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PREPARATION OF SPHERICAL CRYSTAL AGGLOMERATES VIA CRYSTALLO-CO-AGGLOMERATION TECHNIQUE

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The purpose of this research was to obtain directly compressible agglomerates of aceclofenac-paracetamol containing desired ratio of drugs using a crystallo-co-agglomeration technique. Crystallo-co-agglomeration is an extension of the spherical crystallization technique, which enables simultaneous crystallization and agglomeration of 2 or more drugs or excipients. Acetone-water system containing PEG 6000, PVA and HPMC K100M was used in crystallization system. Acetone acted as a good solvent for Aceclofenac and bridging liquid for agglomeration. Aceclofenac was crystallized from acetone and agglomerated with Paracetamol. The agglomerates were evaluated for micromeritic properties, mechanical properties, moisture content, compressibility, packability and *in vitro* dissolution study. The compatibility study was done by DSC, XRPD, FTIR and surface morphology was done by SEM. The spherical agglomerates contained an aceclofenac-paracetamol ratio in the range of 0.20 to 0.201. The result revealed that micromeritic properties (angle of repose <22°, % compressibility <15 and Hausners ratio near to 1) and compactibility (mean yield pressure 28-79 MPa) enabled direct compression without any defect. Results of friability showed higher surface strength of agglomerates containing higher amount of HPMC and PEG. The DSC and FTIR study revealed the compatibility among the ingredients, XRPD showed no change in crystalline form of drug and SEM demonstrated spherical and smooth surface. *In vitro* dissolution study revealed that varying the polymer concentration prolongs the drug release. From the results, the conclusion is that crystallo-co-agglomeration technique is a suitable alternative method to the granulation process and can be used for design of sustained release aceclofenac-paracetamol agglomerates with varying concentration of polymer.

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Keywords: Crystallo-co-agglomeration, Aceclofenac, Paracetamol, Prolonged release.

1. Introduction

In the field of powder technology, attempts are undertaken to design primary and secondary particles of pharmaceutical substances for various applications, such as improvements in solubility, obtaining suitable polymorphs, improvement in micromeritic and compression properties (1-3). Spherical crystallization is a nonconventional particle size enlargement technique that involves crystallization and agglomeration using bridging liquid (4,5). Spherical crystallization has been used mainly to obtain compressible agglomerates of a single, water insoluble large-dose drug; and rarely of a drug in combination with a diluent. Most of the excipients, such as diluents and disintegrating agents, are hydrophilic in nature; hence incorporation of these excipients in the agglomerates formed using organic bridging liquid is difficult. Because of these limitation, spherical crystallization could not be applied to obtain

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*Corresponding Author: pritish1403@gmail.com agglomerates of low-dose or poorly compressible materials. In order to overcome the limitation of spherical crystallization, crystallo-co-agglomeration (CCA) technique was developed by Kadam et al. In the spherical technique, fine crystals produced in the crystallization step or in the reaction process transform into a spherical shape. But CCA is a modification of the spherical crystallization technique, in which drug is crystallized and agglomerated with an excipient or with another drug, which may or may not be crystallized in the system. The agglomeration is performed using bridging liquid. The process enables design of agglomerates containing two drugs or a low-dose or poorly compressible drug in combination with diluents (6,7). The present research was an attempt to design a Crystallo-co-agglomeration method to obtain the agglomerates containing aceclofenac-paracetamol in the ratio of 100:500. The choice of drug combination was made on the basis of significant compressibility problems associated with the drugs. In the process, aceclofenac was crystallized from acetone and agglomerated with paracetamol. Acetone served as the bridging liquid and aqueous phase as bad solvent and HPMC K100M imparts viscosity to the system. PEG 6000 was used to improve the mechanical strength and sphericity of the agglomerates. From the results it can be concluded that agglomerates obtained have improved flowability, wetability and compressibility and the developed method can be used as an alternative to conventional granulation process.

2. Materials and methods

Aceclofenac and paracetamol were gift sample from Aristo Pharmaceuticals Pvt. Ltd., Daman. Hydroxypropylmethylcellulose (HPMC K100M), Polyethylene glycol (PEG 6000) and polyvinyl alcohol were gifted from Colorcon Ltd., UK. Primogel was supplied by Loba chemicals, Mumbai. Acetone and all other chemicals, which are of analytical grade, were procured from Merck Ltd, Mumbai, India.

Crystallo-Co-Agglomeration Technique:

The agglomerates were prepared using the polymer composition shown in table. In crystallization vessel, aceclofenac (1gm) and hydroxypropylmethylcellulose (HPMC K100M) were dissolved in acetone, and paracetamol (5gm) was uniformly dispersed in it by continuous agitation at 100 rpm by magnetic stirrer. An aqueous phase containing polyethylene glycol (PEG 6000) and polyvinyl alcohol was added, and the contents were stirred at 800 rpm by constant speed magnetic stirrer. The temperature of the crystallization system was maintained below 5^{o}C. The stirring was continued untill obtaining agglomerates, which were then filtered and dried overnight at room temperature (7).

Drug Content:

On obtaining agglomerated crystals, the crystals equivalent to drug ratio 1:5 were weighed, crushed and transferred to 100 ml volumetric flask. To this, a little quantity of acetone was added to dissolve agglomerated crystals and volume was maintained by distilled water so as to get 100 µg/ml solutions. After sufficient dilution with water for aceclofenac and paracetamol, the absorbance was measured using UV visible spectrophotometer (Pharma Spec 1700, Shimadzu Corporation, Kyoto, Japan) at 271.8 nm for aceclofenac and 245 nm for paracetamol against a blank sample. The drug contents were calculated from standard solutions (8).

Micrometric Properties:

Particle size and size distribution were studied by sieve shaker analysis (Ro Tap sieve shaker, Labtronics, Haryana, India). Angle of repose of agglomerates were evaluated for flowability by fixes funnel method. The agglomerates which pass through # 120 were treated as fines. The Carr's compressibility index of prepared agglomerated crystals was calculated from respective tapped density and bulk density (9,10).

Surface Topography:

The agglomerates were photographed using a Biowizard 4.1 image processing analysis system. Area (A), and perimeter (P) obtained from tracing of enlarged photomicrographs of agglomerates were used to calculate shape factor (S) (11) using following equation. Twenty granules per batch were evaluated.

$$S = P^2/4\pi A \tag{1}$$

The crystals were splutter coated with platinum before scanning. The agglomerates were observed at ×27 and × 50 magnifications using SEM (Leicas Stereo Scan 430, LEO, UK).

Mechanical Properties and Friability:

The crushing strength of agglomerates was determined by the mercury load cell method using 50ml hypodermic glass syringe (12). Friability of agglomerates was performed after subjecting agglomerates to attrition. Percentage friability index (FI) was calculated each time using the following equation.

$$FI = [(dg)_t/(dg)_o]\times 100 \tag{2}$$

Where, $(dg)_t$ and $(dg)_o$ are mean geometric diameters after time t and initial time respectively (13).

Powder Bed Hydrophilicity Study and Packability:

Prepared spherical agglomerates were placed on a sintered glass disk forming the bottom of the glass tube. The whole device was brought into contact with water and adjusted at 1 mm under the surface of water. Some methylene blue crystals were put on the surface of the agglomerate. The time taken for the capillary rising of water to the surface was noted. This time was visualized by the dissolution of methylene blue crystals with the color of the powder surface intensively. The shortest rising time would correspond to the most hydrophilic substance, leading to good wetability (14). Improve packability had been reported for agglomerates prepared by spherical crystallization. The angle of friction, shear cohesive stress and shear indexes were lower than that of single crystals which improved the packability of the agglomerates. Packability was assessed by analysis of the tapping process with the Kawakitas and Kunos equation using the parameter a, b, 1/b, k in the equation (15).

Moisture Uptake Study:

Moisture uptake study was determined by accurately weighting the quantity of spherical crystals which were placed in crucible at accelerated condition of temperature and humidity, 40°C ± 1 ^{0}C and 75% ± 3% respectively (16).

Powder X-ray Diffraction:

PXRD patterns of agglomerates were obtained (Philips Analytical X Part PRD/SRS Division) using tube anode (Cu Ka $\lambda = 1.5406$) at 45Kv and 40mA. The data were recorded over a range of 2^o to 100^o at a scanning rate of 30.36 s/step cps using continuous scan mode (17).

Differential Scanning Calorimetry:

Thermal studies of agglomerate were performed using DSC (Star E1 Mettler, Tolodo, Swizerland). Accurately weighed samples were hermetically sealed in an aluminum crucible. The system was purged with nitrogen gas at a flow rate of 60mL/ min. Heating was done from 40^{o}C to 300^{o}C at a rate of 10^{o}C/Min (18).

Fourier Transform Infrared Spectroscopy:

FT-IR spectra of all samples of pure drugs and mixtures were recorded using KBr plates in the frequency range 4000-500 cm^{-1} (FTIR 8400S, Shimadzu, Japan).

Tablet Tensile Strength Test:

The tablets were directly compressed (By Direct Compression Method) using 12 mm flat punch on a single punch machine. The prepared tablets from agglomerated crystals were kept in a desiccator (silica gel) for about 24 h, and then a hardness tester was used to measure a load across the diameter of each tablet at a specific compression speed to find the hardness F when crushing. The following equation was then used to calculate the tensile strength T (19).

$$T=2F/\pi dL \quad (3)$$

where: d and L are a tablet’s diameter (m) and thickness (m).

Table I: Polymer Composition for Aceclofenac-Paracetamol Agglomerates

Set	Batch	Aceclofenac (gm)	Paracetamol (gm)	HPMC (% w/w) of Drug	PEG 6000 (% w/w) of Total Solid Content
I	B1	1	5	2	2
	B2	1	5	2	4
	B3	1	5	2	6
	B4	1	5	2	8
	B5	1	5	2	10
II	B6	1	5	4	2
	B7	1	5	4	4
	B8	1	5	4	6
	B9	1	5	4	8
	B10	1	5	4	10
III	B11	1	5	6	2
	B12	1	5	6	4
	B13	1	5	6	6
	B14	1	5	6	8
	B15	1	5	6	10
IV	B16	1	5	8	2
	B17	1	5	8	4
	B18	1	5	8	6
	B19	1	5	8	8
	B20	1	5	8	10
V	B21	1	5	10	2
	B22	1	5	10	4
	B23	1	5	10	6
	B24	1	5	10	8
	B25	1	5	10	10

% Porosity:

Twenty-four hours after ejection, the thickness and diameters of tablets were measured. The % porosity was calculated from the following equation (20,21)

$$\% \text{ Porosity } (\varepsilon) = (V - V_0)/V * 100 \qquad (4)$$

Where, V = Volume of tablet, V_0= volume of material at zero porosity.

***In Vitro* Dissolution Study:**

The prepared spherical agglomerated crystals were compressed into tablets with by direct compression technique using Avicel as a direct compression excipient and Primogel (Sodium Starch Glycolate) as a disintegrant. The *in vitro* dissolution studies were performed using paddle type having 8 Station USP type-II dissolution apparatus (Electrolab TDT – 08L Dissolution Tester, USP). The dissolution studies were carried out in 900mL acid buffer of pH 1.2 for first 2 hours and then it was replaced by 900mL phosphate buffer having pH 6.8 for next 10 hours. The dissolution medium was kept in a thermostatically controlled water bath, maintained at 37±0.5° C. The paddles were rotated at 50 rpm. After each 1 hour 10mL of sample were withdrawn and dilutions were made if necessary. Absorbance were taken using UV-Visible Spectrophotometer at 269.60 nm (pH 1.2), 271.0 nm (pH 6.8) for aceclofenac and at 244.20 nm (pH 1.2), 244.40 nm (pH 6.8) for paracetamol and analyzed for drug released. During each sampling, 10 ml of fresh corresponding dissolution medium was replaced into the dissolution flask (22).

3. Results

Drug loading efficiency was found to be in the range of 90% to 95% w/w and no significant difference was found between various batches ($P < 0.05$). The content of aceclofenac was found in the rage of 14.90% to 15.98% w/w, whereas paracetamol content was found in the range of 74.01% to 79.79% w/w. The formulation contained 100 mg aceclofenac and paracetamol 500 mg ratio (100:500). Aceclofenac-Paracetamol ratio should lie in the range of 0.20 to 0.201. As the polymer concentration increases, the batches showed excellent flowability, as represented by angle of repose (<22°), compressibility (<15) and hausners ratio was near to 1.20.

The shape factor was in the range of 1.09 to 1.33. The scanning electron microscopy (SEM) study revealed that the surface morphology of the prepared agglomerate, spherical in shape (Figure.1a) and pores on the surface due to release of drug molecules (Figure 1b). Mechanical properties of the agglomerates were evaluated by crushing strength and friability (Table II). Batch no. 24 required maximum force for deformation. The change in friability index with time was found to be as a linear function of time (t) with decrease friability index. Hence the data was fitted in a linear equation and constant K and C were determined.

$$Y = KP + C \qquad (5)$$

C – Constant will depend on % fines produced in the initial stage of testing
K – Will reflect overall friability of agglomerates

From crushing strength study it was observed that increase in crushing strength of set second and set forth. From friability study it was observed that, the friability was significantly ($P<0.01$) decreased due to varying polymer ratio (Table II). By continuing friability test for 25 min, it was observed that the % fines were also decreased.

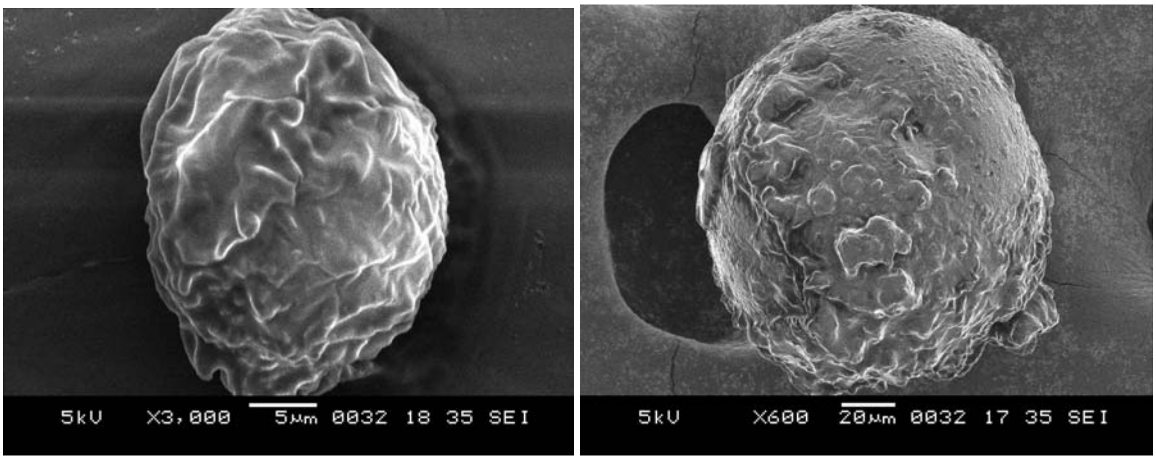


Fig. 1 (a): SEM Photomicrographs of Spherical Crystals.

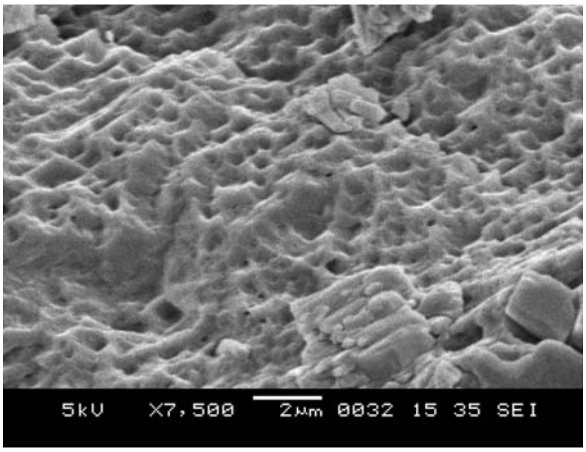


Fig. 1 (b): SEM Photomicrographs of Spherical Crystals after Drug Released

The powder bed study revealed that the prepared agglomerate crystals showed significant shortest rising time (**$P<0.01$) of water represented by dissolution of methylene blue crystal. It results a better wetability (Table II).

Table II: Crushing Strength, Friability and Water Rising Time of Aceclofenac-Paracetamol Agglomerates

Batch	Crushing Strength (gm)	K	C	R	% Friability (5 min)	Water Rising Time (hr)
B1	26.30±0.190	0.159	2.352	0.489	6.40	14.20±0.450
B2	21.95±0.085	0.158	2.561	0.444	5.98	12.50±0.345
B3	29.24±0.050	0.200	3.226	0.444	6.60	12.40±0.285
B4	20.65±0.210	0.167	2.694	0.446	6.16	13.10±0.300
B5	22.45±0.360	0.172	2.760	0.472	6.04	11.15±0.680
B6	22.82±0.078	0.143	2.318	0.445	5.90	12.52±0.455
B7	30.87±0.145	0.177	2.859	0.446	6.44	10.42±0.565
B8	35.64±0.275	0.140	2.213	0.454	5.18	15.20±0.290
B9	32.30±0.068	0.146	2.280	0.462	5.32	11.35±0.250
B10	41.45±0.410	0.138	2.187	0.456	5.16	11.05±0.365
B11	50.26±0.320	0.135	2.101	0.464	4.90	10.40±0.035
B12	45.78±0.009	0.143	2.234	0.462	5.24	10.10±0.605
B13	39.61±0.125	0.156	2.402	0.469	5.42	09.25±0.065
B14	47.23±0.058	0.127	1.967	0.467	4.76	08.50±0.085
B15	40.12±0.020	0.125	1.889	0.476	4.56	08.12±0.105
B16	50.75±0.745	0.119	1.825	0.471	4.16	07.55±0.010
B17	48.56±0.004	0.109	1.647	0.478	3.84	07.20±0.035
B18	52.16±0.500	0.097	1.417	0.498	3.52	06.41±0.065
B19	56.71±0.040	0.078	1.157	0.490	3.18	07.10±0.450
B20	61.46±0.100	0.079	1.038	0.552	2.74	05.45±0.655
B21	70.87±0.165	0.066	0.816	0.557	2.18	05.15±0.135
B22	64.56±0.510	0.071	0.932	0.550	2.50	04.50±0.215
B23	56.90±0.034	0.067	0.837	0.574	2.34	06.22±0.160
B24	79.60±0.780	0.074	0.983	0.545	3.34	05.10±0.450
B25	74.41±0.140	0.079	1.238	0.464	2.84	05.55±0.365

Each value represents the mean ± standard deviation (n=3)

The packability study revealed that the smaller values of parameter ***a*** in Kawakita and Ludde's equation for the agglomerates indicated their higher packability. The apparent packing velocity by tapping, represented by parameter ***b***, for agglomerates was faster than that of conventional crystals, since agglomerates were packed closely even without tapping due to their excellent flowability and packability. The large values of parameter ***K*** in Kuno et al.'s equations for the agglomerates indicate that the rate of packing process was much higher. The result of moisture uptake study was shown (Figure 2).

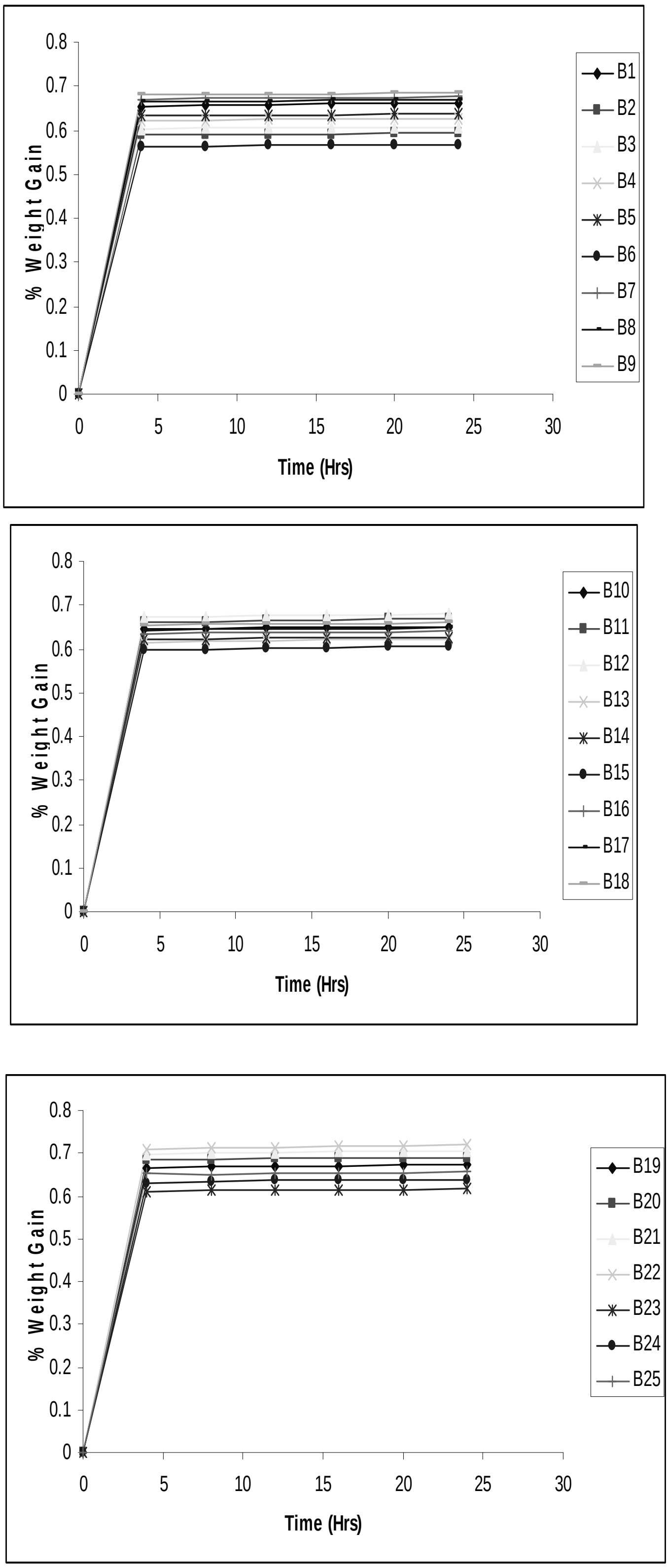


Fig. 2: Moisture Uptake Study of Agglomerated Crystals.

In order to detect the compatibility between drug and excipient, the infrared spectroscopy (IR) and differential scanning calorimetry (DSC) examination were conducted for pure drug and agglomerate. Fourier transform infrared spectroscopy (FTIR) study of aceclofenac, paracetamol pure drug and agglomerate showed all the characteristics peak of the drug (Figure 3).

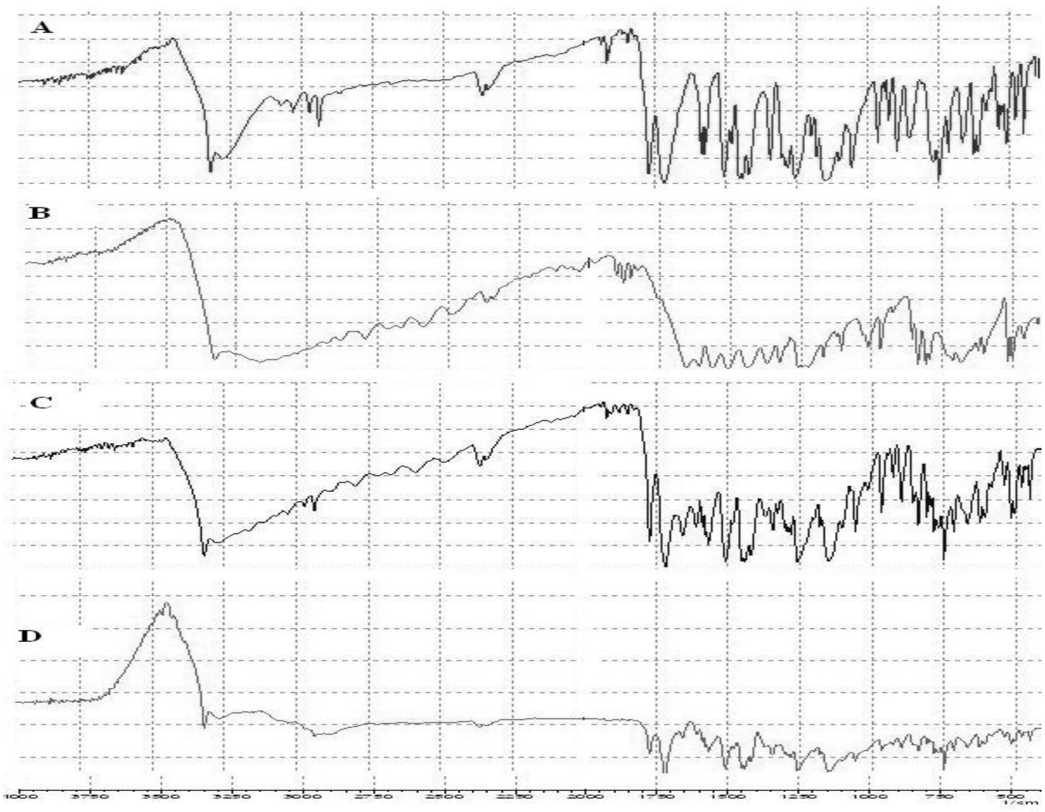


Fig 3. FTIR of (A) Aceclofenac, (B) Paracetamol, (C) Aceclofenac-Paracetamol and (D) Aceclofenac-Paracetamol Agglomerate.

The thermal property of drug and agglomerate were studied using differential scanning calorimetry (DSC) (Figure 4). Aceclofenac and paracetamol have shown melting endotherm at 148° C and 178° C respectively. The agglomerate of aceclofenac and paracetamol showed an interesting change in the thermogram. The endotherm for paracetamol melting 170° C to 172° C remained unchanged while a diffuse endotherm with low enthalpy was observed for aceclofenac. X-ray powder diffractometry (XRPD) was a technique for the identification of crystalline solid phase. X-ray powder diffractometry (XRPD) spectra of agglomerate showed that sharp peaks were obtained (Figure 5). Dissolution of drug from the compacts prepared using agglomerate was studied (Figure 6). The maximum dissolution was observed up to 98%. This was due to the lower concentration of polymer used. As the polymer concentration increases, the dissolution rate decreases. In very high polymer concentration, the dissolution rate was decreased up to 86%. The higher tensile strength showed by compressed tablet from agglomerate crystal. Higher tensile strength was due to greater plastic deformation of the agglomerated crystals resulting in greater permanent interparticle contact and stronger bond force than in the case of original crystals (Table III).

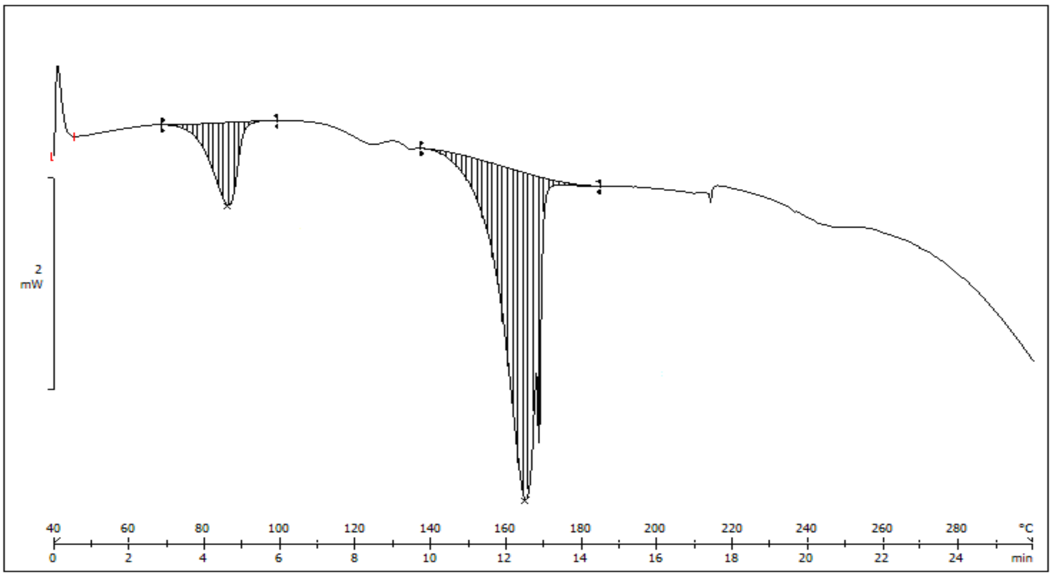


Fig. 4: DSC Thermographs of Aceclofenac-Paracetamol Agglomerate Crystal of Batch No. 22

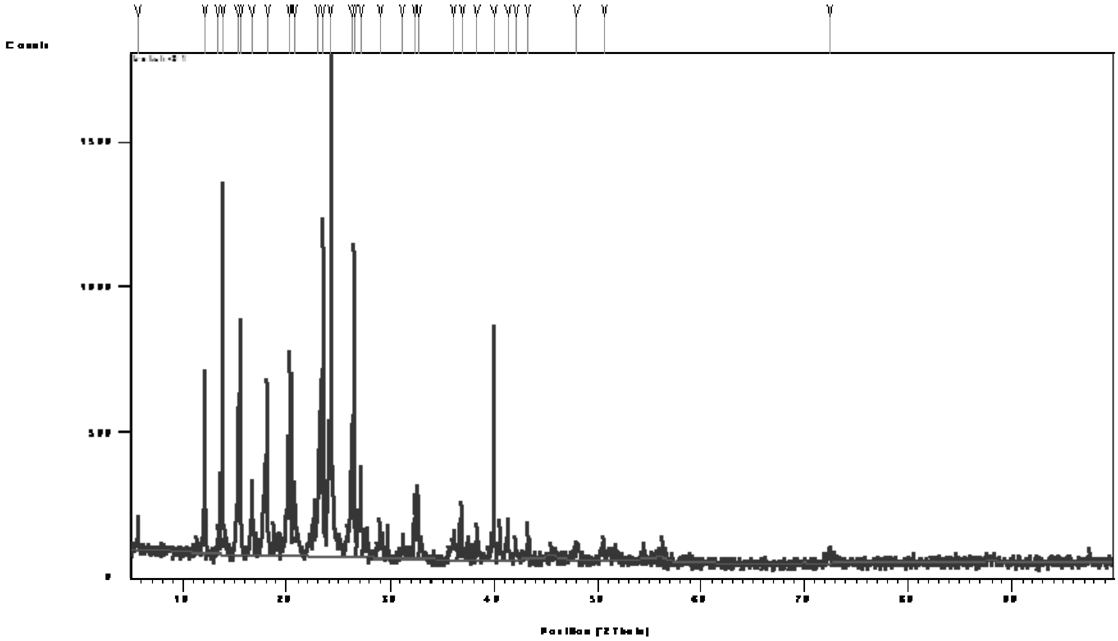
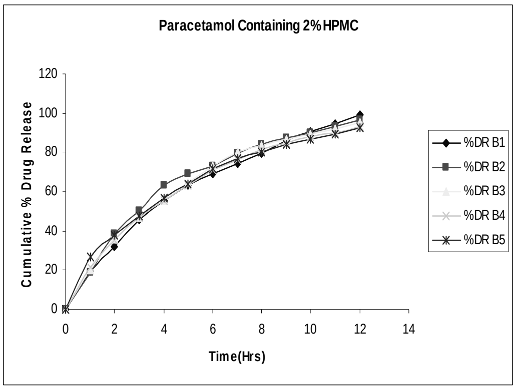


Fig. 5: Powder X-ray Diffraction of Batch No. 22


Paracetamol Containing 2%HPMC
Cumulative % Drug Release
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Time(Hrs)
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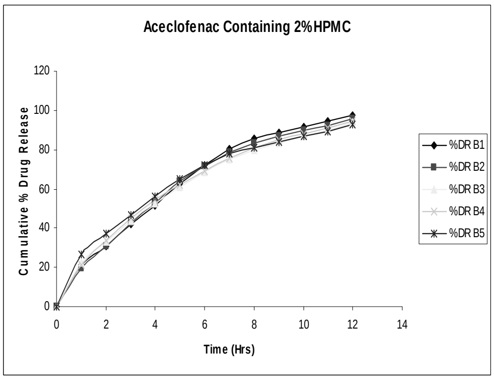
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Cumulative % Drug Release
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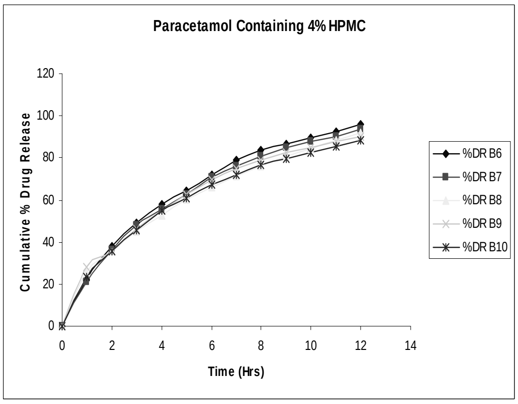
Paracetamol Containing 4% HPMC
Cumulative % Drug Release
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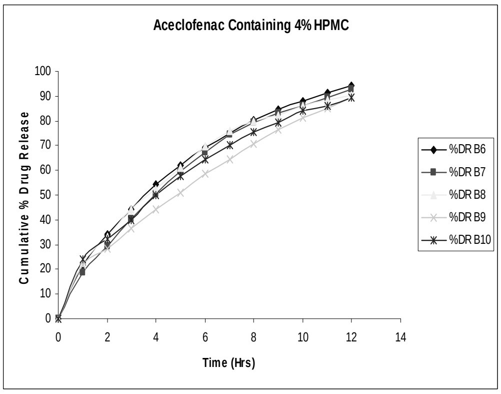
Aceclofenac Containing 4% HPMC
Cumulative % Drug Release
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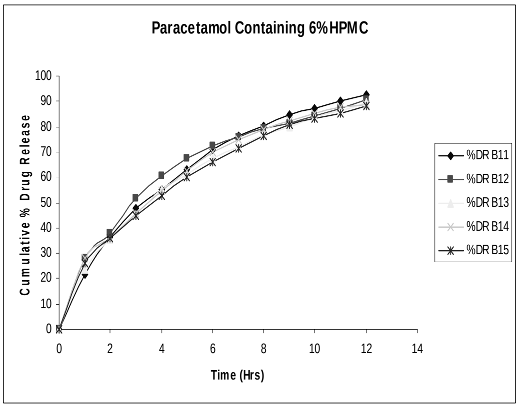
Paracetamol Containing 6%HPMC
Cumulative % Drug Release
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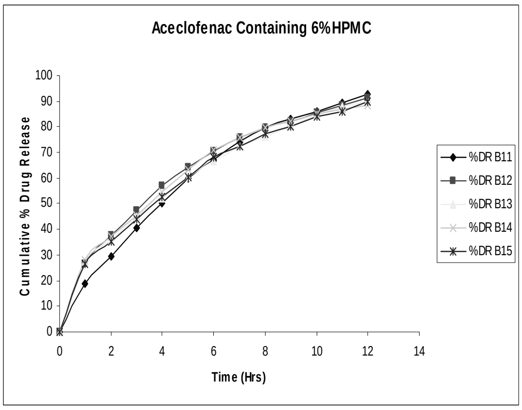
Aceclofenac Containing 6%HPMC
Cumulative % Drug Release
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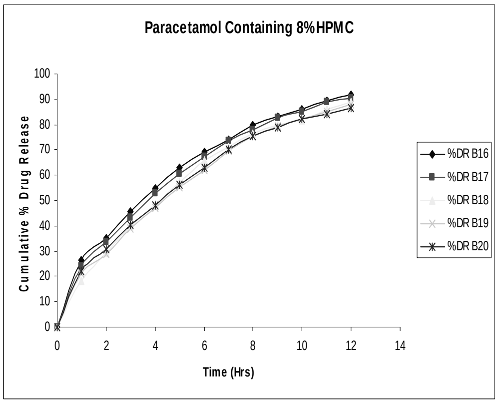
Paracetamol Containing 8%HPMC
Cumulative % Drug Release
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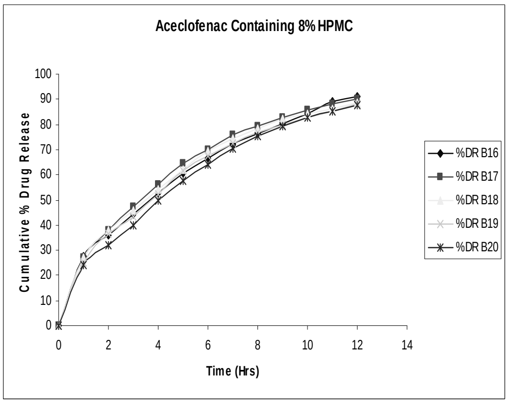
Aceclofenac Containing 8% HPMC
Cumulative % Drug Release
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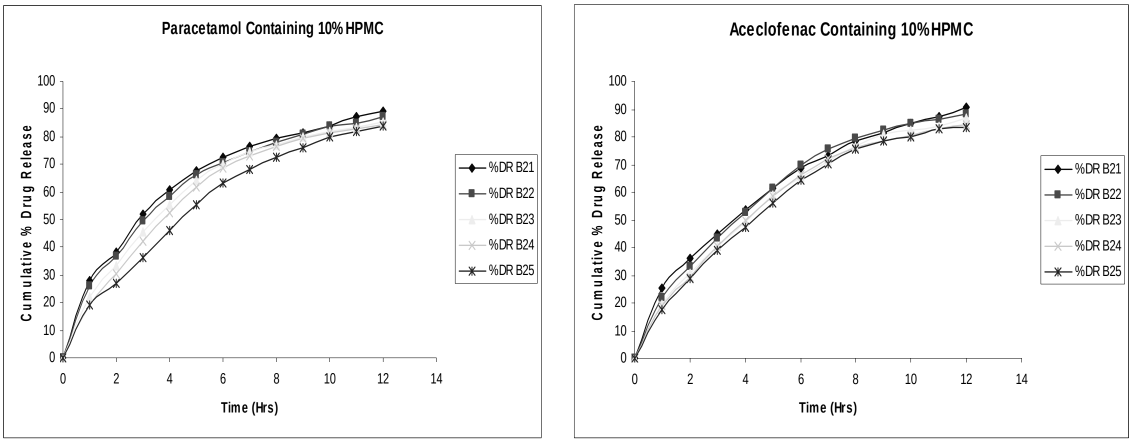

Fig. 6: In Vitro Drug Release Profile of Aceclofenac-Paracetamol

Table III: Tensile Strength and % Porosity of Tablets

Batch	**Tensile Strength (Kg/cm)**	**% Porosity**
B1	13.99±0.01	13.58±0.02
B2	11.58±0.04	20.19±0.11
B3	12.84±0.11	27.29±0.05
B4	12.34±0.10	24.83±0.09
B5	12.81±0.05	18.28±0.15
B6	13.43±0.09	20.87±0.14
B7	08.67±0.12	14.78±0.18
B8	11.58±0.15	19.44±0.12
B9	08.67±0.20	15.41±0.17
B10	13.82±0.25	24.93±0.08
B11	13.60±0.12	22.81±0.17
B12	13.70±0.13	24.45±0.20
B13	10.79±0.18	12.84±0.21
B14	10.58±0.15	13.24±0.15
B15	13.43±0.17	12.50±0.05
B16	12.25±0.08	12.50±0.07
B17	10.37±0.04	12.84±0.01
B18	13.69±0.07	22.29±0.05
B19	12.25±0.16	12.57±0.09
B20	13.23±0.08	11.25±0.10
B21	08.67±0.05	15.13±0.06
B22	10.37±0.17	09.90±0.07
B23	10.23±0.13	10.71±0.10
B24	11.75±0.16	12.50±0.13
B25	09.01±0.03	12.19±0.11

Each value represents the mean ± standard deviation (n=3)

4. Discussion

The size of agglomerates was easily controlled by adjusting agitation speed, temperature of the system, and concentration of acetone, hydroxypropylmethylcellulose and polyethylene glycol content in the system and residence time. Agglomerate size decreased with increasing agitation speed. Increased temperature, difference between acetone and poor solvents results in decreased agglomerate size. The range of shape factor indicates that agglomerates were in the spherical shape. Scanning electron microscopy photomicrographs showed that the prepared agglomerates were spherical in shape which enabled them to flow very easily, with smooth surface. The pores on the surface may represent the release of drugs. The maximum force required to crush the agglomerate crystal of the batch was due to increase in polymer concentration and it may also be due to larger particle size, interparticulate bond strength and physical properties of the particle. In the first, third and fifth set of formulation batches, having a constant composition amount of HPMC (2%, 6% and 10%) and increasing concentration of PEG 6000 (2%, 4%, 6%, 8% and 10%), the crushing strength was not linear, whereas with second and fourth set of formulation batches containing 4% and 8% HPMC and increasing concentration of PEG 6000 (2%, 4%, 6%, 8% and 10%), a somewhat linear correlation between crushing strength and concentration of polymers was observed. From the friability study, it was observed that friability of agglomerate crystal were decreased by the batch due to good surface strength and hardness and it was also observed that it reduces % fines by increase in polyethylene glycol concentration. From powder bed hydrophilicity result, shortest rising time of water was due to the wetting phase during which the particles colloid and at the time of agglomeration process, the hydrophilic polymer polyethylene glycol in poor solvent adheres on the surface droplets to enter inside the droplets and agglomerate crystals. Hence it was found a superior wetability of crystals. From this observation it was found that the time required for shortest rising of water by the batch showed better wetability. Hence batch no. 22 was found to have good wetability. From the packability study it was proved that the flowability and packability of agglomerate crystals were preferably improved for direct tableting. It was observed that the maximum compactibility and packability was showed by batch no. 22 due to excellent flowability. Moisture uptake by the agglomerate was due to increase in hydrophilic polymer concentration. FTIR showed that aceclofenac, paracetamol and the agglomerate crystal clearly showed retention of the characteristic peaks of the pure drug, thus revealing no interaction between drug and polymer. The IR spectra of agglomerate crystal showed no change occurring in the chemical nature. In DSC thermogram the diffused endotherm with low enthalpy was observed for aceclofenac. The early onset and broadening of paracetamol peak was due to partial dissolution in aceclofenac melt. This finding is in accordance with the thermal behavior of binary mixture reported by Lloyd et al (23) where it was shown that the dissolution of higher melting compound in the melt of the lower melting compound during thermal studies caused shifting or complete disappearance of the higher melting component peak. From XRPD study it was observed that, the sharp peaks were obtained, that indicate the agglomerates in crystalline form. From *in vitro* dissolution study it was observed that the dissolution rate was maximum when lower polymer concentration was used, and similarly the dissolution rate was decreased when a higher polymer concentration was used. Hence drug release should be a sustained or prolonged action. From the study of agglomerates and prepared tablets, it was observed that batch no. 22 showed improved flowability, packability, compactibility, wetability, surface morphology and sustained the release of drugs 87.43% for paracetamol and 88.11% for aceclofenac. Hence, batch no. 22 was designed as optimized batch. The higher tensile strength was found due to increase concentration of polyethylene glycol 6000 which results in increased hardness and decreased porosity. The decrease in porosity was due to the decrease of voids spaces between the particles with high compaction force.

5. Conclusion

The Crystallo-co-agglomeration (CCA) method developed in the present study is a promising technique to obtain directly compressible agglomerates of combination of drugs in required proportion. The micromeritics of agglomerates, such as flowability, packability and compactibility were dramatically improved, resulting in successful direct tabletting. The main factor in the improvement of the flowability and packability was a significant reduction in interparticle friction, due to spherical shape of the tableted particles. The dissolution rate was also enhanced. If this process is scaled up to manufacturing level, this technology has the potential to provide the directly compressed tablets with improved bioavailability. However extensive long term stability studies are required before commercialization.

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