

# Preparation, Physicochemical Characterization and *In-Vitro* Dissolution Studies of Ketoprofen Solid Dispersion with PEG 6000 and HPMC 6 cps

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## Abstract

Ketoprofen [2-(3-benzoylphenyl)-propionic acid], a non-steroidal anti-inflammatory drug exhibits poor dissolution pattern. Solid dispersion (SD) techniques were used because it is particularly promising to improve the oral absorption and bioavailability of BCS Class II drugs. This investigation entails solid dispersion of ketoprofen which was formulated and characterized for better release profile and immediate action of the drug. Melting method was applied to prepare solid dispersion by using two immediate release (IR) polymer PEG 6000 and HPMC 6 cps at different weight ratios. In the formulation, a fixed amount of lactose was used as adsorbent. The solid dispersions were investigated for drug entrapment efficiency and dissolution behavior. *In vitro* dissolution study was performed in phosphate buffer (pH 7.4) medium for one hour. Percent cumulative drug release from solid dispersion was found to be minimum 92.19% and maximum 98.95% within one hour, which showed a better dissolution compared to the active drugs. Evaluation of the properties of the solid dispersion was also performed by using Scanning Electron Microscopy (SEM) study and Differential Thermal Analysis (DTA). SEM results indicated that ketoprofen crystallinity in SDs was significantly reduced, and that the majority of ketoprofen was in amorphous form. No interaction was found between drug and polymers from DTA and Fourier-transform infrared (FTIR) spectroscopy analysis. So, solid dispersion technique may be an effective technique to enhance dissolution rate of ketoprofen.

**Key words:** Solid dispersion, ketoprofen, melting method, SEM, DTA, FTIR.

## Introduction

The term solid dispersion consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed in molecular level either in amorphous clusters or in crystalline form (Dhirendra *et al.*, 2009). Drugs those undergo dissolution, rate limited gastrointestinal absorption generally show improved dissolution and bioavailability as a result of reduction in particle size, so to say higher surface exposure. However, micronizing of drugs often leads to

aggregation and agglomeration of particles, which results in poor wettability (Singh *et al.*, 2011). Drug absorption from the GI tract can be limited by a variety of factors in which the most significant contributor having poor aqueous solubility and/or poor membrane permeability of the drug molecule. This article focuses on the former, in particular, the use of solid dispersion technique to improving the dissolution characteristics of poorly water-soluble drugs (Arunachalam *et al.*, 2010).

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Ketoprofen, a Biopharmaceutical Classification System (BCS) class II drug, is a widely used NSAID having analgesic and antipyretic effect. It is freely soluble in ethanol, chloroform, acetone, ether, sparingly soluble in benzene and strong alkali, but practically insoluble in water. However, it has poor water solubility (0.13 mg/ml at 25°C) which may predispose to formulation problems and limit its therapeutic applications and bioavailability (Pankajkumar *et al.*, 2013). Based on these issues, an attempt was made to prepare solid dispersion formulation by using melting method with the help of PEG 6000 and HPMC 6 cps in different weight ratios. By preparing this formulation, it is possible to release the drug immediately within very short time and this is beneficial in the view point of pharmaceutical industry.

## Materials And Methods

### Materials

Active ketoprofen was received as gift sample from Incepta Pharmaceuticals Ltd, Bangladesh. Here all analytical grade reagents like PEG 6000, HPMC 6

cps, lactose, potassium dihydrogen phosphate and sodium hydroxide were used for the study.

### Methods

*Preparation of solid dispersion of ketoprofen by melting method:* Desired amount of ketoprofen and polymer (PEG 6000 and HPMC 6 cps) were taken in glass beaker and melted in hot water bath at 70°C to obtain a viscous mass. The viscous mass was stirred robustly by glass rod for getting uniformity of the mixture. Then it was kept at room temperature for five days until a solid mass was formed. The solidified mixture was ground by using a mortar and pestle and passed through the sieve (mesh size 40) to get solid dispersions. Finally, the resulting samples (SDs) were weighed and transferred in fresh glass vials with proper labeling and stored in a desiccator until further use (Islam *et al.*, 2019).

*In vitro dissolution study of solid dispersion:* *In vitro* dissolution studies were performed as per established protocol (rpm 75, in phosphate buffer at pH 7.4. The release of drug was determined by UV-spectrophotometric analysis at 258 nm (Mogal S. A *et al.*, 2012).

**Table 1. List of solid dispersion formulation of ketoprofen prepared by melting method.**

Serial No.	Formulation code	Carriers	Drug polymer ratio	Amounts
01	E1	PEG 6000	1:1	100 mg:100 mg
02	E2	PEG 6000	1:3	100 mg:300 mg
03	E3	PEG 6000	1:5	100 mg:500 mg
04	K1	PEG 6000: HPMC 6 cps: Lactose	1: 0.5: 1.5: 5	200 mg: 100 mg: 300 mg: 1 gm
05	K2	PEG 6000: HPMC 6 cps: Lactose	1: 0.5: 1: 5	200 mg: 100 mg: 200 mg: 1gm
06	K3	PEG 6000: HPMC 6 cps: Lactose	1: 0.5: 0.5: 5	200 mg: 100 mg: 100mg: 1 gm
07	K4	PEG 6000: HPMC 6 cps: Lactose	1: 0.5: 0.00: 5	200 mg: 100 mg: 000 mg: 1 gm

*Preparation of phosphate buffer (pH 7.4):* 6.8 gm of potassium di-hydrogen phosphate (KH<sub>2</sub>PO<sub>4</sub>) dissolved in 1000 ml distilled water. To maintain the pH 7.4 sodium hydroxide solution was used.

*Preparation of standard curve for ketoprofen:* 10 mg of ketoprofen was taken in a 100 ml volumetric flask and makes up the volume with phosphate buffer (pH 7.4) and named it stock solution, its concentration was 0.1 mg/ml. From the above

solution 0.1, 0.2, 0.4, 0.6, 0.8 and 1 ml was taken in 10 ml volumetric flask and makes up the volume. Its concentration was 1, 2, 4, 6, 8, 10 µg/ml. The average values of absorbance values were plotted against respective drug concentration and thus standard curve of ketoprofen was produced (Figures 1) (Akhter et al., 2016).

*Drug entrapment efficiency (DEE) studies:* 50 mg of formulation was taken in 100 ml phosphate

buffer solution. After filtration, 10 ml filtrate solution was taken in a volumetric flask and the volume was adjusted to 100 ml by phosphate buffer and the absorbance was taken at 258 nm. From the absorbance value the amount of drug entrapped was determined using standard curve (Farheen et al., 2017). The drug entrapment efficiency was calculated by using the following equation -

$$\text{Entrapment efficiency (\%)} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100\%$$

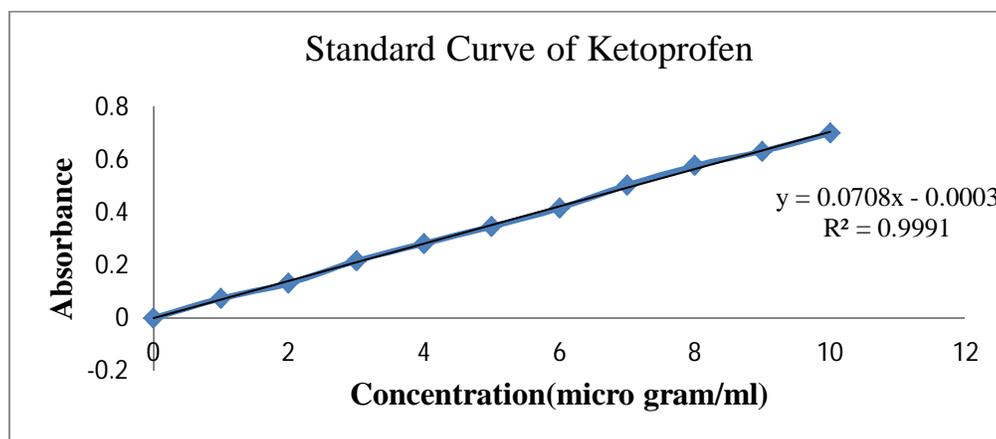


Figure 1. Standard curve of ketoprofen.

*Kinetic data analysis:* The drug release kinetic studies carried out for solid dispersion formulations were evaluated using the linear regression method:

- (1) Zero order kinetic model – cumulative % of drug released versus time ( $T$ );
- (2) First order kinetic model – log cumulative percent drug remaining versus time ( $T$ );
- (3) Higuchi's model – cumulative percent drug released versus square root of time ( $T$ );
- (4) Korsmeyer-Peppas model – log cumulative percent drug released versus log time ( $T$ ) and
- (5) Hixson-Crowell model – Cube root of initial amount - Cube root of drug remaining versus time ( $T$ ) (Ryakala et al., 2015).

#### Characterization of SDs

*Fourier transform infrared spectrophotometric (FTIR) analysis:* The FTIR spectrum of the active drug and solid dispersion formulation were obtained in the range of 4000-6000  $\text{cm}^{-1}$  using FTIR spectrophotometer (Zakaria et al., 2014).

*Differential thermal analysis (DTA):* Thermal analysis was performed using DTA instrument under nitrogen flow of 20 ml/min. Approximately 1.0 mg of ketoprofen, and solid dispersion were placed in a sealed aluminum pan and heated at a rate of 10°C/min from 30°C to 220°C (Sinha et al., 2010).

*Surface morphology study by scanning electron microscope (SEM):* Scanning electron microscopy was used to study the morphology and surface topology of the solid power particles (Akhter et al., 2016).

## Result And Discussion

*Physical appearance:* All solid dispersions were white fine powders. No discolouration was observed during preparation of SD.

*Drug entrapment efficiency (DEE):* From table 2 it is found that Drug Entrapment Efficiency (DEE) was suitable and ranged from 87.82% to 98.52%. DEE% was increased with increased polymeric concentrations. E3 and K1 exhibited the highest % of DEE of 98.52% and 96.96%, respectively and E1 showed minimum DEE% of 87.82%. Considering the amount of polymers used in E1, E3 and K1 the current investigation suggests that drug entrapment efficiency (DEE) increases with increasing polymeric concentrations.

**Table 2. Drug entrapment efficiency of ketoprofen solid dispersion formulations.**

Formulation code	Drug entrapment efficiency (%)
E1	87.82
E2	95.8
E3	98.52
K1	96.90
K2	93.76

*In vitro dissolution studies of active Ketoprofen and solid dispersion formulations:* The *in vitro*

dissolution characteristics of different types of preparations were compared with active drug. The solid dispersions of ketoprofen prepared by melting method with PEG 6000 and HPMC 6 cps showed improved dissolution when compared with active drug. It is due to the use of hydrophilic polymer. PEGs have the ability to solubilize some compounds and improve wettability. The solid dispersion of drugs with PEG 6000 may be useful to increase stability, solubility, dissolution and bioavailability of poorly water-soluble drug. Lactose was utilized as an adsorbent for the preparation of solid dispersion. The role of HPMC 6 cps was as crystallization inhibitor and to prevent recrystallization of poorly water-soluble drug. The effect of PEG 6000 and HPMC 6 cps on percent release of ketoprofen are represented in table 3.

Ketoprofen was released only 31.88% after 5 min and 45.61% within 60 min from active drug. On the other hand, solid dispersion formulation batches E1-E3 and K1-K4 have shown an immediate release profile between 92.19% and 98.95% within 60 min where E3 and K1 showed highest percent of drug release (98.95% and 98.50% respectively) after 60 min.

**Table 3. *In vitro* drug release data of ketoprofen and different ketoprofen solid formulation.**

Formulation no	Formulation code	Drug polymer And ratios	Percent release of drug (after 5 min)	Percent release of drug (after 30 min)	Percent release of drug (after 60 min)
1.	<b>Active ketoprofen</b>	-----	<b>31.88%</b>	<b>40.84%</b>	<b>45.617%</b>
2.	E1	Ketoprofen: PEG 6000 (1:1)	43.84%	71.70%	97.93%
3.	E2	Ketoprofen: PEG 6000 (1:3)	56.06%	77.87%	98.71%
4.	<b>E3</b>	<b>Ketoprofen: PEG 6000 (1:5)</b>	<b>53.20%</b>	<b>85.99%</b>	<b>98.95%</b>
5.	<b>K1</b>	<b>Ketoprofen: PEG 6000: HPMC 6 CPS: Lactose (1: 0.5: 1.5: 5)</b>	<b>48.34%</b>	<b>81.21%</b>	<b>96.48%</b>
6.	K2	Ketoprofen: PEG 6000: HPMC 6 CPS: Lactose (1: 0.5: 1: 5)	51.14%	75.37%	96.48%
7.	K3	Ketoprofen: PEG 6000: HPMC 6 CPS: Lactose (1: 0.5: 0.5: 5)	48.41%	82.90%	94.47
8.	K4	Ketoprofen: PEG 6000: HPMC 6 CPS: Lactose (1: 0.5: 0.00: 5)	42.02%	76.60%	91.19%

**Release kinetics analysis:** Different release kinetics plot (zero order plot, first order plot, Higuchi plot, Korsmeyer-peppas plot, Hixson-Crowell plot) are shown in figure 2 to 13. The release rate constant and correlation co-efficient ( $R^2$ ) value

and the best fit model and mechanism of drug release from ketoprofen solid dispersion batches E1, E2, E3, K1, K2, K3 and K4 are represented in table 4 and table 5 respectively.

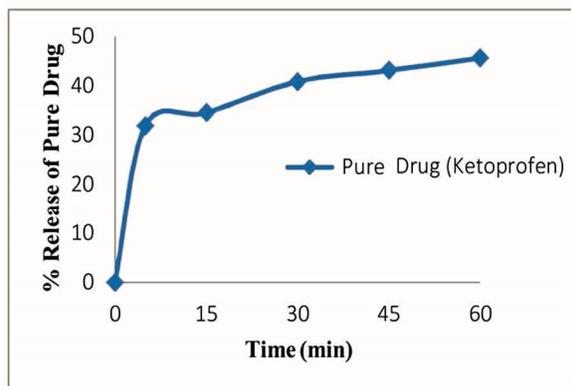


Figure 2. Zero order plot of ketoprofen.

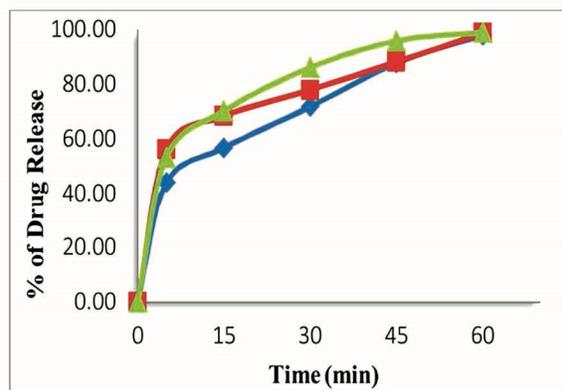


Figure 3. Zero order plot of ketoprofen solid dispersion formulations containing PEG 6000 (E1-E3).

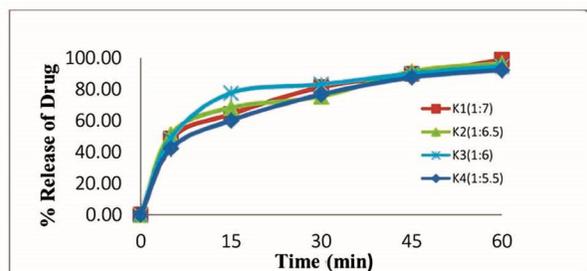


Figure 4. Zero order plot of ketoprofen solid dispersion formulations containing PEG 6000 and HPMC 6 cps (K1-K4).

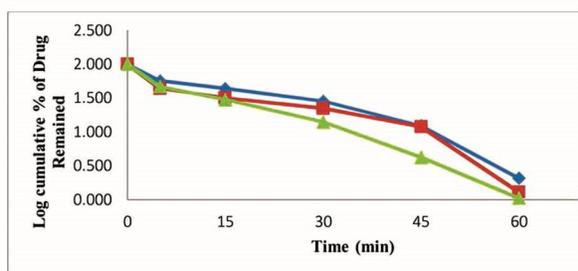


Figure 5. First order plot of ketoprofen solid dispersion formulations containing PEG 6000 (E1-E3).

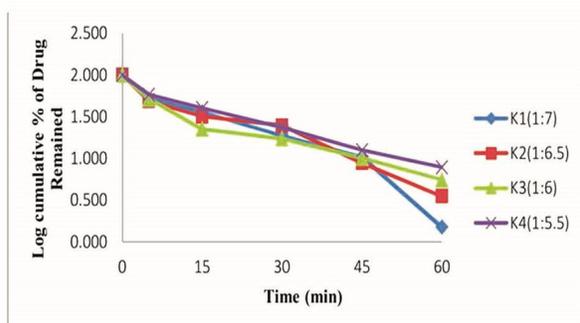


Figure 6. First order plot of ketoprofen solid dispersion formulations containing PEG 6000 and HPMC 6 cps (K1-K4).

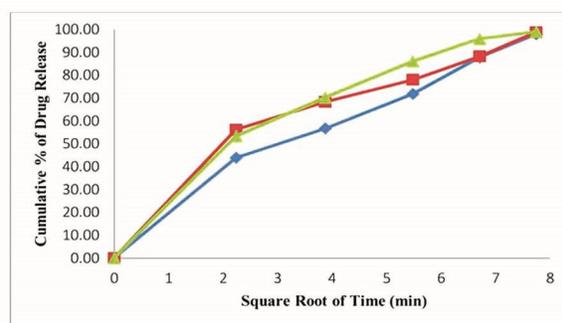


Figure 7. Higuchi plot of ketoprofen solid dispersion formulations containing PEG 6000 (E1-E3).

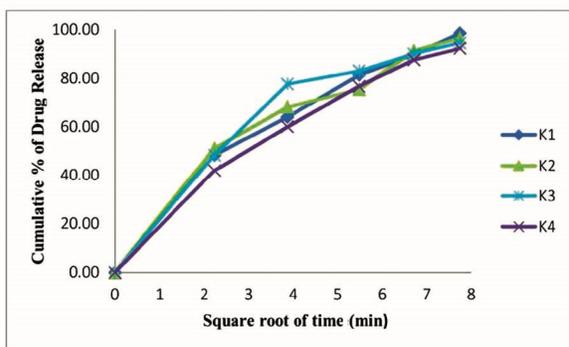


Figure 8. Higuchi plot of ketoprofen solid dispersion formulations containing PEG 6000 and HPMC 6 cps (K1-K4).

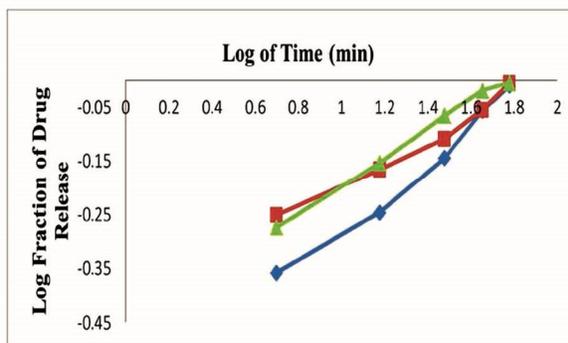


Figure 9. Korsmeyer-Peppas plot of ketoprofen solid dispersion formulations containing PEG 6000 (E1-E3).

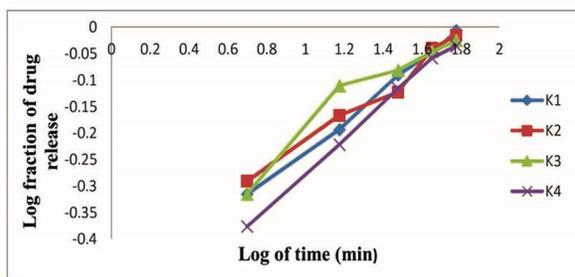


Figure 10. Korsmeyer-Peppas plot of ketoprofen solid dispersion formulations containing PEG 6000 and HPMC 6 cps (K1-K4).

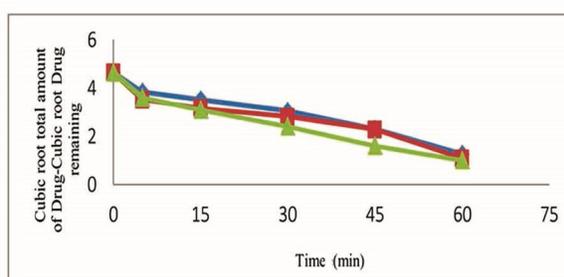


Figure 11. Hixson-Crowell plot of ketoprofen solid dispersion formulations containing PEG 6000 (E1-E3).

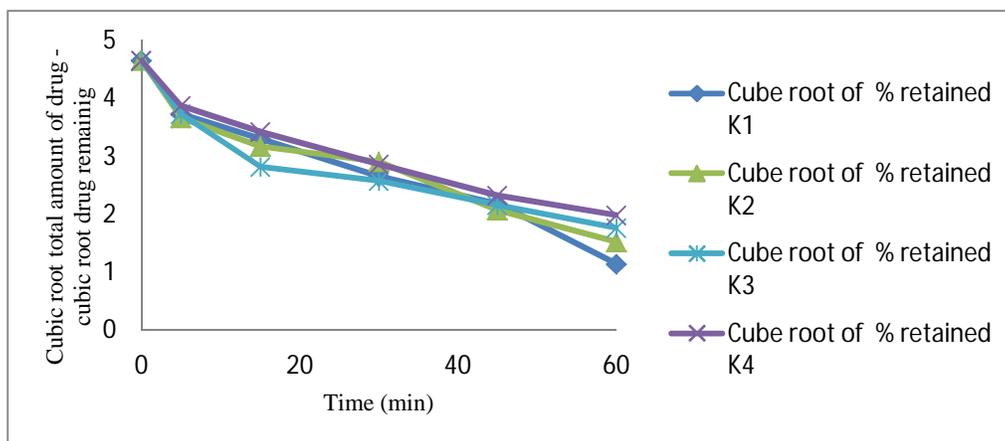


Figure 12. Hixson-Crowell plot of ketoprofen solid dispersion formulations containing PEG 6000 and HPMC 6 cps (K1-K4).

**Table 4. Y-equation (Y=aX+b) and correlation co-efficient (R<sup>2</sup>) of SDs formulation of ketoprofen.**

Formulation code	Zero order		First order		Higuchi model		Hixon-crowell model		Korsmeyer-peppas
	K <sub>0</sub>	R <sup>2</sup>	K <sub>1</sub>	R <sup>2</sup>	K <sub>h</sub>	R <sup>2</sup>	K <sub>hx</sub>	R <sup>2</sup>	n Value
E1	1.370	0.837	-0.024	0.926	1.21	0.67	1.07	0.56	0.324
E2	1.255	0.709	-0.026	0.889	1.17	0.55	1.77	0.70	0.219
E3	1.337	0.718	-0.030	0.983	1.35	0.29	1.38	0.39	0.258
K1	1.342	0.770	-0.026	0.938	1.28	0.55	1.77	0.49	0.288
K2	1.282	0.735	-0.021	0.964	1.19	0.55	1.88	0.61	0.252
K3	1.244	0.663	-0.018	0.932	1.49	0.22	1.35	0.72	0.259
K4	1.306	0.789	-0.017	0.982	1.27	0.65	1.80	0.89	0.324

**Table 5. The best fit model and mechanism of drug release.**

Formulation No	Best fit model	n Value	Release mechanism
E1	First Order	0.324	Fickian transport
E2	First Order	0.219	Fickian transport
E3	First Order	0.258	Fickian transport
K1	First Order	0.288	Fickian transport
K2	First Order	0.252	Fickian transport
K3	First Order	0.259	Fickian transport
K4	First Order	0.324	Fickian transport

*Fourier transform infrared spectroscopic (FTIR) analysis:* Fourier transform infrared spectroscopic studies were conducted for the active drug (Ketoprofen) and the solid dispersion formulation batch K1 (Ketoprofen, PEG6000, HPMC 6 cps and lactose). The FTIR spectra are shown in Figure 14 and 15.

Figure 14 and 15 represent the FTIR spectra of active ketoprofen and batch K1 (Ketoprofen, PEG6000, HPMC 6cps and lactose). Now if this

spectrum is compared with the spectra of ketoprofen then we found that aromatic C-H stretch, carboxylic acid O-H stretch are present at 2978.09. C-H stretch plus OH deformation, (C=O stretch) and CH-CH<sub>3</sub> deformation, are present at 2883.58, 1653.00 and 1440.83 respectively. Another carboxylic O-H out of plane deformation and C-H out of plane deformation for substituted aromatic were seen at 1695.43 and 842.89, respectively.

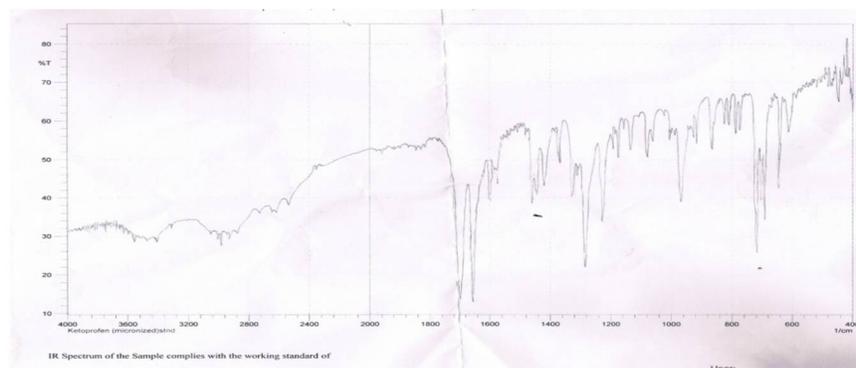


Figure 14. FTIR spectrum of active ketoprofen.

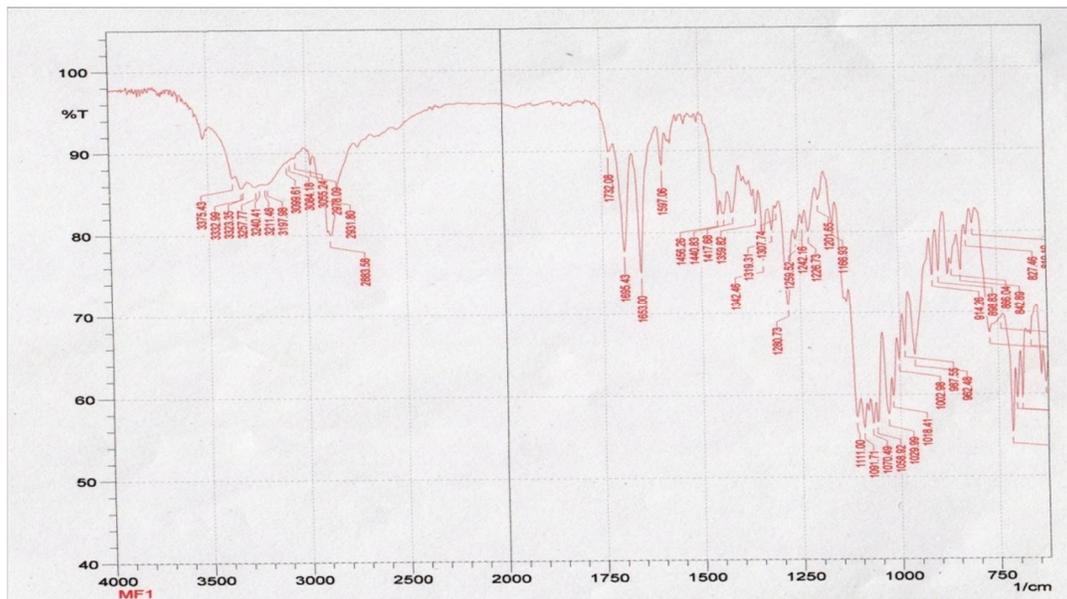


Figure 15. FTIR Spectrum of K1 (Ketoprofen, PEG 6000, HPMC 6 cps and lactose).

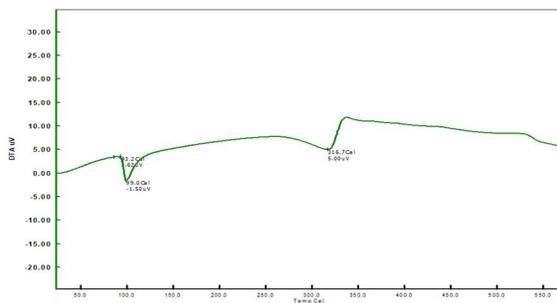


Figure 16. DTA of pure drug (ketoprofen).

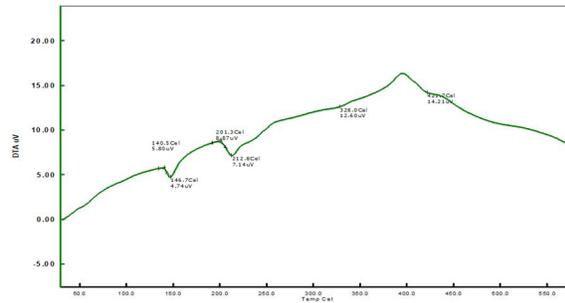


Figure 17. DTA of batch K1 (ketoprofen, PEG6000, HPMC 6cps and lactose).

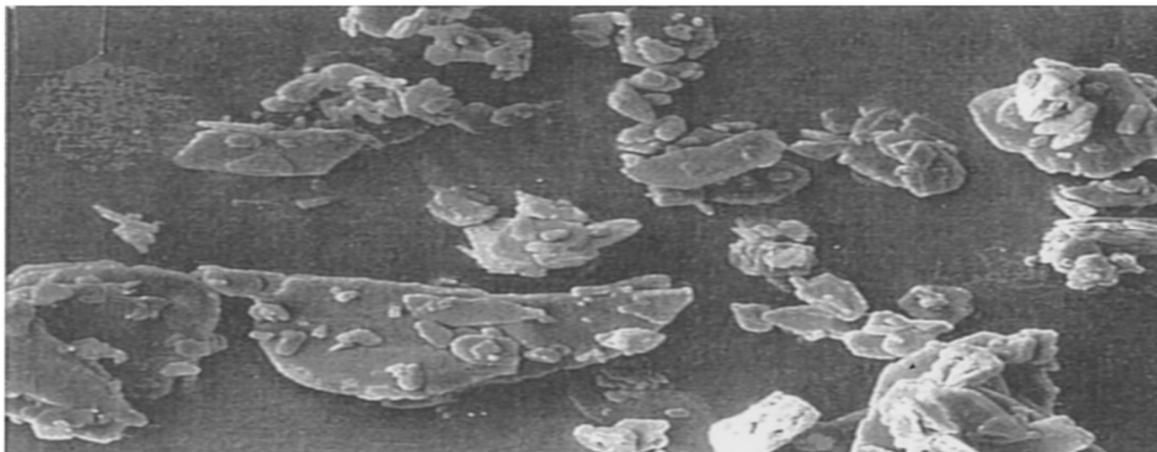


Figure 18. Scanning electronic microscopic image of ketoprofen.

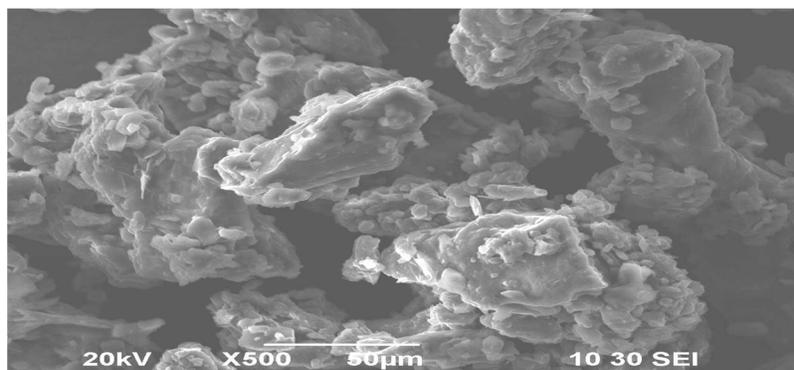


Figure 19. Scanning electronic microscopic image of solid dispersion containing ketoprofen with PEG 6000, HPMC 6 cps and lactose.

**Differential thermal analysis (DTA):** The DTA thermograms of the ketoprofen and SDs batch K1 are shown in figure 16 and 17, respectively. Figure 16 exhibited a single endothermic response corresponding to the melting of drug. Onset of melting was observed at 99°C. Thermograms of solid dispersion (Figure 17) showed the absence of a ketoprofen peak, suggesting that ketoprofen is completely soluble in the liquid phase of polymer or absence of crystalline nature of ketoprofen. However, the melting peak of batch K1 in SDs was observed at 146.7 °C.

**Scanning electron microscopic (SEM) analysis:** Active ketoprofen and solid dispersion of ketoprofen (K1) containing PEG 6000 and HPMC 6 cps were examined by SEM to see the morphological change that occurred due to formulation variation. SEM studies showed that the surface morphological properties of the solid dispersion were in an amorphous state. The surface morphology and representative micrographs are shown in Figures 18 and 19.

### Conclusion

Ketoprofen solid dispersions were prepared by the melting method. The method was easy, economical, and modest. It showed faster dissolution characteristics as compared to active ketoprofen. The solid dispersion of ketoprofen in PEG 6000 (1:5) allowed to achieve 85% dissolved drug after only 30 minutes. The most effective system was ketoprofen: PEG 6000: HPMC 6 cps: lactose which allowed to achieve 98% dissolved drug after 60

minutes. It can be concluded that with a carefully designed experimental technique, the solubility of poorly water-soluble drugs can be improved by using the solid dispersion technique.

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### Conflict of interest

The authors declare no conflict of interest.

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