RESEARCH ARTICLE

# Tailoring of ketoprofen particle morphology via novel crystallocoagglomeration technique to obtain a directly compressible material

Vikash Chavda, Rajesh Kumar Maheshwari

Department of Pharmacy, Industrial Pharmacy Research Lab, Shri G.S. Institute of Technology and Science, 23, Park Road, Indore - 452 003, Madhya Pradesh, India

**Purpose:** The purpose of this research was to develop a novel crystallo-co-agglomeration (CCA) method for ketoprofen to obtain its directly compressible spherical agglomerates with improved flowability and compressibility. **Methodology:** Dichloromethane-water system containing polyethylene glycol (PEG) 6000, polyvinyl alcohol (PVA), and hydroxypropylmethylcellulose (HPMC) 100 Centi Poise was used as the crystallization system. Ketoprofen was crystallized from dichloromethane and agglomerated with talc. Experimental parameters (concentration of PEG, PVA, and HPMC; effect of temperature; and agitation speed) were optimized. The agglomerates were evaluated for micrometric properties, mechanical properties, moisture content, compressibility, packability, and drug-release properties. The agglomerates were characterized by differential scanning calorimetry (DSC), powder x-ray diffraction (PXRD), infrared (IR) spectroscopy, and scanning electron microscopy (SEM). **Main Findings:** Remarkable improvement in micromeritic properties (angle of repose <22°, percentage compressibility <10, and Hausner ratio near to 1) and compactibility (mean yield pressure 55-93 MPa) enabled direct compression without any defect. Results of friability showed higher surface strength of agglomerates containing higher amount of talc. DSC, PXRD, and IR results showed no change in the crystalline form of ketoprofen. Dissolution study of batches KA, KB, KC, and KD(composition given in Table 1) showed 90% drug release in 120, 180, 240, and 420 min respectively. **Principal Conclusions:** Crystallo-co-agglomeration process can be considered as a suitable alternative to conventional granulation process to obtain agglomerates of ketoprofen with improved micromeritic and compressibility parameters. The CCA technique can be used for the design of sustained-release ketoprofen talc agglomerates containing lower amounts of polymers.

***Key words:*** *Crystallo-co-agglomeration, Heckel plot, ketoprofen, packability*

## 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.[6-9] 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 this limitation, spherical crystallization could not be applied to obtain agglomerates of low-dose or poorly compressible materials.

In order to overcome the limitations of spherical crystallization, crystallo-co-agglomeration (CCA) technique was developed by Kadam *et al.* in 1997.[10-11] 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 two drugs or a low-dose or poorly compressible drug in combination with a diluent. CCA method has been used to prepare spherical agglomerates of ibuprofen,

**Address for correspondence:**
*Mr. Vikash Chavda, Industrial Pharmacy Research Lab, Department of Pharmacy, Shri G.S. Institute of Technology and Science, 23, Park Road, Indore - 452 003, Madhya Pradesh, India. E-mail: vikaschavda@gmail.com*

combination of ibuprofen and paracetamol, and bromhexine hydrochloride.[12-14]

Considering the poor flowability and compressibility of ketoprofen, novel crystallo-co-agglomeration method was developed to obtain spherical agglomerates of ketoprofen. In the process, ketoprofen was crystallized from dichloromethane and agglomerated with talc. Dichloromethane served as the bridging liquid and a good solvent for ketoprofen, aqueous phase as the bad solvent, and HPMC imparts viscosity to the system. Polyethylene glycol (PEG) was used to improve the mechanical strength and sphericity of the agglomerates. Talc was selected as an agglomerating agent. Due to its hydrophobicity, it undergoes preferential wetting with bridging liquid (dichloromethane) and is a suitable excipient for incorporation. Results showed that the agglomerates obtained have improved flowability and compressibility, and the developed method can be used as an alternative to conventional granulation process.

## MATERIALS AND METHODS

Ketoprofen was a kind gift from Ranbaxy Laboratories Ltd., Dewas, India. HPMC 100 cps was obtained from Signet Chemical Corporation, Mumbai. Dichloromethane and all other chemicals used were of analytical grade (Merck Ltd., Mumbai, India).

### Crystallo-co-agglomeration technique

An aqueous phase containing mixture of polyethylene glycol 6000 (6.5% w/w of total solid content) and polyvinyl alcohol (0.05% w/v) was previously maintained at a temperature 10°C. Ketoprofen and hydroxy propyl methylcellulose were co-dissolved in dichloromethane, and talc was uniformly dispersed in it. The aqueous phase (20 mL) was added to it with continuous stirring (1000 rpm). The mechanical stirring was carried out for 1 h. Agglomerates collected by filtration were dried at 40°C for 4 h. The effect of different process parameters and concentration of HPMC and talc was optimized. Composition of different batches is shown in Table 1.

### Drug-loading efficiency and yield of agglomerates

Samples of agglomerates (200 mg) were accurately weighed, powdered, and extracted in 25 mL of methanol for half an hour. After sufficient dilution with methanol, ketoprofen content was assayed spectrophotometrically at 258 nm. Drug-loading efficiency is the ratio of the experimentally measured ketoprofen content to the theoretical value expressed as a percentage. The yield were calculated using Eq. (1):

$$\% \text{ yield} = \frac{(\text{total weight of agglomerates/total weight of drug and polymer})}{} \times 100 \qquad (1)$$

**Table 1: Composition for ketoprofen agglomerates**

| Ingredients | Batch codes | | | |
|---|---|---|---|---|
| | KA | KB | KC | KD |
| Talc (gm) | 0.3 | 0.4 | 0.5 | 0.6 |
| HPMC (%w/w of drug and talc amount) | 10.0 | 10.0 | 10.0 | 10.0 |
| PEG-6000 (%w/w of total solid content) | 6.5 | 6.5 | 6.5 | 6.5 |
| Drug (gm) | 2.0 | 2.0 | 2.0 | 2.0 |

### Micromeritic parameters

Particle size distribution was determined by sieve-analysis technique.[15] Geometric mean diameter ($d_g$) and geometric standard deviation ($\sigma_g$) were determined. Angle of repose was determined by a fixed-funnel method.[16] Percent fines were determined using #85. Percentage compressibility was also computed.[17]

### Surface topography

The agglomerates were photographed after observing in optical microscope. Area (A) and perimeter (P) obtained from the tracings of enlarged photomicrographs of agglomerates were used to calculate the shape factor (S) using Eq. 2:

$$S = P^2/4\pi A \qquad (2)$$

The surface morphology was visualized by scanning electron microscopy (Jeol, JSM 5600).

### Crushing strength and friability

Crushing strength was determined by the mercury load cell method using 20-mL hypodermic glass syringe.[18] Friability of agglomerates was performed after subjecting agglomerates to attrition.[19] Percentage friability index (FI) as a function of time was calculated at each time using Eq. (3):

$$FI = [(d_g)_t/(d_g)_0] \times 100 \qquad (3)$$

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

### Heckel plot and packability

Agglomerates (450 ± 5 mg) were compressed using a 15-mm flat-faced punch at a compaction pressure of 57.143, 85.714, 114.286, 142.857, and 171.429 MPa for 1 min, using a hydraulic press. The compacts were allowed to relax for 24 h. The compression behavior of the spherical agglomerates was expressed as parameters[20-23] of the Heckel equation (Eq. 4). The parameters Py, $D_A$, $D_0$, and $D_B$ were calculated using the relationship between compression pressure and ln [1/E]. Tensile strength-pressure profiles were also established.

$$\ln [1/E] = KP + A \qquad (4)$$

where E is the percent porosity of the tablet, P is the applied pressure, K is the slope of Heckel plot, and the reciprocal of K is the mean yield pressure $P_y$. $D_0$ corresponds to the relative density of the powder bed at the moment when the applied

pressure is still nil. $D_B$ describes the phase of rearrangement at low pressure.

Packability parameters ('a', 'b', and 'k') were calculated using Kawakita and Kuno's equations.[24]

### Powder x-ray diffractometry and differential scanning calorimetry

Powder x-ray diffractometry patterns of drug and agglomerates were obtained (Philips Holland, XRD System PW1710) using tube anode (Cu) at 30 kV voltage and current of 30 mA. The data were recorded over a range of °10θ to °60θ at a scanning rate 0.500 s/step cps using continuous scan mode. Thermal studies of drug and agglomerates were performed using DSC (Mettler). Accurately weighed samples were hermetically sealed in aluminum crucible. The system was purged with nitrogen gas at a flow rate of 60 mL/min, and heating was done from 25°C to 240°C at the rate of 10.0°C/min. Infrared spectra of pure drug and agglomerates were recorded using infrared spectrophotometer (FTIR-8400 S, Shimadzu, Japan).

### *In vitro* dissolution study

*In vitro* dissolution test of compacts of all four batches was performed using USP dissolution apparatus (paddle type) (USP II) using 900 mL of dissolution medium (pH-6.8 phosphate buffer) at 37°C ± 0.5°C and 50 rpm. Ten-milliliter aliquots were withdrawn at suitable time intervals; and each time, the aliquot was replaced with fresh 10-mL dissolution medium. The aliquots were analyzed spectrophotometrically at 261 nm.

## RESULTS

Drug-loading efficiency was found to be in the range of 72.19% to 75.18% w/w. Percentage yield of batches was found to be in the range of 75.82% to 79.14%. All four batches showed excellent flowability, as represented by angle of repose (<22°) and compressibility (<10). The agglomerates of batch KD were larger in size. On the basis of geometric mean diameter, batches may be ranked as KD > KC > KB > KA. Value of parameters 'b' (packing velocity index) and 'a' in the Kawakita equation was lower, and value of parameter 'k' in Kuno's equation was higher for all the four batches in comparison to those of original drug crystals [Table 2]. Shape factor was in the range of 1.14 to 1.26, and batches may be ranked as KC < KB < KD < KA. Moisture content was found in the range of 1% to 1.2%.

SEM study revealed that increase in the talc concentration in drug agglomerates has no significant effect on sphericity of the agglomerates. Agglomerates were uniformly packed, having plates of drug (some smaller and some larger plates) with well-developed edges. The agglomerates were spherical but had clumps of polymer containing fine

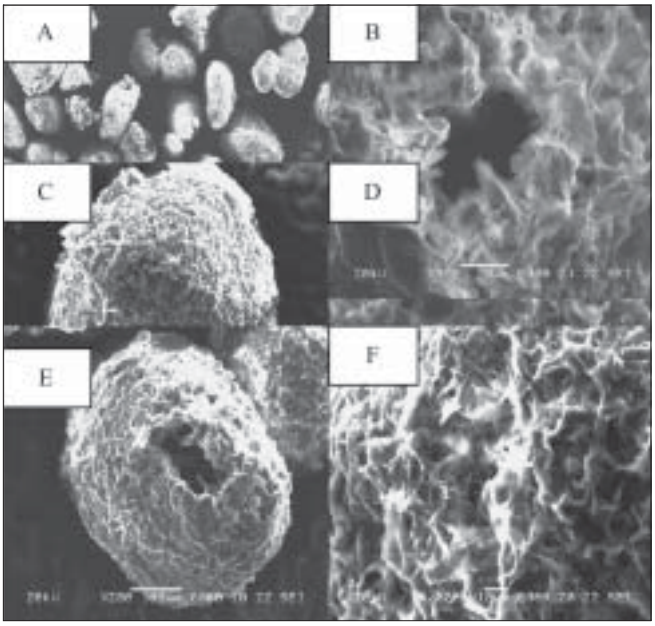


**Figure 1:** Photomicrographs of ketoprofen-talc agglomerates: (A) SEM of batch KA at ×35; (B) SEM of batch KB at ×950; (C) SEM of batch KB at ×2000; (D) SEM of batch KC at ×1300; (D) SEM of batch KD at ×200; (E) SEM of batch KD at ×1000

**Table 2: Micromeritic properties of ketoprofen agglomerates**

| Parameters | Batch code | | | | |
|---|---|---|---|---|---|
| | Pure drug | KA | KB | KC | KD |
| $d_g$ (μm) | - | 446.684 ± 70.184 | 473.151 ± 85.217 | 530.884 ± 64.222 | 562.341 ± 76.524 |
| $\sigma_g$ | - | 1.496 | 1.585 | 1.496 | 1.585 |
| Percentage fines | - | 5.268 ± 2.149 | 6.188 ± 1.953 | 8.643 ± 0.671 | 8.582 ± 2.286 |
| Shape factor | - | 1.26 ± 0.06 | 1.17 ± 0.08 | 1.14 ± 0.05 | 1.22 ± 0.13 |
| Angle of repose (°θ) | 34.76 ± 2.53 | 21.16 ± 2.45 | 20.49 ± 3.14 | 21.47 ± 2.91 | 20.807 ± 2.37 |
| Hausner ratio | 1.458 | 1.100 | 1.095 | 1.075 | 1.075 |
| Packing factor | 1.454 | 1.099 | 1.092 | 1.075 | 1.071 |
| Bulk density (g/ml) *n* = 3 | 0.229 ± 0.084 | 0.182 ± 0.081 | 0.174 ± 0.064 | 0.186 ± 0.077 | 0.182 ± 0.059 |
| Tapped density (g/ml) *n* = 3 | 0.333 ± 0.092 | 0.200 ± 0.086 | 0.190 ± 0.047 | 0.200 ± 0.072 | 0.195 ± 0.063 |
| Carr's index | 31.231 | 9.090 | 8.696 | 6.977 | 6.818 |
| Packability parameters | | | | | |
| 'a' | 0.3755 | 0.0772 | 0.0670 | 0.0556 | 0.0524 |
| 'b' | 0.0964 | 0.1731 | 0.8788 | 0.1414 | 0.1567 |
| 'k' | 0.0159 | 0.0256 | 0.0277 | 0.0205 | 0.0191 |

crystals deposited on the surface (thicker surface deposits). The agglomerates had holes present on their surface [Figure 1].

On the basis of crushing strength, batches may be ranked as KA < KB < KC < KD. Batch KD required maximum force for deformation [Table 3]. The change in friability index with time was found as a linear function of time (t), with decreasing friability index. Hence the data were fitted into a linear regression equation (Eq. 5):

$$FI = -Kt + C \quad (5)$$

where K is the abrasion rate constant (friability rate) and C is a constant reflecting surface strength of the agglomerate (initial friability). On the basis of the values of C obtained, batches may be ranked as KD > KC > KB > KA [Table 3].

In order to detect possible transition during the process, IR spectroscopy, PXRD, and DSC examinations were conducted for the pure drug and agglomerates. DSC thermograms of agglomerates showed sharp melting endotherms [Figure 2]. Enthalpy of melting (J/g) and % crystallinity were reduced by 49.93 to 59.00 J/gm and 43.04% to 50.86% respectively as compared to those of pure drug [Table 4]. PXRD spectra of agglomerates showed reduction in peak intensity [Figure 3]. IR study of agglomerates showed all the peaks of drug [Figure 4].

Tensile strength values for compacts of all four batches (which were compacted at different pressures) were determined. According to the maximum tensile strength obtained, batches may be ranked as KC > KD > KB > KA. Significant increase in the tensile strength was observed at the compression pressure range of 50 to 100 MPa for all four batches. After 150 MPa, decrease in the tensile strength was observed for all four batches [Figure 5]. Heckel plot for different batches are shown in Figure 6. Different parameters ($P_y$, $D_A$, $D_B$, and $D_o$) of Heckel equation were determined [Table 5]. It was observed that the $D_B$ value was higher for the batch KD, and different batches may be ranked as KD > KC > KA > KB. The value of $D_A$ was higher for the batch KD and may be ranked as KD > KC > KA > KB. The values of $P_y$ for the batch KB was lower.

**Table 3: Crushing strength and friability of ketoprofen agglomerates**

| Batch code | Crushing strength (g) | Regression analysis of friability | | | $FI_{5\ minutes}$ |
|---|---|---|---|---|---|
| | | C | K | $R^2$ | |
| KA | 55.243 ± 16.449 | 60.08 | -1.59 | 0.9789 | 53.09 |
| KB | 69.182 ± 21.372 | 79.86 | -2.24 | 0.9823 | 66.83 |
| KC | 78.077 ± 18.250 | 83.69 | -2.10 | 0.9752 | 70.79 |
| KD | 83.391 ± 10.014 | 84.20 | -1.96 | 0.9901 | 74.99 |

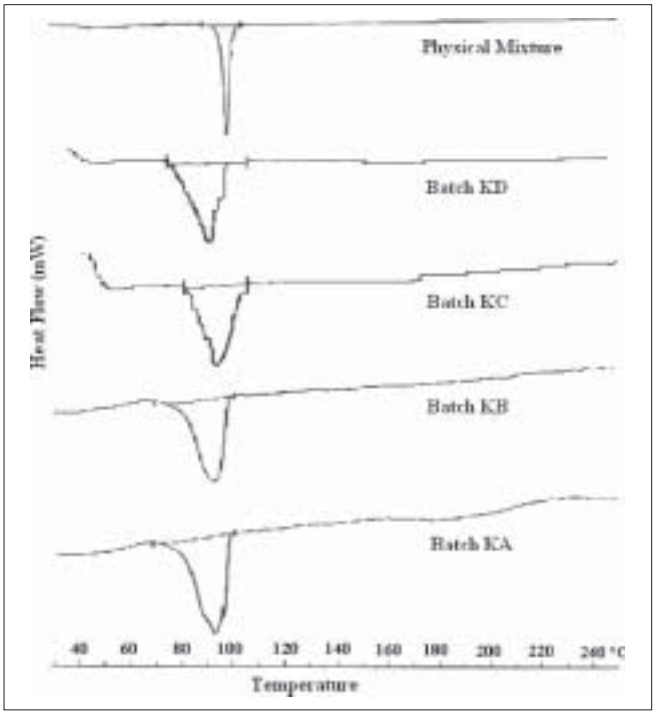


**Figure 2:** DSC thermograms of ketoprofen and ketoprofen-talc agglomerates

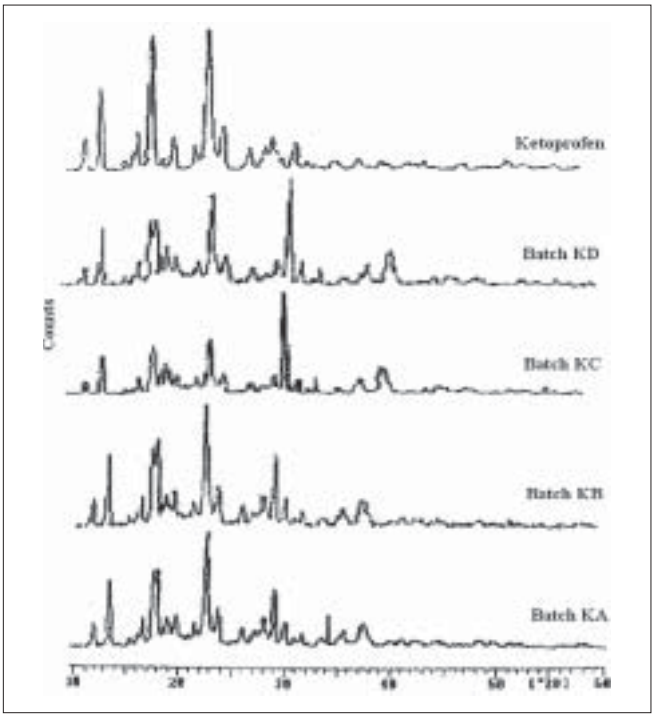


**Figure 3:** X-ray powder diffraction patterns of ketoprofen and ketoprofen-talc agglomerates

**Table 4: Thermal properties of ketoprofen agglomerates**

| Parameter | Pure drug | KA | KB | KC | KD |
|---|---|---|---|---|---|
| Endotherm (°C) | 96.20 | 91.28 | 91.61 | 91.50 | 88.80 |
| Enthalpy (J/g) | 116.00 | 65.45 | 66.07 | 62.3 | 57.00 |
| Crystallinity (%) | 100.00 | 56.42 | 56.96 | 53.77 | 49.14 |

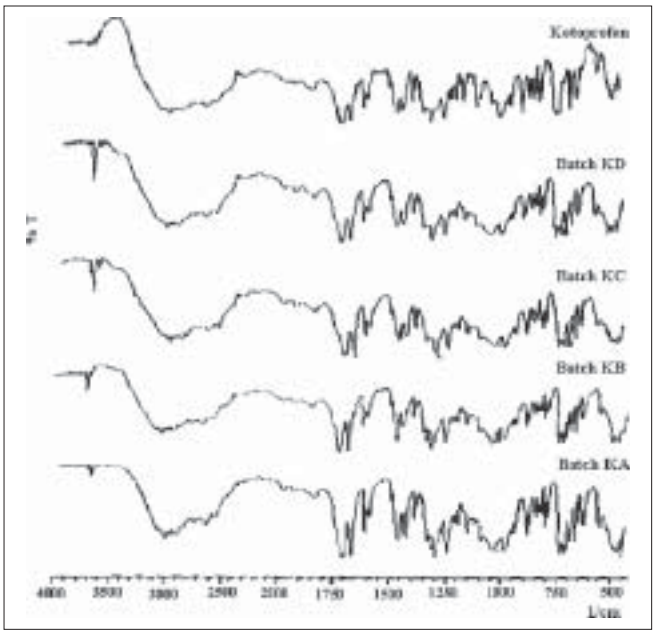


**Figure 4:** IR spectrums of ketoprofen and ketoprofen-talc agglomerates

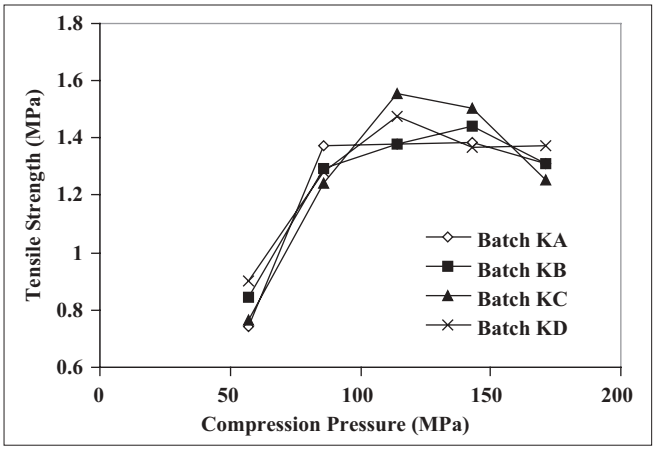


**Figure 5:** Compression behavior: comparative evaluation of tensile strength-pressure profiles of ketoprofen compacts

**Table 5: Estimation of Heckel parameters for various batches**

| Batch code | Heckel plot parameters | | | | | |
|---|---|---|---|---|---|---|
| | K | A | $D_A$ | $D_B$ | $D_0$ | $P_y$ (MPa) |
| KA | 0.0114 | 1.1565 | 0.6854 | 0.4854 | 0.200 | 87.7193 |
| KB | 0.0181 | 0.6961 | 0.5015 | 0.3115 | 0.190 | 55.2486 |
| KC | 0.0119 | 1.2764 | 0.7210 | 0.5210 | 0.200 | 84.0336 |
| KD | 0.0108 | 2.158 | 0.8844 | 0.6894 | 0.195 | 92.5926 |

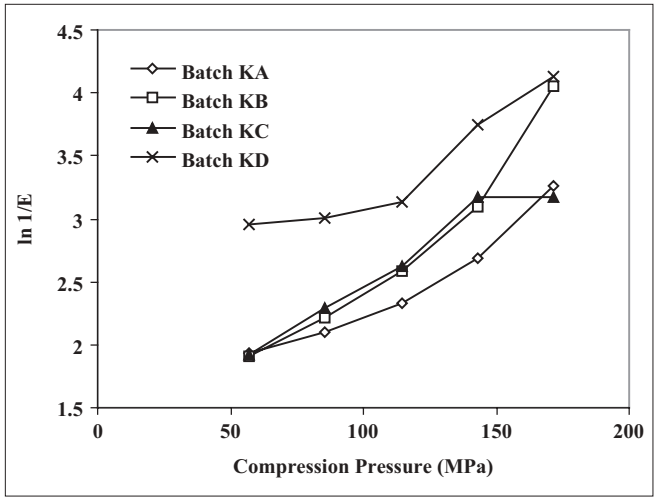


**Figure 6:** Compression behavior (Heckel plot): comparative evaluation of compression pressure and ln [1/E] profiles of ketoprofen compacts

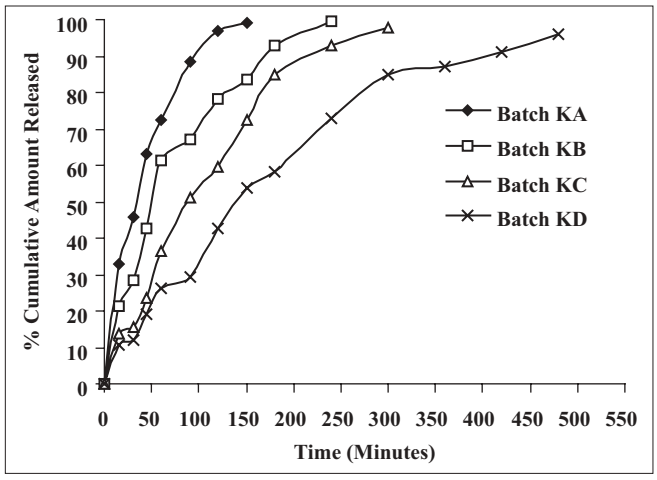


**Figure 7:** *In vitro* dissolution profile of compacted formulation in pH-6.8 phosphate buffer

Drug release profiles indicated initial lower drug release from the compacts of batches KC and KD. Values of $t_{90\%}$ (time in minutes required for 90% drug release) for compacts of batches KA, KB, KC, and KD were 120, 180, 240, and 420 min respectively [Figure 7]. After initial slow release, compacts of batch KC showed faster drug release in comparison to compacts of batch KD.

## DISCUSSION

Values of angle of repose and percentage compressibility suggest excellent flowability of agglomerates. The reason for excellent flowability may be the perfect spherical shape of agglomerates. As the amount of talc was increased, particle size also increased due to squeezing out of more bridging

liquid to the surface favoring the growth of agglomerates. The smaller values of parameter 'a' in Kawakita's equation for the agglomerates indicated their higher packabilities than the original drug. The larger values of parameters 'k' in Kuno's equation for the agglomerates indicated that the rate of their packing process was much higher than that of the original crystals. These findings proved that the flowability and packability of agglomerates were preferably improved for direct tableting. The excellent packability of the agglomerates was attributed to the increase in particle size.

Presence of holes on the surface of agglomerates may be due to the presence of talc, which created more void spaces over their surface. Presence of talc caused uniform distribution of polymer throughout the agglomerates and increased the size of agglomerates.

Requirement of maximum deformation force for batch KD during crushing strength study may be due to higher amount of talc. The agglomerates containing talc did not break but deformed during the test. This explains the significance of the role of talc-polymer interaction in deciding strength of the agglomerates, and it may be due to larger particle size, interparticulate bond strength, and physical properties of particles. Agglomerates of batch KD showed higher surface strength as compared with those of batches KA, KB, and KC, which may be attributed to higher surface deposition of polymer content.

IR spectra of agglomerates of different batches showed all the peaks of drugs, which proves there was no change in the drug. Sharp melting point in DSC graphs indicates that no events such as hydration, salvation, or polymorphic transition had occurred during crystallization of the particles. Decreased peak intensity in PXRD results may be due to dilution and adsorption of the polymer to drug crystals and may be due to coating by the polymer. Though enthalpy of fusion and intensity of peaks were reduced, no change in d-spacing values suggested absence of polymorphic transition. Reductions in enthalpy of fusion and percentage crystallinity may be attributed to the presence of amorphous regions in the crystals or to weakening and disruption of the crystals or crystal lattice and order.

Values of $D_A$ show that the talc provides uniform distribution of polymer to the whole of agglomerates and facilitates the initial packing of the agglomerates formulation in the die. Values of $D_0$ show no significant difference among all four batches. This implies that the initial packing of the formulations as a result of die filling was almost similar to the increment in the talc content. Low value of $P_y$ for batch KB shows that the onset of plastic deformation in batch KB occurred at much lower pressure. The agglomerates containing talc did not break but deformed under applied force. The rank order of average yield pressure ($P_y$) calculated from the slope of Heckel plot was KD > KA > KC > KB.

Drug release from the compacts of batches KC and KD was lower, which might be due to higher content of talc. The significant drug release retardation in case of batch KD compacts might be due to lower rate of dissolution media penetration and reduced rate of disentanglement of polymer in the presence of embedded talc.

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