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Hypromellose Spherical Agglomerates for Sustained Release of Tiaprofenic Acid

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ABSTRACT

The present work aimed to prepare hypromellose (HPMC) spherical agglomerates for sustained release (SR) of Tiaprofenic acid (TPA) with improved flow and compression properties using quasi-emulsion solvent diffusion technique of spherical crystallization. Acetone and 0.1 N HCl were used as good solvent and poor solvent, respectively, while hypromellose was used as release retardant polymers. The prepared agglomerates were subjected to evaluation of micromeritic, mechanical, and compression properties. Scanning electron microscopy (SEM) analysis was performed for studying morphology and release characteristic of agglomerates was evaluated by and *in-vitro* dissolution study. DSC and FT-IR were performed to evaluate the presence of any drug-polymer incompatibility. Spherical agglomerates generated possessed uniform dispersion of drug in the of polymer matrix with average particle size in the range of 200-400 µm. Improved flow, packability, compatibility, and mechanical properties of agglomerates can be attributed to spherical shape. Improved compatibility and mechanical strength of agglomerates were indicated by higher crushing strength, 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. SR of drug for prolonged period of time was revealed in *in-vitro* dissolution study. DSC and FT-IR indicated the absence of drug-polymer incompatibility. Quasi-emulsion solvent diffusion technique has been successfully utilized for the development of directly compressible SR spherical agglomerates of hypromellose containing poorly soluble drugs like tiaprofenic acid.

1. INTRODUCTION

Spherical crystallization is the non-conventional particle size enlargement technique which involves crystallization and agglomeration simultaneously in a single step converting drug crystals into compacted spherical agglomerates.[1-2] This technique has been further developed for use with the polymers, in which the drug and polymers were co-precipitated to produce functional drug devices such as microspheres[3-4], micro balloons[5], biodegradable nanospheres[6] and microcapsules.[7]

Amongst several techniques available for the preparation of sustained release microparticles, spherical crystallization technique has gained more interest as it produces microparticles with desired properties which can be utilized as a directly compressible material. The spherical crystallization technique can be modified to a simple and less expensive process to prepare spherical matrices for prolonged release of drugs. The spherical crystals of various drugs like furosemide[8], Ibuprofen[9] and ketoprofen[10] were directly modified during spherical crystallization using acrylic polymers to prepare microspheres having prolonged release and improved bioavailability.

Tiaprofenic acid is a nonsteroidal anti-inflammatory drug which is a member of the 2-arylpropionic acid (2-APA) class and is effective in rheumatoid arthritis, osteoarthritis, musculoskeletal disorder, soft tissue injuries, and a variety of inflammatory conditions. It inhibits prostaglandin synthetase enzymes which are known to be associated with inflammation and pain.[11-12] The drug is having very fine crystalline form possessing very poor flow and compaction properties which make it incompatible for direct compression. The drug has a relatively short biological half-life of 1.5-2.5 h and therefore, it is required to be formulated in the forms of SR drug delivery system with modified drug release for prolonged duration of action.

The purpose of present study was to prepare sustained release spherical crystal agglomerates of Tiaprofenic acid with hypromellose (hydroxypropyl methylcellulose) by quasi-emulsion solvent diffusion technique of spherical crystallization.

2. MATERIALS AND METHODS

2.1. Materials

Tiaprofenic acid was procured from Ningbo Pharma, China. Hypromellose was procured from Loba Chemie Pvt. Ltd., Mumbai, 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.

2.2. Preparation of agglomerates

The spherical agglomerates of hypromellose containing Tiaprofenic acid were prepared by quasi-emulsion solvent diffusion method using different concentration of polymer as shown in Table-1. Acetone, which also served as a binding liquid, was used as good solvent in which drug and polymer were dissolved and crystallization was carried out by addition of this solution into a beaker containing poor solvent 0.1 N hydrochloric acid solution which was being stirred at the rate of around 500 RPM by using magnetic stirrer and continued to be stirred for about 1 h. The agglomerates generated were then allowed to settle down and removed by filtration and dried for 24 hrs at room temperature. Various parameters were optimized to prepare agglomerates with required characteristics.

Table 1: Formulation of agglomerates

Batch Code	Polymer	Polymer: Drug Ratio	Polymer %
H1	HPMC E15LV	1:3	25.00
H2	HPMC E15LV	1:2.5	28.57
H3	HPMC E15LV	1:2	33.33
H4	HPMC E15LV	1:1.5	40.00
H5	HPMC E15LV	1:1	50.00

2.3. Drug Loading and % Yield of Agglomerates

Drug loading was determined by dissolving accurately weighed quantity of agglomerates in phosphate buffer pH 7.4 in a volumetric flask. After appropriate dilution with same solution, absorbance of diluted solution was measured using UV spectrophotometer at 316 nm.

Experimental drug content was calculated from calibration equation. The % drug loading was calculated using formula:

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

To determine % yield of agglomerates, weight of drug and polymer utilized and weight of agglomerates after drying was determined. The % yield of agglomerates was calculated using formula:

$$\% \text{ yield} = \frac{(\text{total weight of agglomerates formed})}{(\text{total weight of drug and polymer used})} \text{ X } 100$$

2.4. Micromeritic Parameters

The pure drug crystals and agglomerates were subjected to determine micromeritic parameters. Particle size analysis was performed by Optical microscopy method using eyepiece micrometer calibrated with stage micrometer. To determine size and size distribution, the size of randomly selected 50 agglomerates were measured and appropriate mean diameter was calculated.

Angle of repose, Carr's compressibility index and Hausner's ratio were determined to study flow property of the prepared agglomerates. Fixed funnel method was utilized to measure angle of repose. The agglomerates were allowed to flow through a funnel fixed at a constant height (*h*) and the diameters (2r) of the pile of powder were measured and used to calculate angle of repose. The poured bulk density (ρ_0) and tapped bulk density (ρ_t) of drug and its agglomerates were determined using Electrolab tap density tester (USP). Carr's index and Hausner's ratio were calculated using poured bulk density (ρ_0) and tapped bulk density (ρ_t) values.

2.5. Packability and compatibility parameters

Packability and compatibility of agglomerates were evaluated by analysis of the tapping process and determining the parameter a, b, 1/b and k in the Kawakita and Kuno equations. Packability parameters like *a* (compressibility, or amount of densification due to tapping), *1/b* (cohesiveness, or how fast/easily the final packing state was achieved) and *K* (Kuno's

constant) were calculated using Kawakita and Kuno's equations.[13-14] The values of 'a' and 'b' were calculated from the slope and intercept of the linear plot of n/C Vs n/a.

Kawakita Equation: n/C = 1/(ab) + n/a

Where, $C = (V_0 - V_n)/V_0$

Kuno Equation: $\ln(q_t - q_n) = -Kn + \ln(q_t - q_0)$

Where, n is number of tapping; V_0 and V_n are initial volume and volume after n no. of tap; q_0, q_n and q_t are the initial density, density at n tap and density at infinite tap respectively; a, b and K are the constants representing flowability and Packability of powder under mechanical force.

2.6. 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).[15] The punch and die were lubricated using 1 % w/v dispersion of magnesium stearate in acetone. The compression behavior of the agglomerates was expressed as parameters of Heckel equation.[16]

ln [1/E] = KP + A

Where, $\boldsymbol{E}$ is the % porosity of the tablet, $\boldsymbol{P}$ is the applied pressure, $\boldsymbol{K}$ is the slope of Heckel plot; $\boldsymbol{K = 1/P_y}$. $\boldsymbol{P_y}$ is the mean yield pressure. The constant A expresses the densification at low pressure. The value of E can be calculated using following equation.

$$E = 100\left(1 - \frac{4W}{P_t \pi D^2 H}\right)$$

Where, $\boldsymbol{W}$= weight of tablet mass, $\boldsymbol{P_t}$ =true density, $\boldsymbol{H}$=thickness and $\boldsymbol{D}$= diameter

2.7. 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. The thickness of the compacts was measured immediately after ejection (H_c) and after the 24 hour relaxation period (H_e). Elastic recovery was calculated using the equation.[17]

$$\% ER = [(He - Hc) / Hc] X 100$$

After determination of diameter and thickness, the compacts used in the Heckel plot analysis were subjected for the relaxation for 24 h. Then the compacts were subjected to tensile strength measurement in which the force required to break the compacts (F) was measured.[18] The tensile strength of the compacts was calculated using the following equation.[19-20]

$$T = \frac{2F}{\pi D t}$$

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

The crushing strength of the prepared agglomerates was determined by mercury loaded cell method using 10 ml hypodermic glass syringe.[21] The agglomerate was placed inside the syringe and the mercury was added through hollow syringe tube. The total weight of the tube with mercury, at the stage where co-agglomerate breaks, gives the measure of crushing strength of that agglomerate.

2.8. Surface Topography and Sphericity Determination

Photomicrographs of the prepared agglomerates were taken using electric microscope. The surfaces of the agglomerates were observed for surface morphology.

Shape Factor (P) and Circularity Factor (S) for the prepared agglomerates were obtained from the Area (A) and Perimeter (P') of the agglomerates.[22] The photomicrographs of the

agglomerates were taken and tracings of the enlarged photomicrographs were used for the measurement of area and perimeter.

Shape Factor (P) = P"/P'

Where, P" = 2π (A/π) ½

Circularity Factor (S) = (P') 2 /4πA

2.9. Differential Scanning Calorimetry (DSC)

Thermograms of the pure drug and prepared agglomerates were performed using DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to study the thermal behavior of drug and agglomerates. The instrument comprised of calorimeter (DSC 60), flow controller (FCL60), thermal analyzer (TA 60WS) and operating software (TA 60). The samples were heated in hermetically sealed aluminum pans under air atmosphere at a scanning rate of 10°C/min from 45±1° C to 300°C in an air atmosphere. Empty aluminum pan was used as a reference.

2.10. Fourier Transform Infra-Red (FT-IR) Spectroscopy

Infrared spectra of pure drug and prepared agglomerates were recorded using Infrared Spectrophotometer (FTIR 8400 Spectrophotometer, Shimadzu, Japan). The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR Spectra.

2.11. Scanning electron microscopy (SEM)

The shape and surface morphology of pure drug crystals and prepared agglomerates were observed using Scanning Electron Microscope (Make: ZEISS; Model No.: EVO-18-13-04). Sample kept in sputter coater (Make: Emitech, model no. SR7620) for 4 min and process current was 10 mA. The agglomerates were observed at various magnifications to have an idea about the surface treatment (morphology) and agglomeration efficiency (size).

2.12. *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°±0.5°C and 50 RPM. Samples of 5 ml were withdrawn at a pre-determined 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 were analyzed for drug content by UV-visible spectroscopy (Shimadzu UV-1700) at 316 nm and the cumulative percentage drug released was calculated.

3. RESULTS AND DISCUSSION

3.1. Preparation of agglomerates

The spherical agglomerates of drug with polymer were prepared by Quasi-Emulsion Solvent Diffusion method using two solvent system including acetone as a good solvent and 0.1 N HCl as a bad solvent. For preparation of agglomerates, speed (500 RPM), time of stirring (1 Hr), and other processing parameters were optimized through preliminary trials. Mechanism of formation of agglomerates involve formation of quasi-emulsion droplets and then counter diffusion of solvents resulting in simultaneous crystallization and agglomeration of particles leading to formation of matrix beads with uniform dispersion of crystallized drug.

3.2. Drug Loading and % Yield of Agglomerates

The percentage yield and drug loading efficiency of agglomerates were found to be satisfactory as depicted in Table 2. It revealed that the drug and polymer were recrystallized at the maximum extent to form agglomerates without any considerable wastage of drug. Drug loading efficiency of agglomerates was also found to be satisfactory (≈ 90 %) indicating proper distribution of drug in polymer matrix.

Table 2: Drug loading efficiency and % yield of agglomerates

Batch	Drug Loading Efficiency	% Yield
H1	86.77 %	79.75 %
H2	89.54 %	89.71 %
H3	90.00 %	94.67 %
H4	90.77 %	94.80 %
H5	90.15 %	96.25 %

3.3. Micromeritic Parameters

Mean diameter for each batch was calculated using optical microscopy. All the agglomerates obtained were in the size range of 0.2–0.4 mm (Table 3). Rise in mean diameter of agglomerates was about 10–20 folds compared to pure drug particles. This finding indicated that original crystals of drug might be agglomerated simultaneously after crystallization to form spherical agglomerates.

Flow property of agglomerates (Table 3) was excellent compared to pure drug. There was remarkable reduction in Carr's index and Hausner's ratio as well as angle of repose of agglomerates compared to pure drug. It indicated substantial improvement in flow and packing properties of agglomerates. This can be attributed to spherical shape and smooth surface of the agglomerates formed due to process of CCA.[23]

Table 3: Micromeritic properties of drug and agglomerates

Batch	Diameter* (mm)	Angle of Repose# (θ°)	Carr's Index# (%)	Hausner's Ratio#
Drug	0.0197 ± 0.010	45.49 ± 0.970	34.76 ± 0.82	1.53 ± 0.019
H1	0.2032 ± 0.054	28.39 ± 0.215	24.50 ± 2.18	1.33 ± 0.038
H2	0.2893 ± 0.046	24.79 ± 0.754	17.87 ± 1.81	1.22 ± 0.027
H3	0.3448 ± 0.042	23.99 ± 0.122	15.78 ± 1.83	1.19 ± 0.026
H4	0.3640 ± 0.039	23.03 ± 0.288	13.73 ± 1.96	1.16 ± 0.026
H5	0.3496 ± 0.040	23.00 ± 0.340	11.25 ± 1.09	1.13 ± 0.014

*Results are **mean±SD** of **n=50** particles

Results are **mean±SD** of **n=3** observations

3.4. Packability and compatibility parameters

Table 4 shows smaller values of parameter *a* (compressibility, or extent of densification due to tapping) and parameter *1/b* (cohesiveness, or how fast/easily the final packing state was achieved) than the values of pure drug in Kawakita equation. This is an indication of improvement in packability of agglomerates compared to pure drug. Increased values of *K* (Kuno's constant) for agglomerates than pure drug, calculated using Kuno's equation,

showed remarkable improvements in compressibility and packability of agglomerates obtained by spherical crystallization.

The smaller values of parameters "a" and "1/b" in Kawakita's equation for the agglomerates indicated higher packability of agglomerates compared to pure drug. Higher values of parameter "K" in Kuno's equation for agglomerates were indicated higher rate of their packing processes than that of pure drug crystals. The results indicated remarkable improvement in flowability and packability of agglomerates due to increased particle size and sphericity.[24]

Table 4: Packability parameters of drug and agglomerates

Batch	Kawakita's Constants		Kuno's Constants
	a	1/b	K
Drug	0.3557	3.3086	0.0760
H1	0.2606	2.0524	0.0984
H2	0.1832	1.7329	0.1353
H3	0.1596	1.6411	0.1261
H4	0.1388	1.1259	0.1821
H5	0.1391	1.2243	0.1493

3.5. Heckel plot analysis

Here, the density of compacts formed when highest pressure (here, 40 MPa) was applied on the powder/ agglomerates was considered as the true density.[25] The constants of Heckel plot of the pure drug and agglomerates evaluated are depicted in Table 5. Agglomerates showed remarkable improvement in the packability compared to pure drug. It was further confirmed as the Elastic recoveries of agglomerated crystals were smaller than that of original drug crystals (Table 6).

The linearity in the Heckel plot (Figure 1) was an indication of plastic deformation. The slope of Heckel plot "K" is an indication of plastic behavior of the material. Larger the value of "K", greater is the plasticity of material.

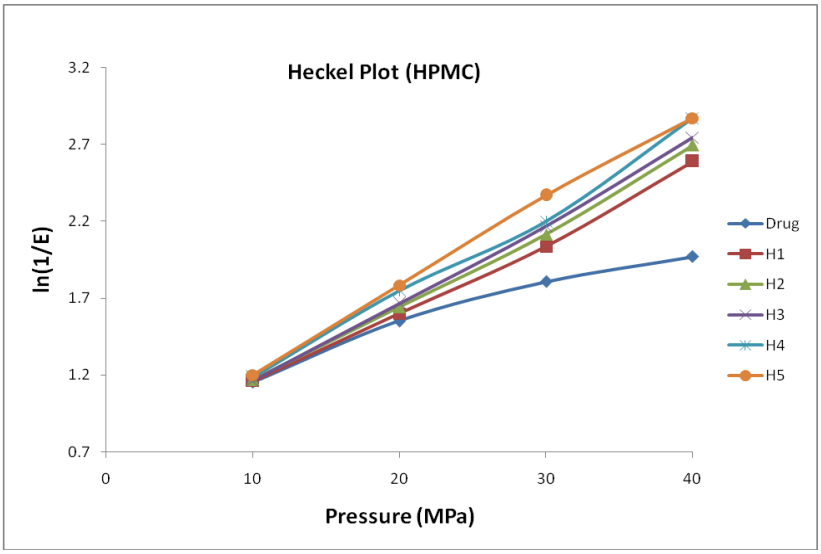

Figure 1: Heckel plots of drug (♦) and agglomerates prepared with HPMC (H1 to H5)

Moreover, smaller values of "A" for agglomerates compared to pure drug suggested that low compression pressure was required to obtain closest packing of the agglomerates. Lower value of yield strength was an indication of low resistance to pressure, good densification, and easy compaction. Thus, Heckel plot data (Table 5) suggested that agglomerates were fractured easily and new surface of crystals produced might contribute to promoting plastic deformation under compression.[26]

Table 5: Heckel Plot Parameters

Batch	Heckel Plot constants		Yield Strength
	Constant (A*)	Yield Pressure (P_y)	(σ_0)
Drug	0.94	37.04	12.35
H1	0.67	21.28	7.09
H2	0.64	20.00	6.67
H3	0.63	19.23	6.41
H4	0.63	18.18	6.06
H5	0.66	18.18	6.06

* indicates densification at low pressure

3.6. Mechanical handling properties

The crushing strength values of prepared agglomerates were higher (Table 6) indicating excellent strength. The higher value of crushing strength was also an indication of higher bonding property. The results of crushing strength of showed improved strength of agglomerates. This could be attributed to increased agglomeration of crystals with good bridging. Improved crushing strength of agglomerates revealed the improvement in mechanical and handling properties. Increased cohesive interaction between particles caused better binding and close packing between crystals.[22]

Higher values of Tensile strength of agglomerates compared to pure drug indicated improved mechanical properties of agglomerates (Table 6). The maximum tensile strength was obtained at compression pressure 40 MPa. High tensile strength of compacts of agglomerates compared to that of pure drug was an indication of strong interparticulate bonding between the particles crystallized by spherical crystallization.[27]

Smaller values of elastic recoveries in the case of agglomerates suggested that agglomerates could easily fracture, and the new surfaces produced might contribute to promoting plastic deformation under compression.[26]

Table 6: Mechanical handling parameters and Elastic recovery

Batch	Crushing Strength* (gm)	Tensile Strength* (kg/cm^2)	Elastic Recovery* (%)
Drug	---	8.755 ± 0.723	3.955 ± 0.451
H1	12.477 ± 2.525	15.482 ± 0.748	1.745 ± 0.228
H2	25.920 ± 3.219	16.784 ± 1.173	1.214 ± 0.405
H3	33.137 ± 2.309	17.578 ± 0.751	1.082 ± 0.239
H4	42.800 ± 3.147	18.046 ± 0.536	0.944 ± 0.230
H5	50.523 ± 2.032	18.943 ± 0.699	0.876 ± 0.123

*Results are **mean±SD** of **n=3** observations

3.7. Surface Topography and Sphericity Determination

Photomicrographs of co-agglomerates from various batches showed marked improvement in the surface morphology and sphericity with compared to pure drug. Pure drug crystals were morphologically irregular with more percentage of fines. As shown in Table 7, agglomerates prepared by crystallo-co-agglomeration showed encouraging results in terms of improved sphericity as well as surface smoothness.

Irregular shapes of particles of pure drug resulted in more electrostatic charges and ultimately lead to very poor flow. Value of shape and circularity factor near to unity showed that agglomerates possessed spherical shape (Table 7). Agglomerates prepared in presence of polymers showed improvements in flow due to reduced interparticulate friction.[28] Improvement in flow properties and compressibility parameters attributed to the shape towards sphericity.[23]

Table 7: Sphericity Parameters of agglomerates

Batch	Shape Factor* (P)	Circulatory Factor* (S)
H1	0.9217 ± 0.0190	1.1782 ± 0.0482
H2	0.9145 ± 0.0107	1.1961 ± 0.0282
H3	0.9476 ± 0.0367	1.1176 ± 0.0871
H4	0.9501 ± 0.0254	1.1096 ± 0.0606
H5	0.9630 ± 0.0128	1.0787 ± 0.0286

*Results are **Mean±SD** of **n=4** particles

3.8. Differential Scanning Calorimetry (DSC)

DSC thermograms for drug and agglomerates confirmed the equality in crystalline structure in all batches (Figure 2). Endothermic peaks for the drug and agglomerates prepared with HPMC were found to be 97.12 °C and 96.95 °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 and also absence of any interaction of drug with excipients during crystallization.

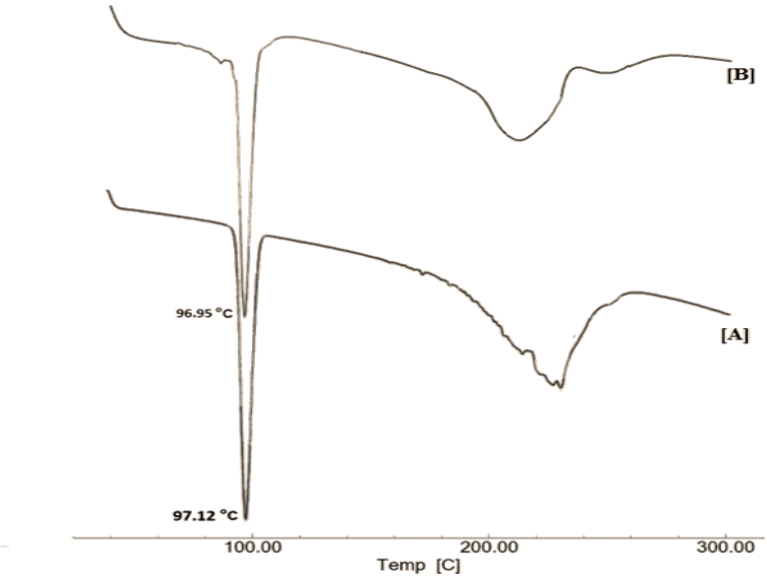

Figure 2: DSC thermogram of drug [A] and agglomerates prepared with HPMC [B]

3.9. Fourier Transform Infra-Red (FT-IR) Spectroscopy

FTIR spectra for drug and agglomerates confirmed the absence of molecular changes in drug. Almost every peaks present in FTIR spectra of the drug were present in FT-IR spectra of agglomerates (Figure 3). FTIR spectra of pure drug and agglomerates showed the peaks for various functional groups like 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 cm^{-1} and 1195.875 cm^{-1}) and monosubstituted aromatic ring (702.09 cm^{-1}). These findings indicated no molecular change in the drug during process of crystallization and agglomeration in presence of polymers as well as absence of drug-polymer interaction.

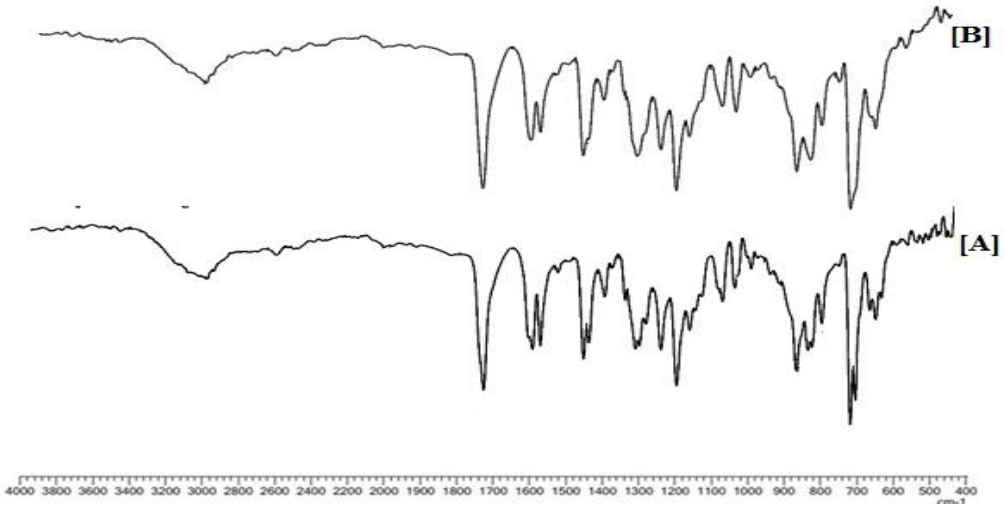

Figure 3: FTIR spectra of drug [A] and agglomerates prepared with HPMC [B]

3.10. Scanning electron microscopy (SEM)

The irregular shape of pure drug crystals makes them unsuitable for direct compression. SEM photographs of agglomerates (Figure 4) 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.

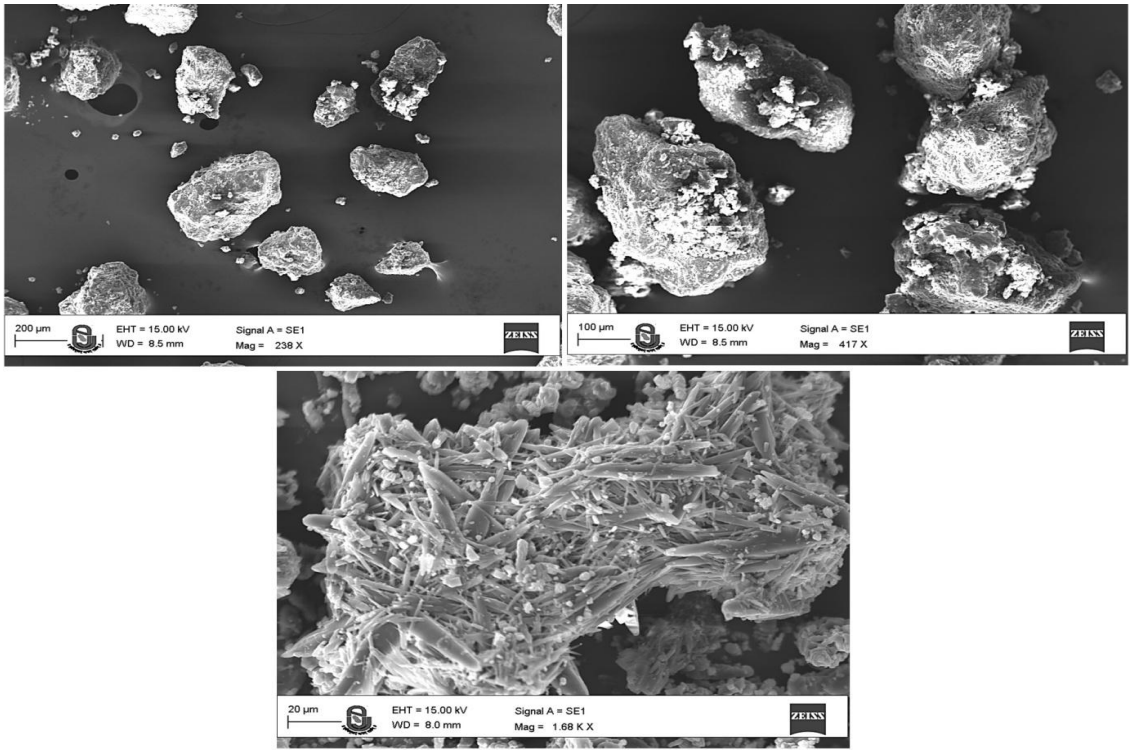

Figure 4: SEM photographs of agglomerates prepared with HPMC

3.11. *In- Vitro* Dissolution Study

Figure 5 shows drug release profile of pure drug crystals as well as agglomerates. The drug release rate from the agglomerates could be modified by adjusting the ratio of polymer to drug in the formulation. The effect of polymer on drug release rate is shown in Figure 5. The drug release rate from agglomerates was dependent on concentration of polymer used. Increase in the amount of polymer resulted in a significant decrease in drug release.

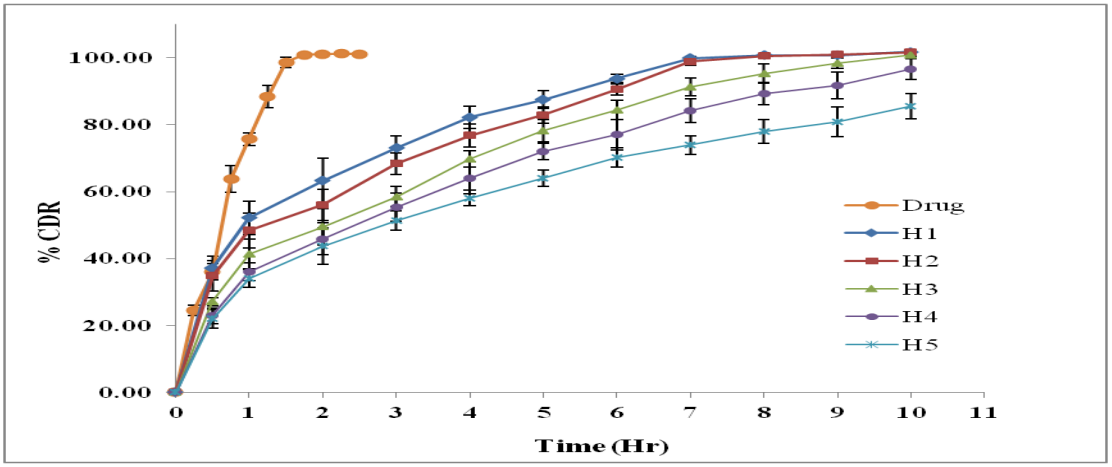

Figure 5: Dissolution profile of drug and agglomerates prepared with HPMC (H1 to H5)

4. CONCLUSION

Sustained release spherical agglomerates of hypromellose containing tiaprofenic acid have been successfully prepared by quasi-emulsion solvent diffusion technique of spherical crystallization. The agglomerates prepared by this method possessed improved micromeritic, mechanical and compression properties making them appropriate for direct compression. Agglomerates prepared with polymers possessed improved flow properties due to formation spherical shape and smooth surface. Compared to pure drug crystals, agglomerates had improved packing and compaction properties as well as improved tensile strength and crushing strength. Results of Heckel plot analysis indicated use of agglomerates for direct compression. *In-vitro* dissolution study indicated sustained release of drug for sufficiently prolonged period of time. Thus, quasi-emulsion solvent diffusion method can be utilized to prepare directly compressible agglomerates of poorly soluble drugs with polymers.

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