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Crystallo-co-agglomeration: A Novel Technique To Obtain Ibuprofen-Paracetamol Agglomerates

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Atmaram P. Pawar,[1] Anant R. Paradkar,[1] Shivajirao S. Kadam,[2] and Kakasaheb R. Mahadik[2]

[1]Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandawane, Pune-411038, Maharashtra State, India

[2]Department of Pharmaceutical Chemistry, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandawane, Pune-411038, Maharashtra State, India

ABSTRACT

The purpose of this research was to obtain directly compressible agglomerates of ibuprofen-paracetamol containing a 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 crystallization of a drug and its simultaneous agglomeration with another drug or excipient. Dichloromethane (DCM)-water system containing polyethylene glycol (PEG) 6000, polyvinyl pyrollidone, and ethylcellulose was used as the crystallization system. DCM acted as a good solvent for ibuprofen and bridging liquid for agglomeration. The process was performed at pH 5, considering the low solubility of ibuprofen and the stability of paracetamol. Loss of paracetamol was reduced by maintaining a low process temperature and by the addition of dextrose as a solubility suppressant. The agglomerates were characterized by differential scanning calorimetry, powder x-ray diffraction (PXRD), and scanning electron microscopy and were evaluated for tableting properties. The spherical agglomerates contained an ibuprofen-paracetamol ratio in the range of 1.23 to 1.36. Micromeritic, mechanical, and compressional properties of the agglomerates were affected by incorporated polymer. The PXRD data showed reduction in intensities owing to dilution and reduced crystallinity. Thermal data showed interaction between components at higher temperature. Ethylcellulose imparted mechanical strength to the agglomerates as well as compacts. The agglomerates containing PEG have better compressibility but drug release in the initial stages was affected owing to asperity melting, yielding harder compacts. The agglomeration and properties of agglomerates were influenced by the nature of polymer.

KEYWORDS: crystallo-co-agglomeration, ibuprofen, paracetamol, drug combination, tableting properties.

Corresponding Author: Kakasaheb R. Mahadik, Department of Pharmaceutical Chemistry, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy, Erandawane, Pune-411038, Maharashtra State, India. Tel: +91-20-254 37237. Fax: +91-20-254 39383. Email: krmahadik@rediffmail.com.

INTRODUCTION

In the field of powder technology attempts are undertaken to design primary and secondary particles of pharmaceutical substances for various applications, such as improvement in solubility, obtaining suitable polymorph, improvement in micromeritic and compression properties, and modification of bioavailability.[1-3]

Spherical crystallization is a nonconventional particle-size enlargement technique that involves crystallization and agglomeration using bridging liquid.[4,5] Different methods have been reported to achieve supersaturation during spherical crystallization.[6-10] Spherical crystallization has been used mainly to obtain directly compressible agglomerates of a single, water-insoluble large-dose drug, and rarely in combination with a diluent.

There are very few reports regarding application of this method for obtaining agglomerates of more than 1 drug.[11] The applications of this method to obtain directly compressible agglomerates without diluents are restricted to water-insoluble large-dose drugs. Most of the excipients, such as diluent and disintegrating agents, are hydrophilic in nature; hence, incorporation of these excipients in the agglomerates formed using organic bridging liquid is difficult. Because of this limitation, spherical crystallization could not be applied to obtain agglomerates of low-dose or poorly compressible materials.

The present study is an attempt to overcome the limitations of spherical crystallization. Kadam et al[12,13] developed the crystallo-co-agglomeration (CCA) technique. It is a modification of the spherical crystallization 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. The agglomeration is performed using bridging liquid. The process enables design of agglomerates containing 2 drugs or a low-dose or poorly compressible drug in combination with diluent. The difference in the physicochemical properties of the drug molecules and the excipients becomes the major challenge in the selection of a solvent system for the crystallo-co-agglomeration.

The present CCA method has been designed to obtain the agglomerates containing ibuprofen and paracetamol in the

Table 1. Polymer Composition for Ibuprofen-Paracetamol Agglomeration*

Ingredients	IPEC-1	IPEC-2	IPPG-1	IPPG-2
Ethylcellulose (mg)	100	200	-	-
PEG 6000 (mg)	-	-	800	1200
PVA (mg)	1.0	1.0	0.5	0.5

*IPEC indicates ibuprofen ethylcellulose; IPPG, ibuprofen polyethylene glycol; PEG, polyethylene glycol; and PVA, polyvinyl alcohol.

ratio 400:325. The choice of drug combination was made on the basis of significant compressibility problems associated with the drugs. In the process, ibuprofen was crystallized from dichloromethane and agglomerated with paracetamol. Dichloromethane served as the bridging liquid and aqueous phase as the bad solvent. The agglomerates obtained were evaluated using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), powder x-ray diffraction (PXRD), and tableting and drug release properties.

Materials and Methods

Materials

Ibuprofen was a kind gift from Seksaria Chemicals (Mumbai, India). Paracetamol was supplied as a gift sample by Vamsi Labs Ltd (Maharashtra, India). Polyethylene glycol (PEG 6000, BDH Chemicals, Mubai, India) and polyvinyl alcohol (PVA, Research Labs, Mumbai, India) were purchased. Primogel was supplied by Get-Rid Pharma (Pune, India). Dichloromethane (DCM) and all other chemicals were of analytical grade (Merck Ltd, Mumbai, India).

Crystallo-Co-Agglomeration

The agglomerates were prepared using the polymer composition given in Table 1. In a crystallization vessel, as described by Morishima et al,[14] ibuprofen (8 g) and ethyl cellulose were dissolved in DCM (24 mL), and paracetamol (6.6 g) was uniformly dispersed in it by continuous agitation at 100 rpm. An aqueous phase (60 mL of pH 5) containing dextrose (10% wt/vol), PEG, and PVA was added, and the contents were stirred at 800 ± 25 rpm using a constant speed stirrer (Eurostar power control-visc, IKA Labortecnik, Staufen, Germany). The temperature of the crystallization system was maintained below 5°C. The stirring was continued to obtain agglomerates, which were then filtered and dried overnight at room temperature.

Yield and Drug Content

Agglomerates were weighed after drying, and process yield was calculated. Agglomerates (725 mg) were powdered, from which powder equivalent to 100 mg paracetamol was weighed and extracted using 3 portions of 25 mL each of 1 N hydrochloric acid. Each portion was filtered through a G-4 sintered glass filter and volume was adjusted to 100 mL. After sufficient dilution with 1 N hydrochloric acid, samples were analyzed spectrophotometrically at 242.5 nm (Shimadzu 160, Kyoto, Japan). Paracetamol content was calculated by comparison with standard solution.[15] The residue retained on the sintered funnel was reserved for estimation of ibuprofen.

The entire residue present on the sintered funnel was dissolved in 3 portions of 25 mL each of methanol, and volume was adjusted to 100 mL. After sufficient dilution, the samples were analyzed spectrophotometrically at 263.8 nm, and ibuprofen content was calculated by comparison with standard solution.[15]

Surface Topography

Photomicrographs of primary drug particles suspended in liquid paraffin were taken using a polarized microscope (Nikon Lab Phot-Pol, Tokyo, Japan) fitted with a camera. The agglomerates were photographed using an optical microscope with camera (Nikon FX- 35X) at original magnification × 22.5. Area (A) and Perimeter (P) obtained from tracings of enlarged photomicrographs of agglomerates were used to calculate shape factor (S). Twenty granules per batch were evaluated.

$$S = P_{actual}^2/(4\,\pi\,A_{actual}) \quad (1)$$

After gold coating in a Polaron SC 7640 sputter coater (Polaron, Hertfordshire, UK), the agglomerates were observed at ×60 and ×700 magnifications using an SEM (Lieca Stereoscan 440, Wetziar, Germany).

Differential Scanning Calorimetry

Thermograms of ibuprofen, paracetamol, ethylcellulose, PEG, and agglomerates were performed using DSC (Mettler Toledo, model 821 with software star^e, Greifensee, Switzerland). Indium was used as standard to calibrate the DSC temperature and enthalpy scale. Accurately weighed samples were hermetically sealed in an aluminum crucible. The system was purged with nitrogen gas at a flow rate of 60 mL/min. Heating was done from 30°C to 180°C at a rate of 10°C/min.

Powder X-ray Diffraction

PXRD patterns of ibuprofen, paracetamol, and agglomerates were obtained (Philips X-ray diffractometer, PW-1729, Netherlands), using Cu K_α radiation (λ = 1.542 Å) at 30 kV, and 30 mA. The data were recorded over a range of 2° to 100° at a scanning rate of 5 × 10^3 cps using a chart speed of 5 mm/2°.

Micromeritic Properties

Agglomerates were evaluated for flowability by a fixed funnel method. Particle size distribution was studied by sieve analysis (Ro-Tap sieve shaker, Labtronics, Haryana, India). The weight of agglomerates retained on sieves was subjected to analysis by Rosin-Rammler distribution[16] as:

$$\text{Ln (2-log } R) = \text{Ln } (a \text{ log e}) + b \text{ Ln d} \quad (2)$$

Where, R is cumulative residual percentage by weight, d is the particle size (μm), and a and b are constants.

Mechanical Properties

Crushing strength of agglomerates of 3 different size fractions, 855, 567, and 390 μm, were determined by the mercury load cell method.[17]

Friability of agglomerates was performed after subjecting to attrition.[7] After sieve analysis, every time mean geometric diameter was obtained fitting the data in Rosin-Rammler distribution. Percentage friability index (FI) was calculated each time using the following equation:

$$\text{FI} = [(dg)_t/(dg)_o] \times 100, \quad (3)$$

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

Pressure-Relative Density Relationship

Agglomerates (500 ± 10 mg) were compressed at compaction pressures of 0.52, 1.57, 3.15, 4.20, 5.25, 6.30, and 14.70 mPa for 1 minute using a hydraulic press. The compacts were allowed to relax for 24 hours. Pressure (P) – relative density (ρ_r) data were analyzed using the Heckel Equation.[18,19]

$$Ln\ (1 - \rho_r) = \text{K P} + \text{A}, \quad (4)$$

where, K is the Heckel constant; $K = 1/3\sigma_0$, where σ_0 is yield strength, and mean yield pressure P_y is equal to $3\sigma_0$. The constant A expresses densification at low pressure.

Pressure-Tensile Strength Relationship

After determination of diameter (D) and thickness (t), the compacts used for P-ρ_r relationship study were subjected to determination of the force (F) required to break the compacts. The data were subjected to tensile (σ_t) determination.[20]

$$\sigma_t = 2 \text{ F } /\pi \text{ Dt} \quad (5)$$

Dissolution Studies

The agglomerates (800 ± 10 mg) were compacted at a pressure of 1 ton for a dwell time of a minute. Ten percent wt/wt of sodium starch glycolate (Primogel) was added as a disintegrating agent. The dissolution was performed in United States Pharmacopeia (USP) dissolution test apparatus (DA-6, Veego Scientific, Mumbai, India). The dissolution medium used was 900 mL of phosphate buffer IP (Pharmacopoeia of India), pH 7.2 at 37°C ± 2°C. The paddle speed was 100 rpm. Samples were collected and analyzed on multicomponent mode spectrophotometrically at 222.0 nm and 242.0 nm for ibuprofen and paracetamol, respectively.

Results and Discussion

The CCA technique was developed to obtain ibuprofen-paracetamol agglomerates. Aqueous phase was 10% dextrose solution containing required polymer maintained at 5°C. The aqueous phase composition, pH, and processing temperature were adjusted, taking into consideration drug stability and minimization of drug loss to aqueous phase. The pH of maximum stability for paracetamol lies between 5 and 7, whereas ibuprofen shows significant increase in solubility above its pK_a (ie, 5.3). Therefore, aqueous phase adjusted to pH 5 was used. Processing temperature was kept at 5°C to minimize drug loss into the aqueous phase. But at pH 5, paracetamol still showed significant solubility (1 g/81mL), and average process yield was 86% wt/wt. Etman and Nagger[21] demonstrated paracetamol solubility suppression by dextrose by decreasing hydrophobic interactions. Therefore, dextrose was added to the aqueous phase. Use of aqueous phase containing 10% wt/vol dextrose showed significant improvement in average yield from 80% wt/wt to 98% wt/wt. PVA, an emulsifier, has been used in low concentration to obtain smaller globules during process as reported for similar processes.[22,23] PEG 6000, a plastically deforming agent, was incorporated to improve tableting properties. Apart from this, PEG 6000 has been reported to favor the wetting of crystallized drug by reducing interfacial tension of the bridging liquid.[24,25] Ethylcellulose, being a hydrophobic polymer, partitions in favor of the bridging liquid and imparts strength to the agglomerates.

The agglomerate yield was in the range of 90% to 98% wt/wt, and no significant difference was found between the yields of various batches ($P < .05$). The content of ibuprofen was in the range of 51% to 58% wt/wt, whereas paracetamol content was 39% to 41% wt/wt. Chaw and Leung[26] have reported lower yields of the paracetamol agglomerates, which were 13% and 54% with water and drug-saturated solution as external phase, respectively.

The commercial tablet formulation contains 400 mg and 325 mg of ibuprofen and paracetamol, respectively. On the basis

Table 2. Micromeritic Properties of Ibuprofen-Paracetamol Agglomerates*

Parameter	IPEC-1	IPEC-2	IPPG-1	IPPG-2
Shape factor	0.8749 ± 0.127	0.9824 ± 0.030	1.0736 ± 0.002	1.0326 ± 0.094
Rosin-Rammler diameter (μm)	577.388	579.167	660.305	972.675
Angle of repose (°)	24.260 ± 0.666	23.589 ± 0.250	24.994 ± 1.668	27.106 ± 0.378

*IPEC indicates ibuprofen ethylcellulose; and IPPG, ibuprofen polyethylene glycol.

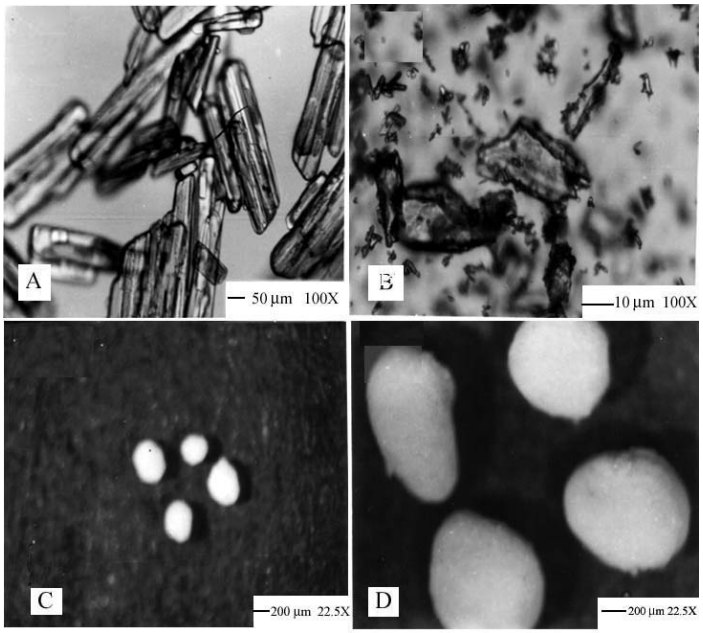

Figure 1. Photomicrographs of ibuprofen, paracetamol, and agglomerates. (A) Ibuprofen crystals at original magnification ×100; (B) Paracetamol crystals ×100; (C) IPEC-2 agglomerates ×22.5; and (D) IPPG-2 agglomerates ×22.5.

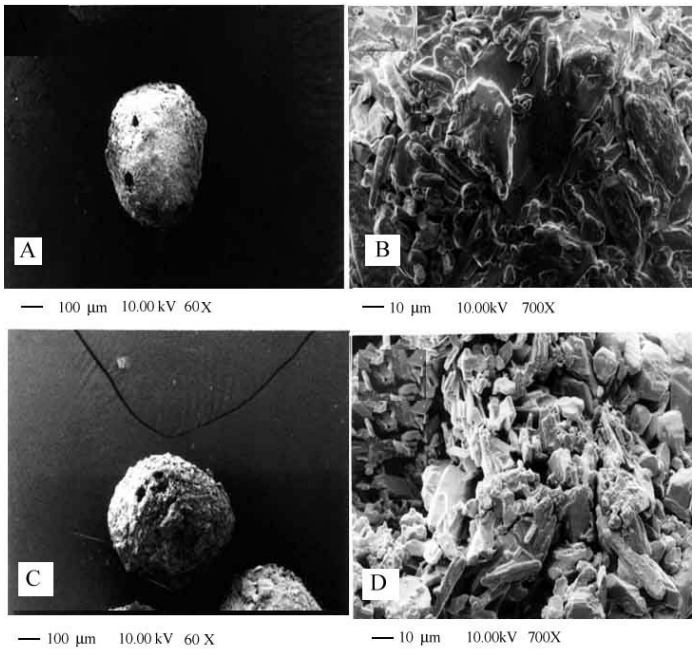

Figure 2. SEM photomicrographs of ibuprofen-paracetamol agglomerates. (A) IPEC-2 at original magnification ×60; (B) IPPG-2 ×60; (C) IPEC-2 ×700; and (D) IPPG-2 ×700.

of pharmacopeial requirements for drug content, tablets should contain 95% to 100% drug (ie, ibuprofen to paracetamol ratio should be in the range of 1.23 to 1.36). Ibuprofen content was comparatively lower in agglomerates containing ethyl cellulose (IPEC batches) as compared with that containing PEG (IPPG batches). The IPPG batches showed that the ratio of drugs exceeded the desired limit because of loss of paracetamol from these batches, which may be owing to increase in solubility in the presence of PEG.

Photomicrographs of ibuprofen, paracetamol, and agglomerates are shown in Figure 1. Ibuprofen crystals were tubular shaped with narrow crystal size distribution. Paracetamol was composed of a mixture of needle- and plate-shaped crystals. The agglomerates of all the batches were spherical in shape with shape factor values in the range of 0.87 to 1.07 (Table 2). As compared with the IPPG batches, IPEC batches produced smaller and denser agglomerates with a smoother surface. The lower values of Rosin-Rammler diameter of agglomerates containing ethylcellulose polymer may be attributed to reduction in particle-particle interaction (Table 2). Comparatively higher affinity of the bridging liquid for hydrophobic crystals and slow diffusion due to increased viscosity may affect the rate of squeezing of the bridging liquid, which may cause a reduction in the rate of ball growth owing to insufficient surface cohesion. In addition, IPEC batches contain a higher concentration of the hydrophilic emulsifying agent PVA. The reduction in interfacial tension in the presence of PVA may also aid in the formation of smaller agglomerates. The agglomerates containing PEG were comparatively loosely packed crystals with well-developed edges and with rougher agglomerate surface. SEM photomicrographs of agglomerates are shown in Figure 2. The number of holes on the surface of agglomerates containing PEG were fewer as compared with ethyl cellulose containing agglomerates. The increase in the viscosity of the bridging liquid owing to dissolution of ethyl cellulose and ibuprofen reduces the rate of squeezing and favors entrapment of bridging liquid in the interstices. The delayed evaporation during filtration results in the formation of more holes on the agglomerate surface. The loosely packed crystals in agglomerates containing PEG provided sufficient area for rapid escape of the bridging liquid. The drug crystals in IPEC batches exhibited rounded corners and underdeveloped edges with polymer coat on the surface imparting smoothness. Paracetamol crystals in the IPPG agglomerates were cubes with layered structure. Such layered structure has been reported by Wang and Zang.[3]

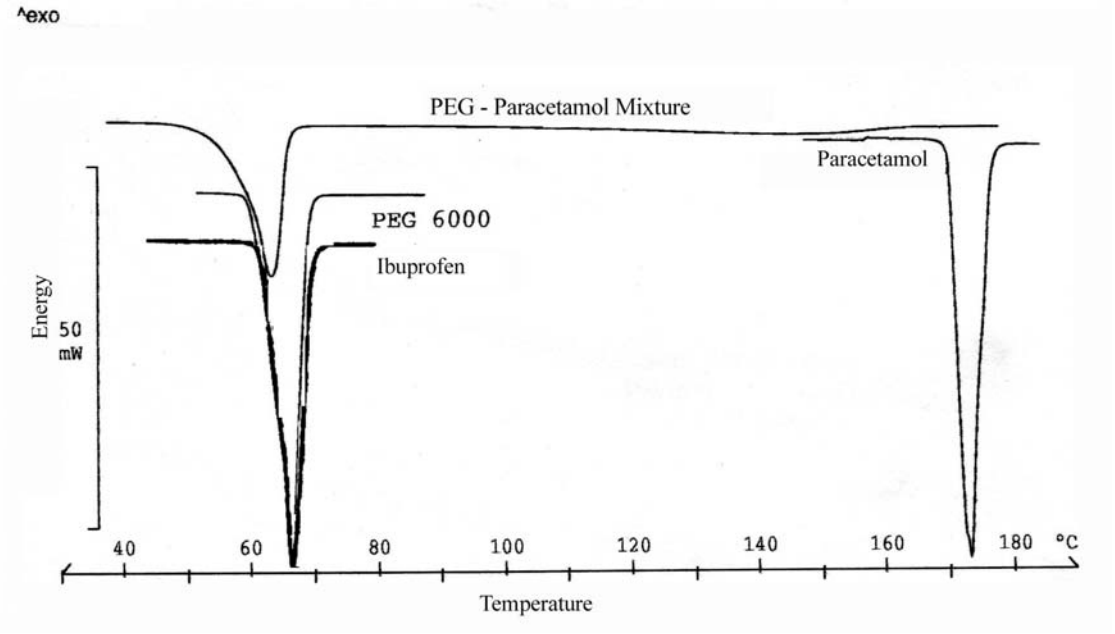

Figure 3. DSC thermograms of ibuprofen, paracetamol, PEG 6000, and PEG-paracetamol mixture.

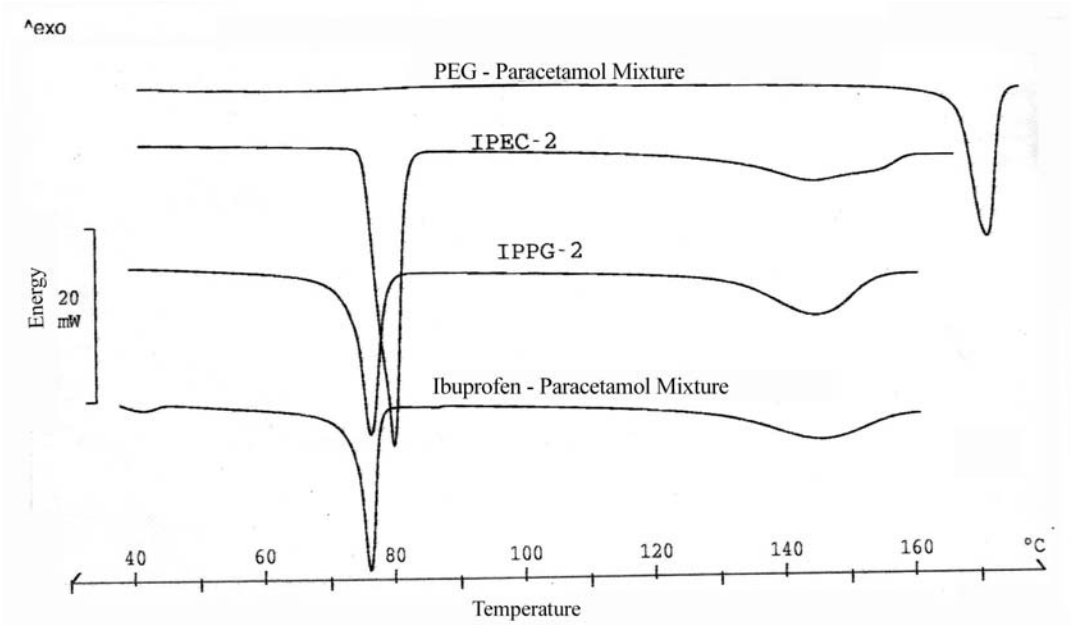

Figure 4. DSC thermograms of ibuprofen-paracetamol mixture, paracetamol-ethylcellulose mixture, IPEC-2 agglomerates, and IPPG-2 agglomerates.

Thermal properties of drugs and agglomerates were studied using DSC (Figures 3 and 4). Ibuprofen and paracetamol have shown melting endotherms at 78.07°C and 170.27°C with normalized heat of fusion 125.0 J/g and 186.37 J/g, respectively.[1] The binary mixture of ibuprofen and paracetamol showed an interesting change in the thermogram. The endotherm for ibuprofen melting (129°C to 159°C) remained unchanged, whereas diffused endotherm with low enthalpy was observed for paracetamol. The early onset and broadening of the paracetamol peak was due to its partial dissolution in ibuprofen melt. This finding was in accordance with the thermal behavior of binary mixtures reported by Lloyd et al,[27] where it was shown that the dissolution of the higher melting component in the melt of the lower melting component during thermal studies causes shift or complete disappearance of the peak of the higher melting component. Similar behavior was observed for binary mixtures containing paracetamol and PEG 6000, but a binary mixture with ethyl cellulose did not exhibit any shift or broadening of the paracetamol peak.

Presence of drug such as ibuprofen significantly affects the thermal properties of a polymer such as T_g.[28,29] But in the present study, as the ratio of drug:polymer is very high, these changes could not be observed in the thermograms.

Table 3. Friability of Ibuprofen-Paracetamol Agglomerates*

Parameter	Regression Analysis of Friability			$FI_{5\ minutes}$
	C	K	r	
IPEC-1	80.148	1.865	0.913	77.959
IPEC-2	80.462	2.145	0.929	73.758
IPPG-1	72.627	2.179	0.931	66.476
IPPG-2	77.600	2.375	0.941	70.258

*C indicates a constant reflecting the surface strength of the agglomerate; K, abrasion rate constant; R, coefficient of correlation; FI, friability index; IPEC, ibuprofen ethylcellulose; and IPPG, ibuprofen polyethylene glycol.

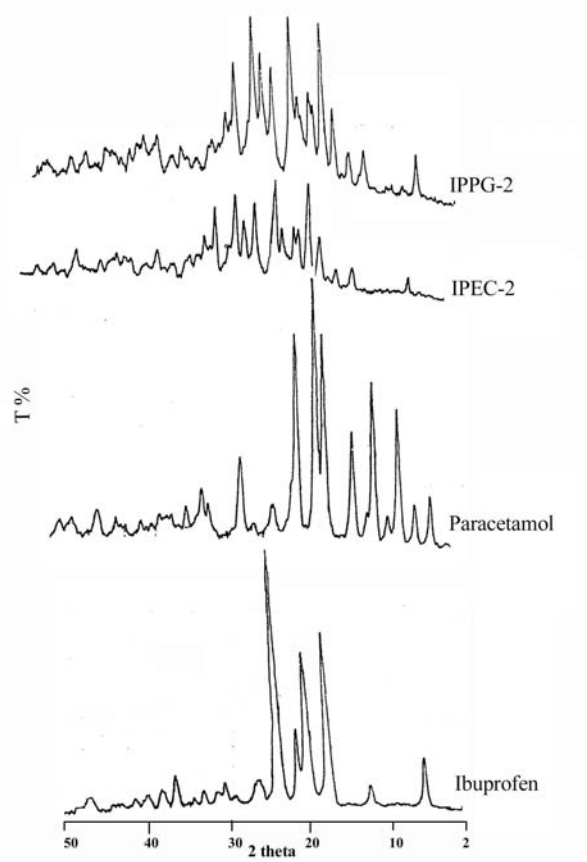

Figure 5. PXRD patterns of ibuprofen, paracetamol, IPEC-2 agglomerates, and IPPG-2 agglomerates.

Significant reduction in the peak intensities was observed in PXRD patterns of agglomerates (Figure 5), which indicated reduced crystallinity of the drugs. The intensity has been found to reduce to a greater extent in the presence of ethyl cellulose as compared with the presence of PEG. It may be attributed to the inhibition of nucleation and crystal growth due to ethyl cellulose.

Mechanical properties of the agglomerates were evaluated by crushing strength and friability. The crushing strength of agglomerates containing ethyl cellulose and lower level of PEG was low. The IPPG-2 agglomerates containing a higher level of PEG showed high values of crushing strength, possibly due to the larger size of agglomerates. The effect of particle size on crushing strength of the IPPG-2 agglomerates can be explained by following equation:

$$F_g = -0.499\ D^{0.802}, \quad (6)$$

where, F_g is crushing strength in *g*, and D is average diameter of agglomerates in μm.

When the change in FI with time was studied, the FI was found to decrease linearly with time (t).

$$FI = -Kt + C, \quad (7)$$

where K is the abrasion rate constant and C is a constant reflecting surface strength of the agglomerate. The higher value of C and lower values of K indicated that agglomerates containing ethyl cellulose have better surface strength as well as overall strength as compared with agglomerates containing PEG (Table 3). The better overall strength of IPEC-1 agglomerates as compared with IPEC-2 agglomerates may be owing to uniform packing of the crystals and uniform distribution of the ethyl cellulose in IPEC-1 agglomerates. The slow diffusion of viscous solvent in IPEC-2 batches and delayed precipitation leads to accumulation of a higher concentration of ibuprofen and polymer on the surface of the agglomerate. This was reflected in good surface strength and poor core strength of the agglomerates. The agglomerates containing PEG have shown poor surface strength as well as overall strength as a result of comparatively loose packing.

The agglomerates containing PEG showed rapid densification. The compressibility of agglomerates of IPPG-1 batches may be attributed to low mechanical strength of agglomerates. The lower P_y and A values of agglomerates containing PEG than agglomerates containing ethyl cellulose may be attributed to plastic deformation and asperity melting of PEG as compared with relatively high pressure required for deformation of ethyl cellulose (Table 4). Agglomerates containing ethyl cellulose yielded compacts of high tensile strength. Presence of the coating of ethyl cellulose along with ibuprofen at intergranular contact points contribute to bonding. The effect of asperity melting of PEG has not been reflected in compressional properties as it is distributed throughout the agglomerate.

Dissolution of drug from the compacts prepared using agglomerates was studied (Figure 6). IPPG-2 batches showed initial

Table 4. Compression Properties of Ibuprofen-Paracetamol Agglomerates*

	Heckel Plot		Tensile Strength	
Parameter	P_y (tons)	A	TS @ P_r = 0.9 (Kg/cm^2)	Rate of Increase of TS (Kg/cm^2/ton)
IPEC-1	0.865 ± 0.059	2.719 ± 0.227	3.561 ± 0.0632	0.8974 ± 0.0642
IPEC-2	1.083 ± 0.065	2.771 ± 0.057	3.640 ± 0.177	1.4229 ± 0.167
IPPG-1	–	–	2.353 ± 0.379	0.331 ± 0.003
IPPG-2	0.838 ± 0.116	2.449 ± 0.102	1.486 ± 0.037	1.1091 ± 0.0060

*TS indicates tensile strength; IPEC, ibuprofen ethylcellulose; and IPPG, ibuprofen polyethylene glycol.

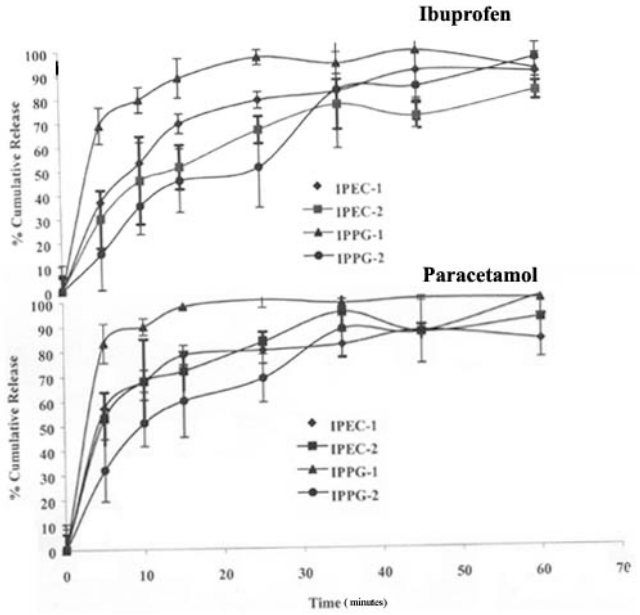

Figure 6. Dissolution profile of ibuprofen-paracetamol agglomerates obtained by CCA.

slow dissolution of paracetamol up to the first 30 minutes, followed by a steep rise in dissolution rate. The total drug was dissolved in 60 minutes. IPPG-1 batches have shown faster dissolution of paracetamol, with complete drug dissolution in 20 minutes. The initial fast dissolution followed by comparatively slower release of paracetamol was observed in IPEC batches. The initial fast release of ibuprofen followed by slow phase of drug dissolution was observed in the case of agglomerates containing ethyl cellulose, and the reverse was observed in case of agglomerates containing PEG. The initial slow release of paracetamol from IPPG-2 compacts correlates with the slower disintegration of the compacts. It may be attributed to reduced effectiveness of Primogel due to asperity melting of ibuprofen and to moisture content.[30] Moisture content was found to be 2.32%, 2.17%, 2.71%, and 2.74% wt/wt for IPEC-1, IPEC-2, IPPG-1, and IPPG-2 batches, respectively.

The higher crushing strength of agglomerates of IPPG-2 batches is responsible for initial slow drug release. Compacts of the IPPG-1 batch have shown fast drug release owing to low tensile strength and lower moisture content. The faster disintegration of compacts of IPEC agglomerates owing to lower packing fraction showed initial faster drug release. After disintegration, presence of hydrophobic polymer dominates, resulting in slow dissolution.

Conclusion

The CCA method developed in the present study is a promising technique to obtain directly compressible agglomerates of combination of drugs in required proportion. Optimization of polymer concentration is important to obtain desired processing and biopharmaceutical properties of the agglomerates and their compacts.

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