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CONTENTS

Effect of Polymers on Crystallo-co-agglomeration of Ibuprofen-Paracetamol: Factorial Design

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The purpose of this research was to study the effect of concentration of polyethylene glycol and ethyl cellulose on the properties of agglomerates of ibuprofen-paracetamol obtained by crystallo-co-agglomeration technique. The process of crystallo-co-agglomeration involved recrystallization of ibuprofen and its simultaneous agglomeration with paracetamol in presence polymers. The effect of combination of polyethylene glycol and ethylcellulose was studied by 2^2 factorial design. Ibuprofen content of the agglomerate increased with increase in ethyl cellulose while paracetamol content was decreased with increase in polyethylene glycol. Differential scanning calorimetry thermograms of agglomerates showed the unchanged endotherm for ibuprofen melting, whereas paracetamol endotherm was diffused with low enthalpy. The agglomerates were spherical but increase in polyethylene glycol caused its deformation. Agglomerates containing ethylcellulose with polyethylene glycol have higher resistance for fragmentation, modulus of elasticity but impart high tensile strength.

Key words: Crystallo-co-agglomeration, ibuprofen-paracetamol, ethylcellulose, polyethylene glycol

The crystallo-co-agglomeration (CCA) technique 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[1-6]. The process is applicable to obtain directly compressible agglomerates containing two drugs or a low-dose or a poorly compressible drug in combination with excipient. Recently, Pawar *et al.*[1,2] reported preparation of agglomerates containing paracetamol with ibuprofen and ibuprofen with talc by CCA technique. Polymers with different physicochemical categories were used in agglomeration process. Hydroxypropylmethylcellulose (HPMC) increased size, abrasion resistance and compactibility of the ibuprofen-talc agglomerates[2]. Ethylcellulose (EC) and polyethylene glycol (PEG) also influenced CCA process and properties of paracetamol-ibuprofen agglomerates. EC produced agglomerates with low particle size, friability, moisture content and the compacts of these agglomerates were of higher tensile strength and mean yield pressure. The effect of disintegrant was unimpaired showing faster initial drug release from compacts. Incorporation of PEG yielded agglomerates with higher moisture content, particle size and crushing strength. The compacts of agglomerates containing PEG have lower P_y values and tensile strength and it shows slower initial drug release[1]. Therefore, it was thought appropriate to combine the EC and PEG so as to minimize the limitation of each of it.

The present research was an attempt to study effect of combination of a hydrophilic and a hydrophobic polymer on properties of agglomerates containing ibuprofen and paracetamol in the ratio 400:325. The batches of agglomerates containing EC and PEG in proper proportion were obtained as per 2^2 factorial designs. 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

Ibuprofen was a kind gift from Seksaria Chemicals (Mumbai, India). Paracetamol was supplied as a gift sample by Vamsi Labs Ltd (India). Polyethylene glycol (PEG 6000) and ethyl cellulose (EC 15 cps) were procured from BDH Chemicals, Mumbai, India. Polyvinyl alcohol (PVA) was purchased from Research

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Labs, Mumbai, India. Primogel was supplied by Get-Rid Pharma (Pune, India). Dichloromethane (DCM) and all other chemicals, which are of analytical grade were procured from Merck Ltd, Mumbai, India.

Crystallo-co-agglomeration:

The agglomerates were prepared by the CCA technique[1]. EC and PEG were used in combination as per 2^2 factorial design technique. Experimental variables and their coded levels with actual values are given in Table 1. Amount of PVA in the system was kept constant at 0.1 mg.

In a crystallization vessel, as described by Morishima *et al*.[7], ibuprofen (8 g) and EC 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% w/v), 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°. 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[8]. 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[8].

TABLE 1: EXPERIMENTAL VARIABLES AND THEIR CODED LEVELS

Code	Amount of EC (X1 in mg)	Amount of PEG (X2 in mg)
IBP -1	-1 (100)	-1 (800)
IBP -2	+1 (200)	-1 (800)
IBP -3	-1 (100)	+1 (1200)
IBP -4	+1 (200)	+1 (1200)

Surface topography:

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) using the formula, $S = P_{actual}^2/(4\pi A_{actual})$. Twenty granules per batch were evaluated. 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 drugs, polymers 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° to 180° at a rate of 10°/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[9] as: Ln(2-log R)= Ln(a log e)+b Lnd, 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[10]. Friability of agglomerates was performed after subjecting to attrition[6]. 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, FI= $[(dg)_t/(dg)_o]\times100$, where, $(dg)_t$ and $(dg)_o$ are mean geometric diameters after time t and initial time, respectively.

Compressibility studies:

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 min using a hydraulic press. The compacts were allowed to relax for 24 h. Pressure (P)– relative density (ρ_r) data were analyzed using the Heckel Equation[11,12], $Ln(1-\rho_r)= KP+A$, 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.

Compactibility studies:

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[13], $\sigma_t= 2F/\pi Dt$.

Dissolution studies:

The agglomerates (800±10 mg) were compacted at a pressure of 1 ton for a dwell time of 1 min. Sodium starch glycolate (Primogel, 10% w/w) was added as a disintegrating agent. The dissolution was performed in 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°±2°. The paddle speed was 100 rpm. Samples were collected and analyzed on multicomponent mode spectrophotometrically at 222 nm and 242 nm for ibuprofen and paracetamol, respectively.

RESULTS AND DISCUSSION

The process yield was in the range of 93 to 97%. Drug content of the agglomerates was dependent on the crystallization rate of the ibuprofen and relative affinity of both the drugs towards the bridging liquid and effect of additives. In design of CCA process for combination of drugs achieving the desired ratio of the drugs is most critical step. Higher percentage of hydrophilic polymer alters solubility of the component and affects drug content of the agglomerate. The drug content of various batches was in the range of 53.01-56.47% w/w for ibuprofen and 39.40-41.39% w/w for paracetamol (Table 2). Generally, the commercial tablet formulation contains 400 mg and 325 mg of ibuprofen and paracetamol, respectively. Therefore, required ibuprofen to paracetamol ratio should be in the range of 1.23 to 1.36 and all the batches lies in the satisfactory range of 1.28 to 1.39.

Microphotographs of agglomerates are shown in fig. 1. The agglomerates containing lower level of EC have shown smoothened crystal and agglomerate surface. Whereas at higher levels of EC the deposits of polymer with crystals entrapped were observed (fig. 1c and 1e). The growth of crystal and deposition of polymer on the surface occurs during agitation. The agglomerates prepared using higher levels of ethyl cellulose contained high viscosity bridging liquid, which escapes at relatively slower rates during filtration and drying through the small holes. The bridging liquid, during evaporation deposit EC and fine crystals of drug mainly ibuprofen, on the surface reducing the number of holes on the surface. IBP3 agglomerates have shown smoother surface; though

TABLE 2: EVALUATION PARAMETERS FOR AGGLOMERATES OBTAINED BY 2^2 FACTORIAL DESIGN EXPERIMENTS

Parameter	IBP-1	IBP -2	IBP -3	IBP -4
Ibuprofen content (% w/w)	53.01±0.134	56.47±0.298	54.49± 1.043	54.63±0.895
Paracetamol content (% w/w)	41.29±0.475	40.60±0.632	39.40±0.712	41.39 (0.665)
Drug ratio	1.28	1.39	1.38	1.31
Shape factor	1.031±0.043	1.104±0.059	1.025±0.015	1.023±0.013
Rosin-Rammler diameter (µm)	702.549±5.017	844.841±16.39	813.272± 28.64	1000±87.28
Angle of repose (°)	25.82±1.020	30.33±1.393	27.46±0.990	29.066±1. 622
Bulk density (g/cc)	0.3024±0.004	0.3194±0.000	0.2927±0.002	0.3213±0.004
Crushing strength (g)	53.6562±5.014	75.861±24.75	78.249±22.44	116.687±39.64
$FI_{5\ min}$ (%)	58.411	71.238	53.055	77.780
Mean yield pressure (tones)	0.583±0.09	1.214±0.12	0.989±0.117	--
Tensile strength at $P^f = 0.9$ (Kg/cm^2)	3.579±0.138	2.525±0.155	2.388±0.195	2.854±0.052
Moisture Content (%w/w)	2.5732±0.085	2.226±0.140	2.623±0.086	2.674±0.000

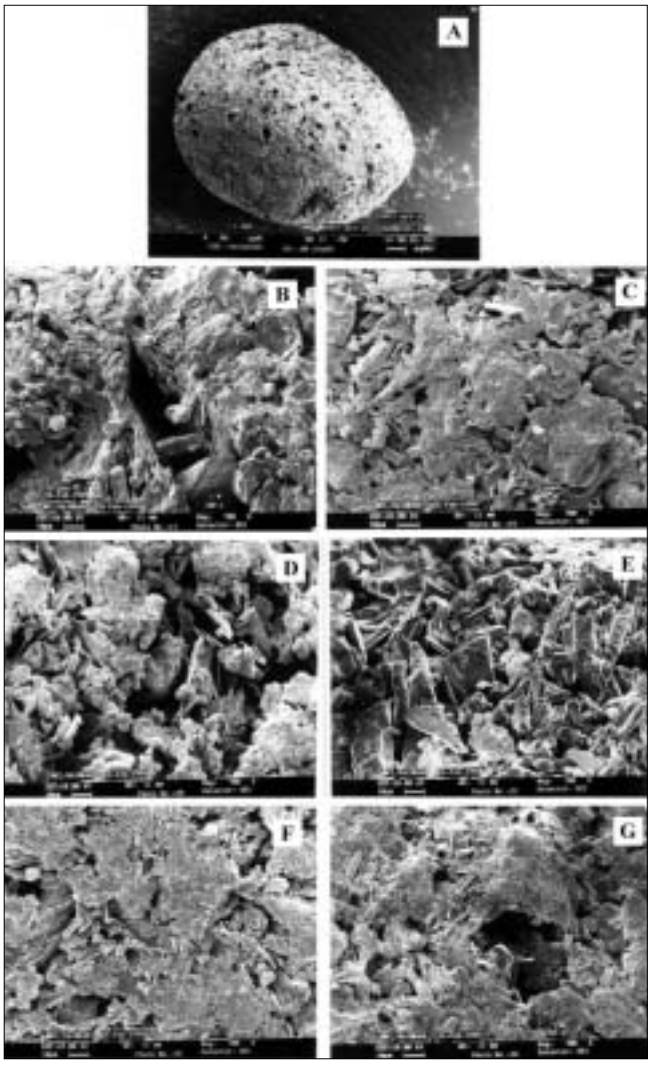

Fig. 1: Scanning electron microphotographs of ibuprofen-paracetamol
SEM Photographs of (a) IBP-1 at 60X, (b) IBP-1 at 700X, (c) IBP-2 at 700X, (d) IBP-3 at 700X, (e) IBP-4 at 700X, (f) IBP-2 AT 700X and (g) IBP-4 at 700X

the crystal surface is coated with the polymer the coat is thin and uniform. The edges of the crystals are comparatively well developed.

The microphotographs of IBP2 and IBP4 have shown that the different portions of the same agglomerate show different in the extent of deposition of EC and in turn number of holes (fig. 1f and 1g). The escape of the bridging liquid must have been favoured through the portion, which appears to be dense, due to orientation of the agglomerate during the processing steps such as filtration or drying.

Ibuprofen and paracetamol have shown melting endotherms at 78.07° and 170.27° (fig. 2). DSC thermograms of agglomerates showed the unchanged

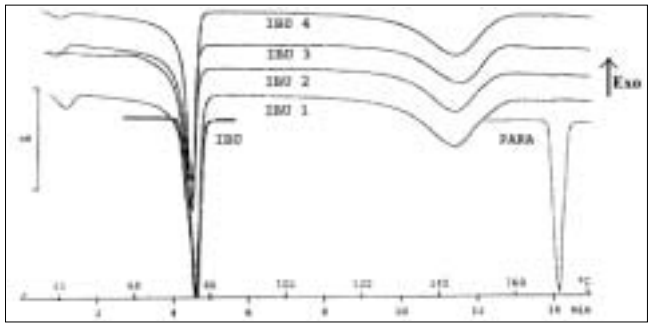

Fig. 2: DSC thermograms of ibuprofen, paracetamol and their agglomerates
DSC thermograms of (a) ibuprofen, (b) paracetamol, (c) IBP-1, (d) IBP-2, (e) IBP-3 and (f) IBP-4

endotherm for ibuprofen melting, whereas paracetamol endotherm was diffused with low enthalpy[1]. An additional low enthalpy endotherm at around 40-43° was observed in all batches except batch IBP-2 that containing higher level of EC. The batches containing higher levels of EC only exhibit glass transition temperature, which was 102.8° and 101.5°, respectively for IBP-2 and IBP-4 batches. At low concentration of EC it was difficult to locate the glass transition. Significant reduction in the peak intensities was observed in PXRD patterns of agglomerates and it was greater in batches containing higher levels of EC (fig. 3), which was in accordance with our previous observation[1].

Responses obtained from the batches of factorial designed experiments were subjected to multiple regression analysis using statistic software UNISTAT ver 3.0. The data was fitted in the equation, $Y= \beta_0 + \beta_1X_1+ \beta_2X_2 + \beta_{12}X_{12.}$ Insignificant effects were removed by backward elimination method. The results of multiple regression analysis are summarized in Table 3. The response surface plots were generated using graph mode of PCPRSM software.

Ibuprofen content of the agglomerates increased with increase in the EC concentration (fig. 4a). EC has shown significantly different behaviour at higher and lower levels of PEG. EC increases the viscosity of bridging liquid, which causes reduction in the rate of diffusion of ibuprofen. Secondly, ibuprofen is coated to the greater extent with EC, this imparts hydrophobicity to the crystal reducing its affinity towards aqueous phase. The interaction term though significant is low as compared to the β_1 value. Paracetamol content of the agglomerates was found to decrease with increase in PEG (fig. 4b). It is due

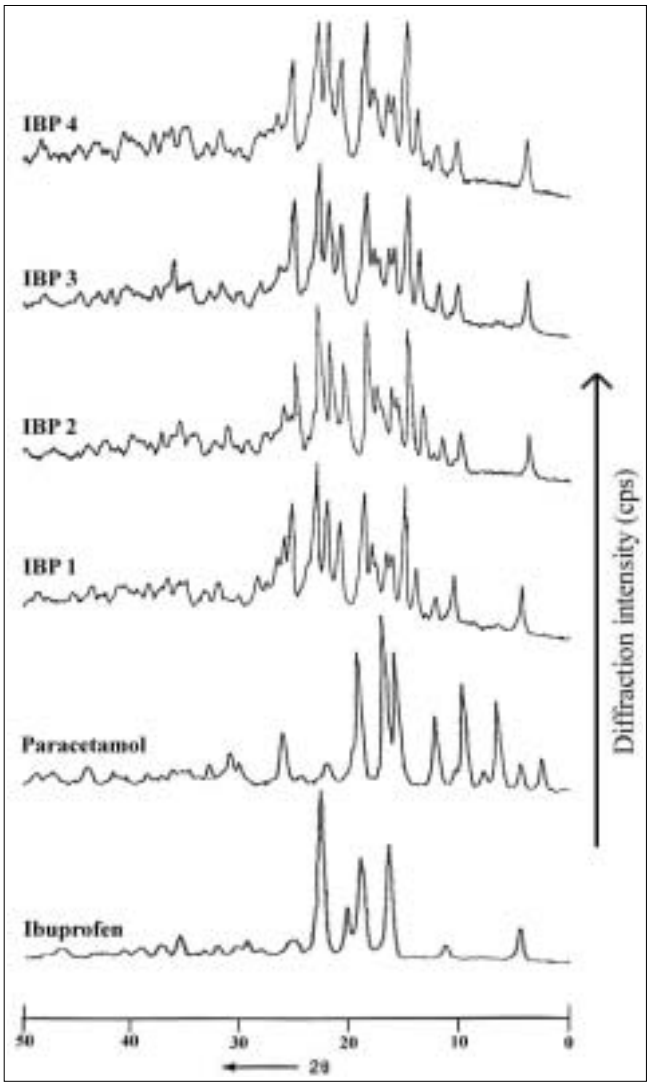

Fig. 3: X-ray powder diffraction patterns of ibuprofen, paracetamol and their agglomerates
X-ray spectra of (a) ibuprofen, (b) paracetamol, (c) IBP-1, (d) IBP-2, (e) IBP-3 and (f) IBP-4

to more loss of drug in aqueous phase because of enhanced solubility in presence of PEG. The surface hydrophobicity imparted by EC may also contribute in rise in paracetamol content, which is reflected by positive interaction term (Table 3).

The regression analysis data showed increase in agglomerate size with increase in concentration of either of the polymer and the interaction between the polymers is insignificant (Table 3). Shape factor values are close to one indicating spherical shape (fig. 4c). It was found to increase with increase in PEG concentration. The batches containing PEG produced larger size globule with comparatively low viscosity with respect to EC that could deform under shear of agitation causing deviation from the sphericity with increase in PEG concentration. The agglomerates have shown good flowability. As reported previously[1], the flowability of agglomerate was attributed to the surface smoothness imparted by EC surface coat. However, as compared to only EC, surface of agglomerates containing EC and PEG had thick clumps of polymer and fine drug particles. The friction between such surfaces increased inter-particular friction, increasing angle of repose. As compared to PEG, the increase in bulk density with increase in EC may be attributed to dense, spherical agglomerates having smooth surface (fig. 4d).

The response surfaces for crushing strength and friability index (fig. 4e and 4f) revealed the increase in mechanical strength with increase in EC. The increase in cohesive interaction between particles by EC caused better binding and closed packing between crystals. Secondly, both the polymers contributed towards increase in agglomerate size and in turn its crushing strength. The thicker surface deposits of polymer increased resistance to abrasion of agglomerates.

Mean yield pressure data can not be treated by regression analysis as the batch containing higher levels of both the polymers (IBP 4) has very low mean yield pressure well below the range in which the experiment was carried out. In remaining batches the P_y value increased with increase in concentration of EC. The agglomerates with surface deposits of EC required higher pressure for deformation and

TABLE 3: REGRESSION ANALYSIS DATA OF EVALUATION PARAMETERS FOR AGGLOMERATES OBTAINED BY 2^2 FACTORIAL DESIGN

Parameter	β_o	β_1	β_2	β_{12}	r^2	Significant
Ibuprofen content (% w/w)	54.65	0.90	-	-0.83	0.61	0.000
Paracetamol content (% w/w)	40.65	-	-0.28	0.67	0.45	0.069
Shape factor	1.042	-	0.335	0.034	0.523	0.054
Rosin-Rammler diameter (μm)	840.2	82.34	66.47	-	0.877	0.000
Angle of repose (°)	29.03	2.382	-	-	0.531	0.007
Bulk density (g/cc)	0.308	0.011	-	0.003	0.958	0.000
Crushing strength (g)	81.11	15.16	16.35	4.058	1.000	0.000
$FI_{5\ min}$ (%)	65.12	9.38	0.296	2.974	1.000	0.000
Tensile strength at P_f = 0.9 (kg/cm^2)	2.826	-0.14	-0.21	0.377	0.953	0.000

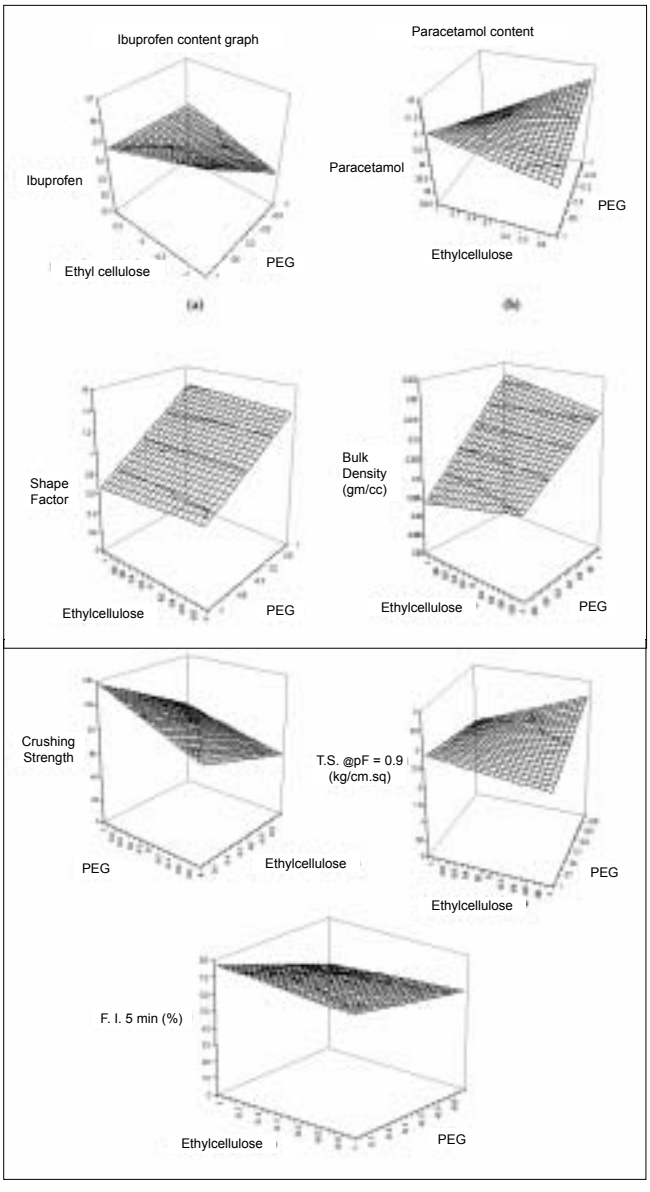

Fig. 4: Effect of variables on the properties of ibuprofen-paracetamol agglomerates
Effect of variables on the properties of ibuprofen-paracetamol agglomerates; (a) ibuprofen content, (b) paracetamol content, (c) shape factor, (d) bulk density, (e) crushing strength, (F) friability index and (g) tensile strength.

showed high mean yield pressure. The higher packing of agglomerates containing low levels of both the polymers may be attributed to easy deformation/ fragmentation of agglomerates.

Tensile strength of the compacts was surprisingly found decrease with increase in EC concentration (fig. 4g) . Leuenberger[14] has explained the phenomenon of compaction on the basis of percolation theory and suggested that in a binary mixture the property such as tensile strength shows sudden change when an infinite cluster of one of the components have been formed, that is at percolation threshold[15]. Agglomerates containing EC with PEG have higher resistance for fragmentation, modulus of elasticity but impart high tensile strength. The increase in crushing strength and thicker surface deposition is expected to increase percolation threshold above 0.9 packing fraction; below this increase in the amount of ethyl cellulose will not show any significant increase in the tensile strength rather decrease. In binary mixture it was observed that an infinite cluster having highest strength decided the tensile strength of the compact. Increase in the PEG concentration increased the percolation threshold for ethyl cellulose and thus decreased tensile strength of the compact.

Dissolution of drug from the compacts prepared using agglomerates was studied (fig. 5). Batches containing higher level of EC showed faster dissolution of both the drugs. It may be attributed to low tensile strength of compacts and low moisture content. It is also

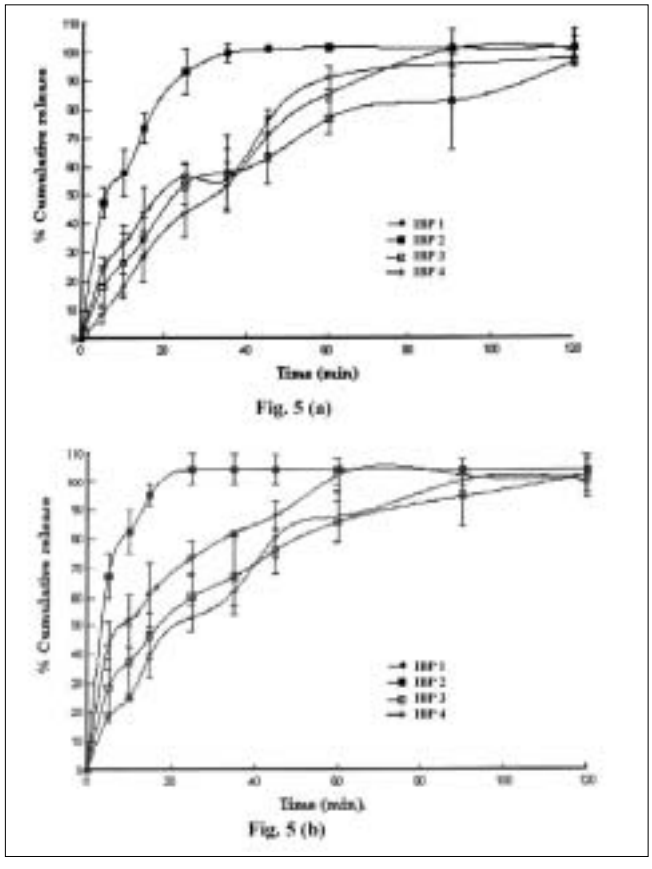

Fig. 5: Drug release from ibuprofen - paracetamol agglomerates. (A). Percent cumulative ibuprofen release with time from agglomerates IBP 1 (—◆—); IBP 2 (—■—); IBP 3 (—□—) and IBP 4 (—I—). (B) Percent cumulative ibuprofen release with time from agglomerates IBP 1 (—◆—); IBP 2 (—■—); IBP 3 (—□—) and IBP 4 (—I—).

expected that the presence of disintegrating agent may have interfered with the complete percolation of EC cluster. Faster consolidation, lower tortuosity and comparatively higher moisture content are responsible for slower release of drugs from batches containing PEG at higher levels.

In conclusion, crystallo-co-agglomeration process and properties finished product are not merely depends on the physicochemical properties of the drug component but these are simultaneously affected by polymer induced properties such as salting out of polymer, interfacial tensions, viscosity and the rate of vaporization of solvent used. The complex polymer system due to the polymer-polymer, polymer-drug and polymer-solvent interactions may act differently than an individual polymer.

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