.941	37.037	12.346
A1	0.635	20.000	6.667
A2	0.634	19.608	6.536
A3	0.641	19.231	6.410
A4	0.656	18.519	6.173
A5	0.630	17.857	5.952
B1	0.607	19.231	6.410
B2	0.588	18.182	6.061
B3	0.585	17.544	5.848
B4	0.583	16.949	5.650
B5	0.585	16.393	5.464

*Indicates densification at low pressure

The parameters of Heckel plot for the pure drug crystals and agglomerates are depicted in Table 5. The true density was calculated as the density of compacts formed when maximum pressure (here 60 MPa) was applied on the powder/agglomerates.[35] The results indicated notable improvement in the compactibility of agglomerates compared to pure drug crystals. The linearity in the Heckel plot [Figures 4 and 5] was a suggestion of plastic deformation. Plastic behavior of the material was represented by the value of "K" in Heckel equation, i.e., larger the value of "K", greater is the plasticity in material. Smaller values of "A" for agglomerates compared to pure drug suggested that closest packing of the agglomerates can be obtained by applying low compression pressure.[36]

Lower values of yield strength in case of agglomerates were sign of a little resistance to pressure, good densification, and easy compaction. Moreover, the lower Py and A values of agglomerates containing polymers compared to drug crystals may be attributed to plastic deformation. Thus, Heckel plot parameters [Table 5] indicated the formation of agglomerates which were easily fractured to form new surface of crystals and might promote plastic deformation under pressure and can be compressed into compacts or tablets easily with lower pressure compared to pressure required to compress pure drug crystals.[37]

Excellent mechanical strengths of prepared agglomerates were revealed in higher values of crushing strength [Table 6]. The results of crushing strength showed higher bonding properties and enhanced strength of agglomerates which could be accredited to improved agglomeration of crystals with good bridging and bonding due to the presence of polymers. These might be due to the larger size of the agglomerates and better binding and close packing between crystals as a result of increased cohesive interaction between particles during agglomeration with polymers.[32] The presence of polymer also contributed to increase the strength

as crushing strength increased with the increase in polymer concentration. Improvement in mechanical properties of agglomerates was also indicated in higher values of tensile strength [Table 6]. Higher values for tensile strength of compacts of agglomerates compared to that of pure drug were sign of strong interparticulate bonding between the particles due to agglomeration in the presence of polymers. The formation of stronger bonds may be led by increase in fragmentations of the large size fraction due to the formation of fresh surface.[38] As shown in Table 6, values of elastic recoveries of agglomerates were lesser than that of pure drug crystals. Remarkable reduction in elastic recoveries indicated that agglomerates might fracture easily, and the fresh surfaces formed to promote plastic deformation under pressure.[37] The overall improvement in the strength of agglomerates may be owing to uniform packing of the crystals and uniform distribution of the polymer in agglomerates.

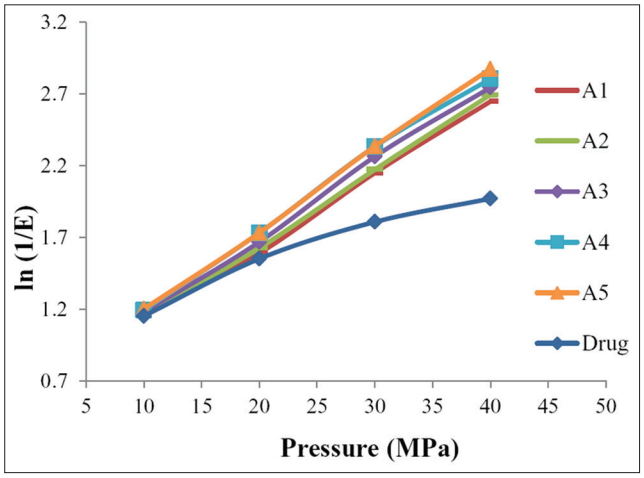

Figure 4: Heckel plots of drug (♦) and agglomerates prepared with Eudragit RS 100 (A1 to A5)

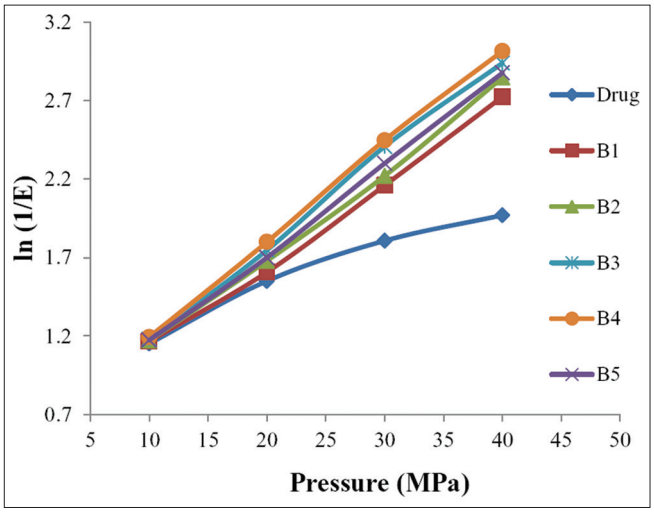

Figure 5: Heckel plots of drug (♦) and agglomerates prepared with Eudragit RL 100 (B1 to B5)

Thus, agglomerates could be easily compressed into tablet by applying lower pressure compared to pressure required for compression of pure drug crystals. Agglomerates prepared by quasi-emulsion solvent diffusion technique possessed improved micromeritic, mechanical, and compression properties making them suitable for direct compression omitting time consuming and tedious processing steps involved in conventional granulation technique.

The results revealed in Table 7 show value of shape and circularity factors near unity (1.0). Agglomerates prepared in the presence of polymers showed good agglomeration with spherical shape and smooth surface resulting into improvements in flow due to reduced interparticulate friction. Shape and circularity factor near to unity showed that agglomerates possessed nearly spherical shape. This could be further supported by encouraging results of flow properties and compressibility parameters which can be attributed to the shape toward sphericity.

DSC thermograms for drug and agglomerates confirmed the equality in crystalline structure in all batches [Figure 6].

Table 6: Mechanical handling parameters and elastic recovery

Batch	Crushing strength* (g)	Tensile strength* (kg/cm²)	Elastic recovery* (%)
Drug	-	8.755±0.723	3.955±0.451
A1	14.293±1.802	15.918±1.028	1.342±0.229
A2	28.527±2.836	17.009±0.984	1.147±0.117
A3	39.607±3.064	17.365±0.891	1.081±0.244
A4	49.843±3.123	17.808±1.052	0.948±0.231
A5	53.150±2.788	19.020±0.789	0.808±0.201
B1	13.587±1.316	14.339±1.086	1.417±0.205
B2	26.733±2.805	17.175±1.271	1.280±0.114
B3	33.380±2.468	17.248±1.108	1.150±0.120
B4	47.963±2.046	18.095±1.101	1.078±0.118
B5	54.597±3.280	18.634±0.820	0.810±0.204

*Results are mean±standard deviation of *n*=3 observations

Table 7: Sphericity parameters of agglomerates

Batch	Shape factor* (P)	Circulatory factor* (S)
A1	0.9357±0.0403	1.1469±0.0989
A2	0.9403±0.0110	1.1313±0.0260
A3	0.9769±0.0129	1.0482±0.0276
A4	0.9829±0.0163	1.0358±0.0349
A5	0.9899±0.0040	1.0281±0.0133
B1	0.9485±0.0123	1.1120±0.0284
B2	0.9738±0.0068	1.0546±0.0148
B3	0.9912±0.0040	1.0179±0.0083
B4	0.9956±0.0038	1.0089±0.0078
B5	0.9968±0.0023	1.0064±0.0047

*Results are mean±standard deviation of *n*=4 particles

Endothermic peaks for the drug and agglomerates prepared with Eudragit RS100 and Eudragit RL100 were found to be 97.12°C, 96.49°C, and 95.79°C, respectively, showing no significant variation in melting points. All thermograms possessed sharp melting point with flat baseline which indicated that material was not affected by the process of crystallization and agglomeration in the presence of polymers and also the absence of any interaction of drug with excipients during crystallization. FT-IR spectra for drug and agglomerates confirmed the absence of molecular changes in drug.

Almost every peaks present in FT-IR spectra of the drug were present in FT-IR spectra of agglomerates [Figure 7]. FT-IR spectra of pure drug and agglomerates showed the peaks for various functional groups such as aromatic C-H (2974.23 cm^{-1}), C=C in aromatic ring (1591.27 cm^{-1} and 1452.40 cm^{-1}), C=O acid (1726.29 cm^{-1}), C-O stretching (1159.22 and 1195.875 cm^{-1}), and monosubstituted aromatic ring (702.09 cm^{-1}). These findings indicated no molecular change in the drug during the process of crystallization and agglomeration in the presence of polymers as well as the absence of drug-polymer interaction.

The irregular shape of pure drug crystals as depicted in scanning electron microscopy (SEM) photographs [Figure 8] make them unsuitable for direct compression. SEM photographs of agglomerates [Figures 9 and 10] showed good agglomeration of crystals with spherical shape and smooth surfaces. These findings were further supported by the results obtained in sphericity determination. Improvement in size due to agglomeration was also confirmed by SEM photographs. Further, improved flow and compaction properties can also be attributed to spherical shape with smooth surfaces of agglomerates prepared using polymers compared to pure drug crystals.

The drug release rate from the agglomerates could be modified by adjusting the ratio of polymer to drug in the

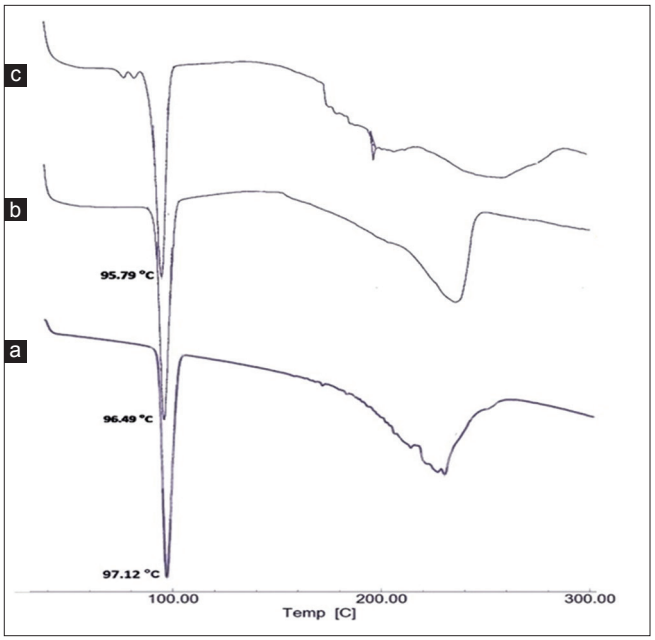

Figure 6: Differential scanning calorimetry thermogram of drug (a) and agglomerates prepared with Eudragit RS100 (b) and Eudragit RL100 (c)

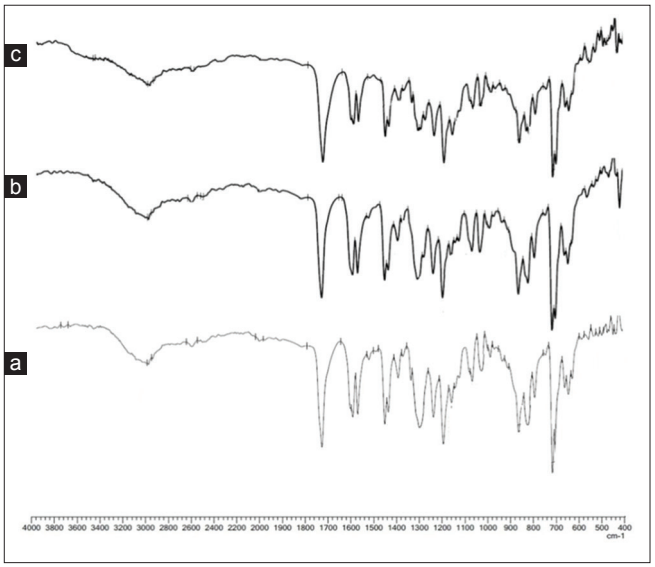

Figure 7: Fourier transform-infrared spectra of drug (a) and agglomerates prepared with Eudragit RS100 (b) and Eudragit RL100 (c)

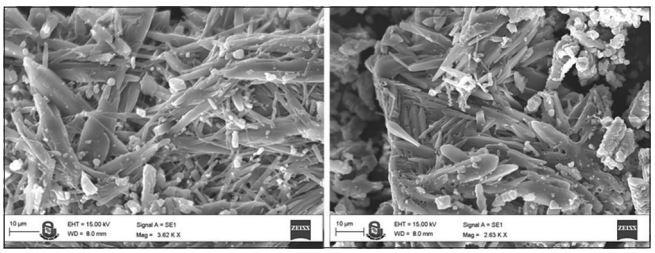

Figure 8: Scanning electron microscopy photographs of pure drug crystals

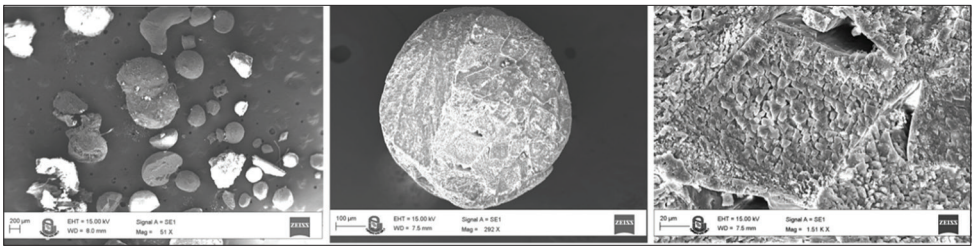

Figure 9: Scanning electron microscopy photographs of agglomerates prepared with Eudragit RS100

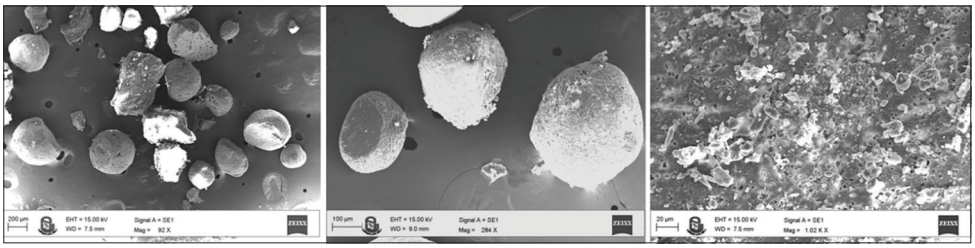

Figure 10: Scanning electron microscopy photographs of agglomerates prepared with Eudragit RL100

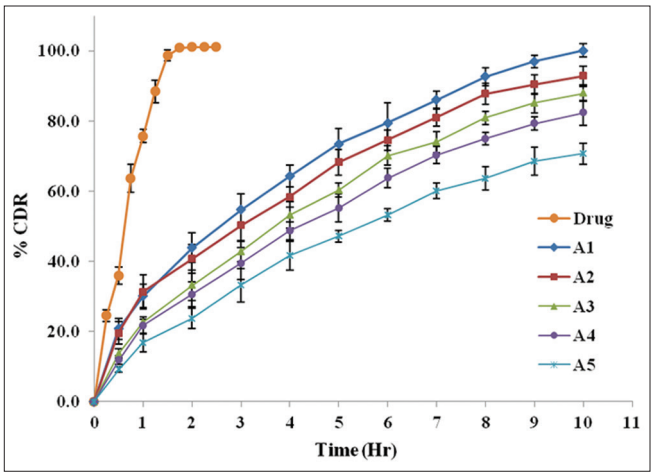

Figure 11: Dissolution profile of Drug (•) and agglomerates prepared with Eudragit RS100 (A1 to A5)

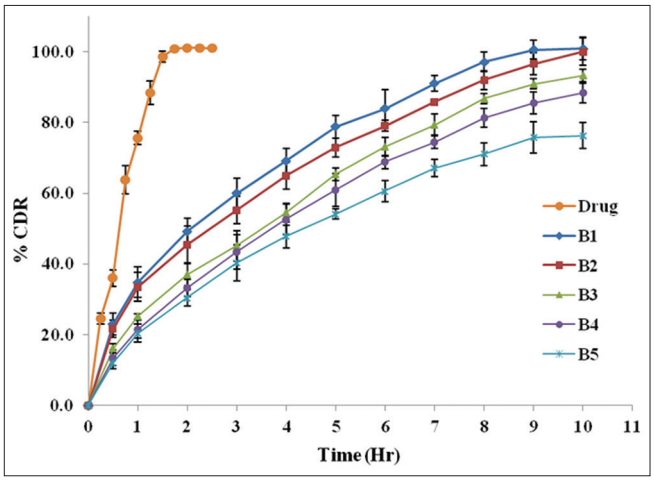

Figure 12: Dissolution profile of Drug (•) and agglomerates prepared with Eudragit RL100 (B1 to B5)

formulation. The effect of polymer on drug release rate is shown in Figures 11 and 12. The drug release rate from agglomerates was dependent on the type and concentration of polymer used. Agglomerates prepared with Eudragit RL100 showed comparatively faster rate of drug release than that of Eudragit RS100 which may be attributed to the fact that Eudragit RL has more amount of quaternary ammonium groups compared to Eudragit RS, and therefore, Eudragit RL is more permeable to water resulting in less release retardant effect. Furthermore, increase in the amount of polymer resulted in a significant decrease in drug release.

CONCLUSION

SR spherical agglomerates of TPA have been successfully prepared by quasi-emulsion solvent diffusion technique of spherical crystallization in the presence of methacrylate polymers. The agglomerates prepared by this method possessed excellent micromeritic, mechanical, and compaction properties making them suitable for direct compression. Agglomerates prepared with polymers possessed improved flow properties due to formation of compacted agglomeration with spherical shape and smooth surface. Compared to pure drug crystals, agglomerates had improved packing and compaction properties with improved tensile strength and crushing strength. Results of Heckel plot analysis suggested utilization of agglomerates for direct compression into tablets. *In-vitro* dissolution study indicated SR of drug for sufficiently prolonged period which can reduce dosing frequency and improve patient compliance. Thus, quasi-emulsion solvent diffusion method can be utilized to prepare directly compressible agglomerates of poorly soluble drugs with polymers.

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