

Screening of Ketoprofen-Poloxamer and Ketoprofen-Eudragit solid dispersions for improved physicochemical characteristics and dissolution profile

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The aim of the present study was to enhance the dissolution rate of an NSAID drug Ketoprofen by formulating it into solid dispersions with water soluble carrier Poloxamer 188 and Eudragit S 100. The solid dispersions of Ketoprofen with Poloxamer 188 were prepared at 1:1, 1:1.5 and 1:2 (Ketoprofen: Poloxamer 188) ratio by Solvent evaporation methods. The same concentration ratio was used for the preparation of solid dispersion with Eudragit S 100 by melting/fusion technique. Further, solid dispersions were investigated by solubility, ATR-FTIR, XRD, DSC, surface morphology, in-vitro dissolution and accelerated stability study. Results demonstrated that both Poloxamer 188 and Eudragit S 100 improve solubility of drugs by 8–10 folds. The result of ATR-FTIR study showed the slight shifting/broadening of principle peaks. *In vitro* dissolution studies showed that in the solid dispersion system containing Ketoprofen: Poloxamer 188 batch P2 (1:1.5) gives faster dissolution rate of Ketoprofen than the physical mixtures. The solid dispersion with Eudragit S 100, batch E1 (1:1) gives faster dissolution rate of Ketoprofen than the physical mixtures. In phase solubility study with Poloxamer 188 showed concentration dependent solubilization of drug but Eudragit S 100 produced opposite result. The effect of pH on solubility of Eudragit S 100 was carried out which showed solubility at pH 7.4. The dissolution profile of solid dispersion with Eudragit S 100 at pH 7.4 gives excellent result. The Accelerated stability of solid dispersions & its physical mixtures were studied at $40\pm 2\text{ }^{\circ}\text{C}/75\pm 5\% \text{ RH}$ for a period of 1 month. In these studies, Solid Dispersion batches produced an unstable formulation. The Ketoprofen solid dispersions with Poloxamer 188 and Eudragit S 100 could be introduced as a suitable form with improved solubility.

Keywords: Ketoprofen. Solid Dispersion. Poloxamer 188. Eudragit S 100. Accelerated stability.

INTRODUCTION

The aqueous solubility of a drug is a significant limitation to its oral absorption. Poorly water-soluble drugs are associated with slow drug absorption leading ultimately to inadequate and variable bioavailability (Amidon *et al.*, 1995; Leuner, Dressman, 2000). The Biopharmaceutical Classification System (BCS) is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. BCS class II and IV drugs which have low

solubility provide a number of challenges for formulation and scientists are constantly working on the oral delivery of these drugs (Lobenberg, Amidon, 2000). Oral intake is the most convenient and commonly used route of drug delivery due to its convenience of administration, high patient compliance, cost-effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. (Blagden, De Matas, Gavan, 2007)

Solid Dispersion (SD) technique has been extensively used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs. The dispersion method allows preparation of physically modified forms of drug that is much more rapidly soluble in water

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than pure compound. Solid Dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. (Abu, 1999; Chiou, Riegelman, 1971; Dehghan, Jafar, 2006; Jachowicz, Nurnberg, Pieszczek, 2000; Patil *et al.*, 2010)

Ketoprofen is an NSAIDs BCS Class II drug and used for the treatment of rheumatoid arthritis with well-known antipyretic and analgesic properties as well as treatment of mild to moderate pain (Kim, Choi, 2002). Also, it is an inhibitor of prostaglandin synthetase (Yalcin, Gulgun, Umit, 1999). However, it is practically insoluble in water and causes systemic disorder in the gastrointestinal tract (Jachowicz, Nurnberg, Pieszczek, 2000). So that the improvement of its solubility and oral bio-availability remains one of the most challenging aspects of drug development mainly for oral drug delivery system. The *in vivo* and *in vitro* characteristics and the problems in achieving conventional and reproducible *in vivo/in vitro* relationship are often suitably difficult to develop formulation due to solubility issue. One way to enhance the solubility of poorly soluble drugs is through the formation of solid dispersion.

With these, we have carried out a study to enhance the solubility of Ketoprofen through the preparation of its solid dispersions with Poloxamer 188 and Eudragit S 100. Further, SDs were evaluated by Phase solubility, Infrared spectroscopy (ATR-FTIR), X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC), scanning electron microscopy (SEM), *in vitro* dissolution studies and accelerated stability study.

MATERIAL AND METHODS

Material

Ketoprofen was received as a gift sample from BEC Chemical Ltd (Roha, Raigad, Maharashtra). Poloxamer 188 and Eudragit S 100 were from Fine Laboratories (Mumbai) and all other materials and reagents used were of analytical grade.

Phase solubility study

Phase-solubility studies were carried out by adding an excess of drug (20 mg) in 10 mL of aqueous solution of different (1:0, 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10) Poloxamer 188 and Eudragit S 100 polymer concentrations. The suspensions were continuously stirred on an electromagnetic stirrer at 370 °C and 300 rpm for 48 h.

The suspensions were filtered through a Whatman filter paper no. 0.45 micron. The filtrates were suitably diluted and analyzed by UV Spectrophotometry at 256 nm.

The Gibbs free energy of transfer (ΔG_{0tr}) of Ketoprofen from pure water to the aqueous solution of the carrier was calculated as follows:

$$\Delta G_{0tr} = -2.303 RT \log S_0/S_S$$

Where, S_0/S_S is the ratio of molar solubility of Ketoprofen in aqueous solutions of the carrier to that of the same medium without a carrier.

1:1 complex apparent stability constant (K_a) was determined as follows:

$$K_a = \frac{\text{Slope}}{\text{Intercept} (1 - \text{Slope})}$$

Where slope and intercept was obtained from the graph of % w/v of Ketoprofen Vs aqueous concentration of carrier (poloxamer188/Eudragit S 100 in % w/v).

In reported literature, it was observed that Eudragit, S 100 is soluble and releases active ingrents at pH 6.5 and above (Mehta *et al.*, 2013; Sonje, Chandra, 2013). To further check this phenomenon we have carried out phase solubility study at different pH i.e. 2.4, 3.4, 5.4 and 7.4 in phosphate buffer.

Preparation of solid dispersion

Solvent evaporation method

The solid dispersion of Ketoprofen and Poloxamer 188 was prepared with different concentrations of drug & carrier by dissolving in common solvent i.e. Ethanol. Then the solvent was evaporated at 40 °C, obtained mass was preserved in well-closed glass containers in desiccators under vacuum (by using anhydrous CaCl₂) at 18-20 °C for 2 days. Prepared formulation was crushed & passed through sieve mesh no. 20.

Melting/Fusion method

The solid dispersion of Ketoprofen and Eudragit S 100 was prepared by heating drug and a carrier directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under vigorous stirring. The prepared formulation was milled & passed through sieve no. 20.

Preparation of a physical mixture

A physical mixture of Ketoprofen and Poloxamer 188 was prepared separately by thoroughly mixing the two components in a mortar for 15 min until a homogeneous mixture was obtained. Dry mass was pulverized and sieved through sieve mesh no. 20.

The Table I summarizes the concentrations of drug and carrier in different batches of physical mixture and solid dispersions.

Attenuated total reflectance fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR spectra of solid dispersion with their physical mixtures were obtained using ATR-FTIR spectrophotometer (carry 630 FTIR, Agilent technologies). The scanning range was 400-4000 cm^{-1} .

In vitro dissolution study

Preparation of dissolution media

0.1N HCl: 8.33 ml of conc. HCl was dissolved in 1000 ml of distilled water.

The dissolution test of prepared solid dispersions, physical mixtures and plain Ketoprofen was performed using the United States Pharmacopoeia (USP) dissolution apparatus II at 50 rpm. Formulations were placed in the dissolution vessel containing 1000 mL of 0.1 N HCl in purified water maintained at 37 ± 0.5 °C. Samples from the dissolution medium were withdrawn and concentrations were determined by the spectrophotometric method at 256 nm. The dissolution study was carried out in triplicate and the plot of mean values versus time was obtained. For Eudragit S 100 the dissolution study was repeated at pH 7.4.

Differential Scanning Calorimetry (DSC)

DSC was carried out to detect crystalline nature. About 3-5 mg of sample in 100 μL aluminum pan was measured with a DSC 1 (Mettler-Toledo, DSC 1 star system, Mumbai, India). A scanning rate of 10 $^{\circ}\text{C min}^{-1}$ and a nitrogen gas flow of 40 ml/min were applied. The measurement was conducted in a temperature range of 400 to 150 $^{\circ}\text{C}$.

X-Ray Diffraction (XRD)

To determine the physical state of pure Ketoprofen, solid dispersion and physical mixture, X-ray diffraction study was carried out. A transmission diffractometer (rigaku miniflex, Mumbai, India) was used to investigate crystalline nature in prepared solid dispersion, physical mixture and Ketoprofen. Diffraction patterns were obtained at a voltage of 45 kV and at a current of 40 mA. Samples were scanned in a 2θ range from 50 to 700 with a scanning speed of 20/min and an intensity of 1000 cps.

Scanning Electron Microscopy (SEM)

The surface morphology of the solid dispersion, physical mixture and pure Ketoprofen was analyzed by a scanning electron microscope model JEOL, JSM-5400 (Japan) coupled with energy dispersive X-ray analysis (EDAX).

Accelerate stability study

Accelerated stability study was carried out by storing optimized batches of solid dispersions and physical mixtures at 400 ± 2 $^{\circ}\text{C}/75 \pm 5\%$ RH for 1 month in a stability chamber. All the preparations were studied

TABLE I - Drug & polymer conc. ratio for solid dispersions and physical mixtures

Batch no.	Solid Dispersion		Batch no.	Physical Mixture		Batch no.	Solid Dispersion		Batch no.	Physical Mixture	
	Keto	Polox 188		Keto	Polox 188		Keto	Eudr S 100		Keto	Eudr S 100
P ₁	1	1	P _{1p}	1	1	E ₁	1	1	E _{1p}	1	1
P ₂	1	1.5	P _{2p}	1	1.5	E ₂	1	1.5	E _{2p}	1	1.5
P ₃	1	2	P _{3p}	1	2	E ₃	1	2	E _{3p}	1	2

for their physical characterization, λ_{\max} , calibration curve, ATR-FTIR and in-vitro dissolution studies.

RESULT AND DISCUSSION

Phase solubility studies

The plots of drug solubility against the polymer concentration (Figure 1) indicate a linear relationship in the investigated polymer concentration range. Gibbs free energy of transfer (ΔG_{0tr}) and apparent stability constants (K_a) derived from figure 1 are shown in Table II which show that all values of ΔG_{0tr} were negative at all levels of carrier's i.e. Poloxamer 188 demonstrating spontaneity of drug solubilization process. The values show a declining trend with an increase in the carrier concentration too construing that the process is more favorable at higher carrier levels. The result shows that the solubility of Ketoprofen increased with increasing carrier concentration. The phase solubility plots of drug solubility against the polymer Eudragit S 100 concentration (Figure 2) indicate, there is no linear relationship in the investigated polymer concentration range. The pH versus solubility profile of Eudragit S 100 is given in figure 3, which indicates that increase in pH increases the solubility of Eudragit S 100. The highest solubility was observed at pH 7.4 which was 94%. Then the phase solubility was calculated at pH 7.4 for Eudragit S 100 and Gibbs free energy of transfer (ΔG_{0tr}) and apparent stability constants (K_a) derived from figure 4 are shown in Table II. Table II shows that the values of ΔG_{0tr} were negative at all levels of carriers, demonstrating that the drug solubilization process is more favorable at higher concentrations. It was observed that pH affects on phase solubility of drug with Eudragit S 100. At pH 7.4 all the values of ΔG_{0tr} were negative at all levels of Eudragit S 100.

TABLE II - Gibbs free energy values and apparent stability constants (K_a) of Ketoprofen - Poloxamer 188 and Eudragit S 100 interactions

Concentration (% w/v)	ΔG_{0tr} (kJ/mol)		
	Poloxamer 188	Eudragit S 100	Eudragit S 100 at pH 7.4
5	-7.38	42.83	-8.63

(continuing)

TABLE II - Gibbs free energy values and apparent stability constants (K_a) of Ketoprofen - Poloxamer 188 and Eudragit S 100 interactions

Concentration (% w/v)	ΔG_{0tr} (kJ/mol)		
	Poloxamer 188	Eudragit S 100	Eudragit S 100 at pH 7.4
10	-17.96	34.60	-20.03
20	-31.70	29.38	-27.91
30	-32.07	28.63	-36.71
40	-32.94	24.48	-36.80
50	-34.33	24.29	-37.12
Intercept	0.4838	0.2266	0.5129
Slope	0.0119	-0.0011	0.0178
K_a	0.0250	-0.0048	0.0273

Drug content

TABLE III - % Drug content of prepared solid dispersion

Sr. No.	Poloxamer 188 (Solvent Evaporation Method)			Eudragit S 100 (Melting/Fusion method)		
	Batch No.	Ratio	Drug content	Batch No.	Ratio	Drug content
1	P1	1:1	83.11%	E1	1:1	91.06%
2	P2	1:1.5	92.02%	E2	1:1.5	85.25%
3	P3	1:2	87.79%	E3	1:2	87.93%

The solid dispersion of Ketoprofen: Poloxamer 188 by the solvent evaporation method showed drug content of 83.11 to 92.02%. The % drug content of solid dispersions prepared by solvent evaporation technique is shown in Table II. The drug content of batch P1 (1:1) was 83.11 %, batch P2 (1:1.5) was 92.02% & batch P3 (1:2) was 87.79%. The batch P2 produced high % drug content than batch P1 and P3 respectively. The solid dispersion

by Melting methods using Eudragit S 100 compositions has a drug content of 85.25 to 91.06% (Table II). The drug content of batch E1 (1:1) was 91.06%, batch E2

(1:1.5) was 85.25% & batch E3 (1:2) was 87.93%. The batch E1 produced high % drug content than batch E2 and E3 respectively.

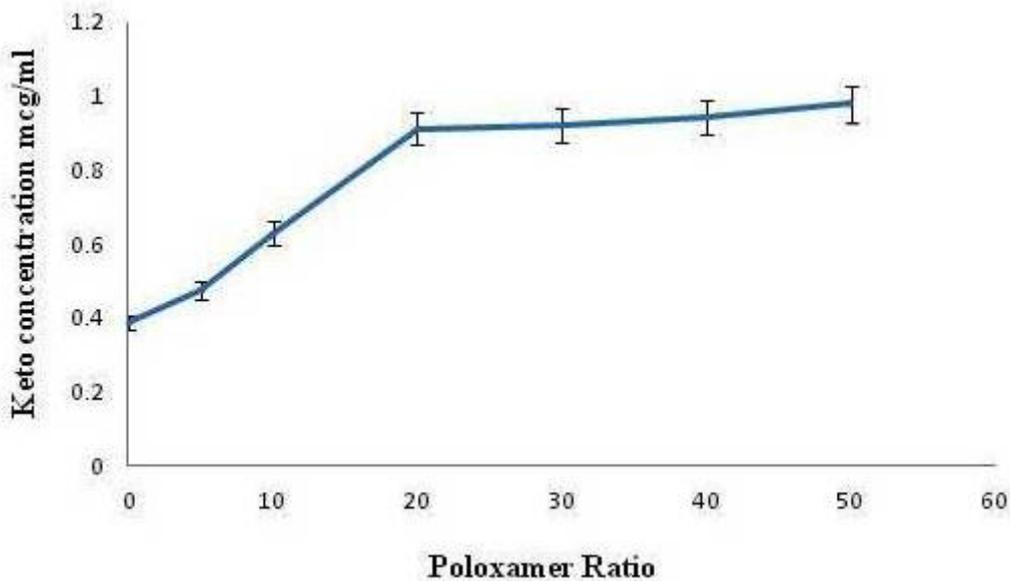


FIGURE 1 - Phase solubility of Ketoprofen:Poloxamer 188.

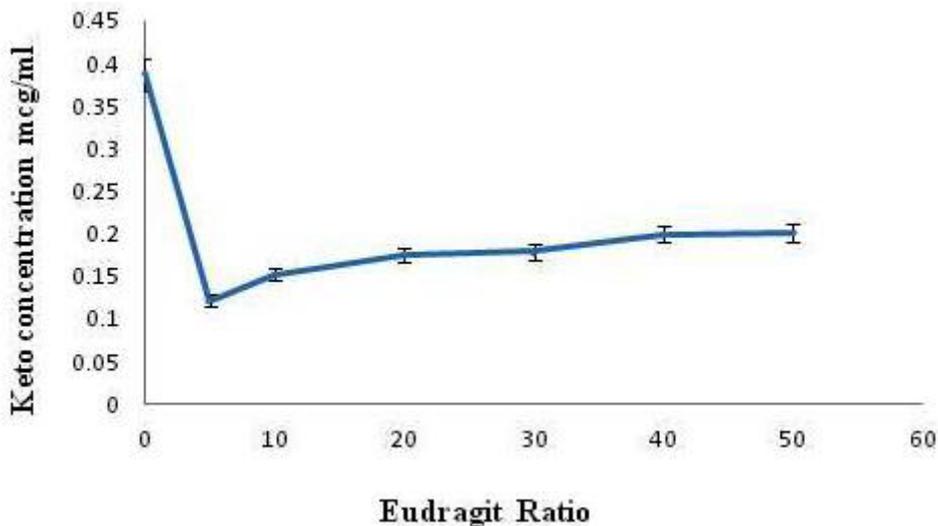


FIGURE 2 - Phase solubility of Ketoprofen:Eudragit S-100.

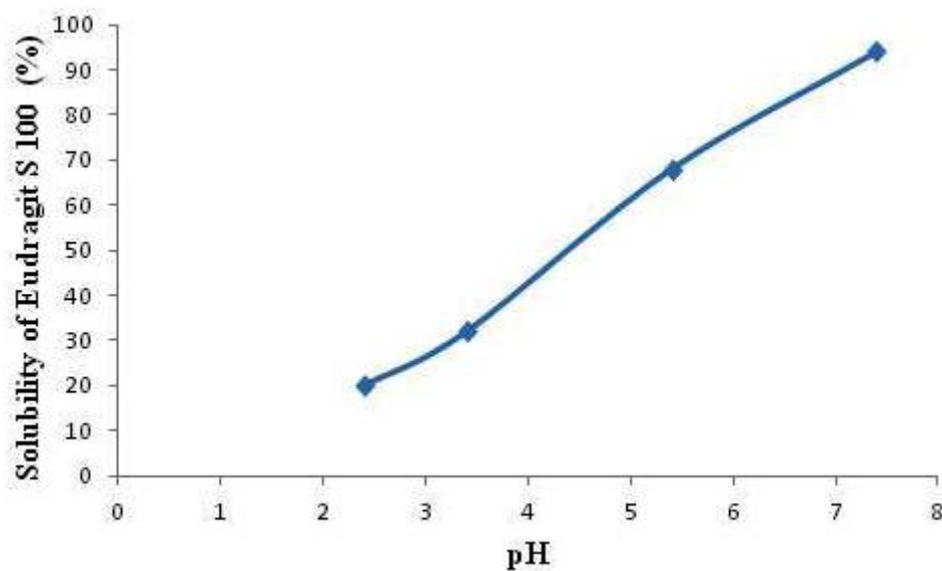


FIGURE 3 - % Solubility of Eudragit S 100 at different pH.

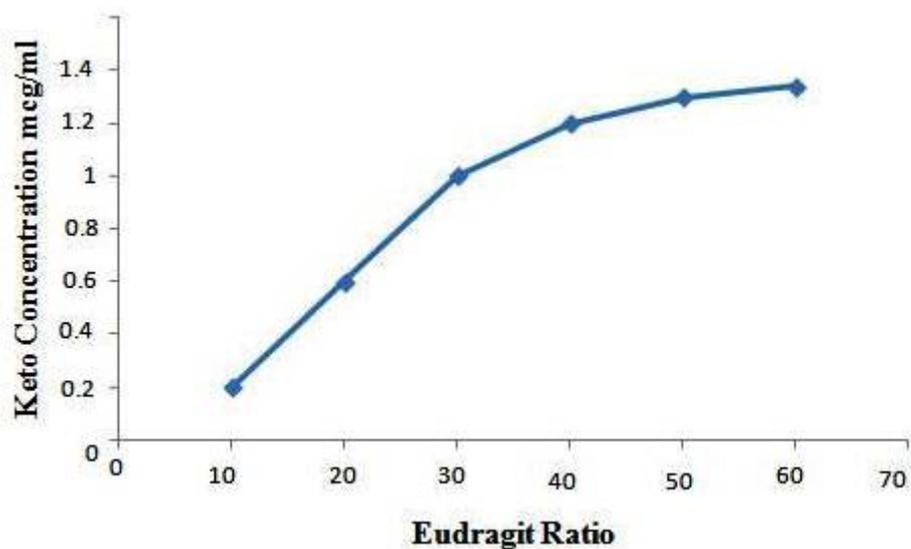


FIGURE 4 - Phase solubility of Ketoprofen:Eudragit S-100 at pH 7.4.

ATR-FTIR spectroscopy

The FTIR spectrum of Ketoprofen was recorded using FTIR (Cary-630 Agilent technology), bands were observed at 3050.166 cm^{-1} (O-H stretching), 2644.006 cm^{-1} (C-H stretching), 1284.104 cm^{-1}

(C-H deformation), 1695.602 cm^{-1} (C=O stretching), 787.989 cm^{-1} (Aromatic-H). The spectra are shown in Figure 5 and 6. The IR studies of SDs & physical mixtures revealed that there is not any chemical interaction between Ketoprofen & Poloxamer 188 and Eudragit S 100 observed.

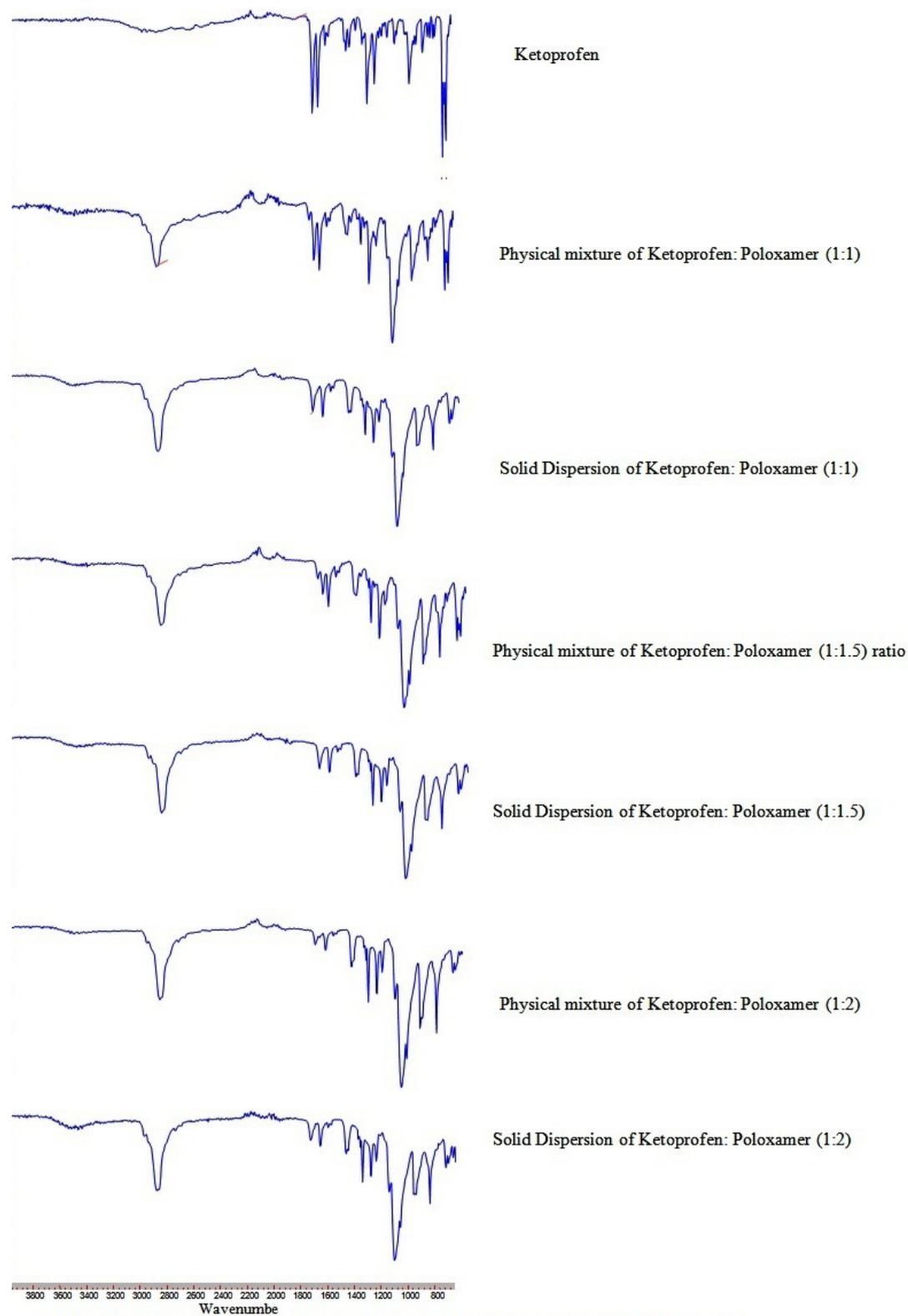


FIGURE 5 - ATR-FTIR of Ketoprofen, physical mixtures and solid dispersions with Poloxamer 188.

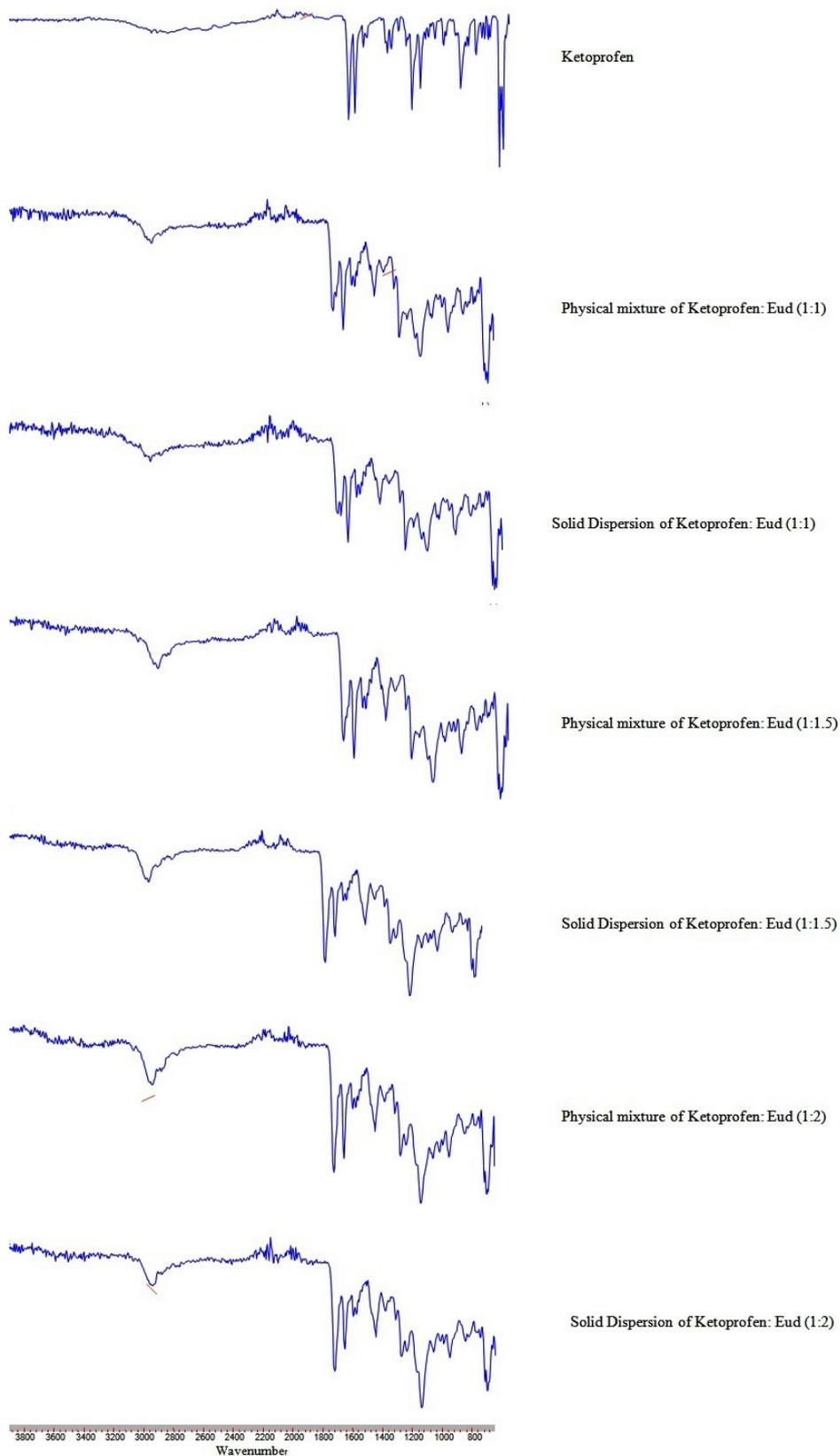


FIGURE 6 - ATR-FTIR of Ketoprofen, physical mixtures and solid dispersions with Eudragit S 100

In vitro drug dissolution study

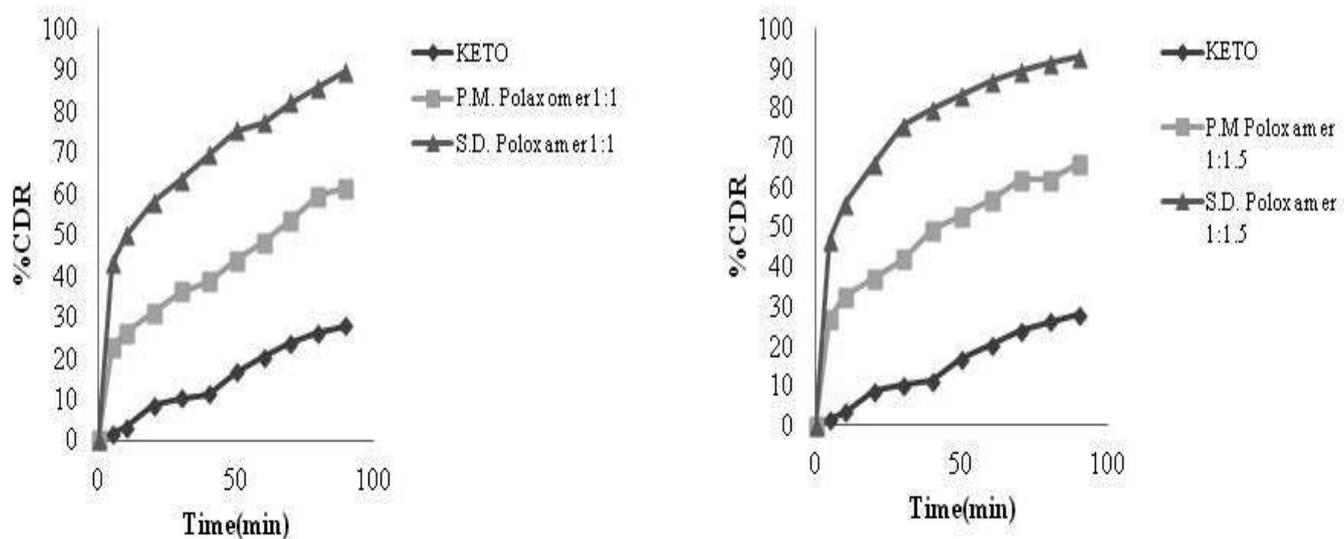
The dissolution profile of Ketoprofen, different concentration of physical mixtures and solid dispersions with poloxamer 188 in 0.1 N HCl as a dissolution medium is shown in Figure 7. The result indicates that pure Ketoprofen, physical mixture of Ketoprofen: Poloxamer 188 (1:1) batch P1p and solid dispersion batch P1 (1:1) showed 27.91 ± 0.015 , 61.53 ± 0.0256 and $89.64 \pm 0.236\%$ CDR after 90 min respectively. The physical mixture of Ketoprofen: Poloxamer 188 batch P2p (1:1.5) and solid dispersion batch P2 (1:1.5) showed 65.99 ± 0.056 and $91.83 \pm 0.563\%$ CDR after 90 min respectively. The physical mixture of Ketoprofen: Poloxamer 188 batch P3p (1:2) and solid dispersion batch P3 (1:2) showed 67.99 ± 0.123 and $90.98 \pm 0.124\%$ CDR after 90 min respectively. It is evident that the solid dispersion technique improved the dissolution rate of the drug to a great extent than a physical mixture. The result indicates that Ketoprofen: Poloxamer 188 in the batch P2 (1:1.5) showed 91.83% drug release in 90 min which was the highest dissolution rate followed by the batch P1 (89.64%) & batch P3 (90.98%).

The dissolution profile of Ketoprofen, Physical mixtures, prepared solid dispersions with Eudragit S 100 in 0.1 N HCl as a dissolution medium is shown in figure 8. The result indicates that pure Ketoprofen, physical mixture of Ketoprofen: Eudragit S 100 batch E1p (1:1) and solid dispersion batch an E1 (1:1) produced 27.91 ± 0.015 , 58.09 ± 0.015 and $89.72 \pm 0.640\%$ CDR after 90 min respectively. The physical mixture of Ketoprofen: Eudragit S 100 batch E2p (1:1.5) and solid dispersion batch E2 ratio (1:1.5) produced 62.25 ± 0.060 and $85.54 \pm 0.139\%$ CDR after 90 min respectively. The physical mixture of Ketoprofen: Eudragit S 100 batch E3p (1:2) and solid dispersion batch E3 (1:2) produced 64.89 ± 0.392 and $86.45 \pm 0.382\%$ CDR after 90 min respectively. Solid dispersion technique improved the dissolution rate of the drug to a great extent than Physical mixture. The result indicates that Ketoprofen: Eudragit S 100 in batch E1 (1:1) showed 89.72% drug dissolution in 90 min which was the highest dissolution rate followed by batch E2 (85.54%) & batch E3 (86.45%). At pH 7.4 the Eudragit S 100 produced maximum drug release which was found to be $96.23 \pm 0.810\%$ CDR for batch E3 (1:2), at same pH physical mixture showed E3p $68.61 \pm 0.102\%$ CDR. The result has been given in Figure 8.

Differential Scanning Calorimetry (DSC).

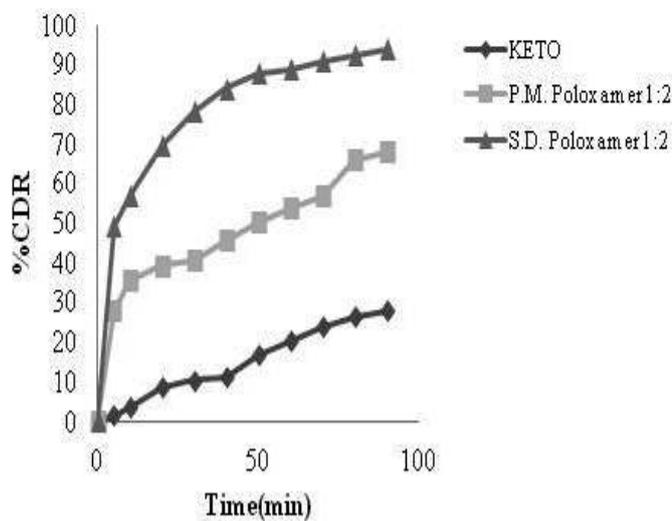
The thermal analysis by DSC, usually offers information about several physicochemical properties such as crystalline nature and thermal stability. The thermogram of the unprocessed Ketoprofen (Figure.9a) exhibited a sharp endothermic peak at temperature $98.09\text{ }^\circ\text{C}$ with (enthalpy change) $\Delta H = 76.40\text{ J/g}$ and $\Delta H_m = 1942\text{ kJmoles}^{-1}$. The sample shows melting onset temperature i. e. Tonset = $92.90\text{ }^\circ\text{C}$. The DSC thermogram of the physical mixture of the batch P2p (1:1.5) (fig. 9b) showed a slight change in melting point recording with peak temperature $95.68\text{ }^\circ\text{C}$ and enthalpy change $\Delta H = 73.61\text{ J/g}$ and $\Delta H_m = 18.71\text{ kJmoles}^{-1}$. The melting point of $52.65\text{ }^\circ\text{C}$ was observed in the DSC thermogram of a solid dispersion of batch P2 (1:1.5) (Figure 9c). The change in enthalpy (ΔH) = 42.81 J/g and $\Delta H_m = 10.88\text{ kJmoles}^{-1}$. It is observed that there is a disappearance of the endothermic peak and also changes in peak intensity when compared with thermogram of pure Ketoprofen & physical mixture. The absence of endothermic peak might be due to the formation of the solid dispersion of the drug in the presence of Poloxamer 188 polymer, where the drug could be transformed into an amorphous state. The melting point and enthalpy change (ΔH) of crystalline pure Ketoprofen was $98.09\text{ }^\circ\text{C}$ & 76.40 J/g respectively. The melting point and enthalpy change (ΔH) for solid dispersion was observed as $52.65\text{ }^\circ\text{C}$ and 42.81 J/g respectively.

The DSC thermogram of the physical mixture of the batch E1p (1:1) (Figure 9d) showed slightly change in melting point recording with peak temperature $95.37\text{ }^\circ\text{C}$ and change in enthalpy $\Delta H = 73.50\text{ J/g}$ and $\Delta H_m = 18.68\text{ kJ moles}^{-1}$. In the DSC thermogram of a solid dispersion of batch E1 (1:1) (Figure 9e) showed a change in the melting point recording with peak temperature $89.27\text{ }^\circ\text{C}$ and change in enthalpy $\Delta H = 64.10\text{ J/g}$ and $\Delta H_m = 16.29\text{ kJ moles}^{-1}$. Here also the disappearance of the endothermic peak observed. The change in peak intensity compare than thermogram of Ketoprofen & physical mixture of batch E1p was recorded. DSC studies also showed that there no interaction between drug and carrier at a molecular level in both the solid dispersions and physical mixtures



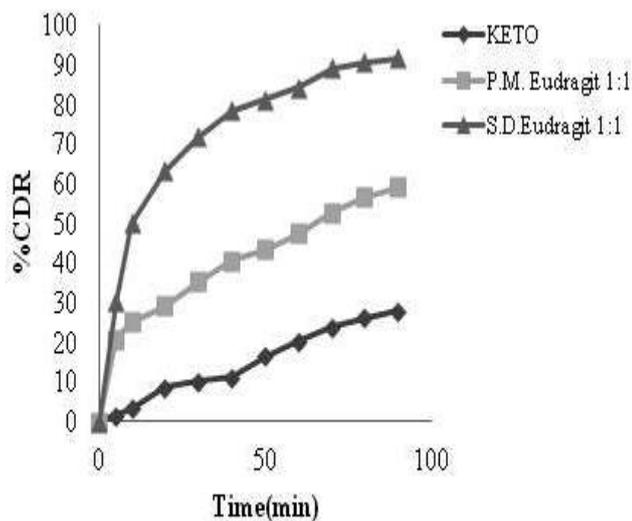
Dissolution Profile of Ketoprofen: Poloxamer, Physical mixture & Solid Dispersion (1:1)

Dissolution Profile of Ketoprofen: Poloxamer, Physical mixture & Solid Dispersion (1:1.5)

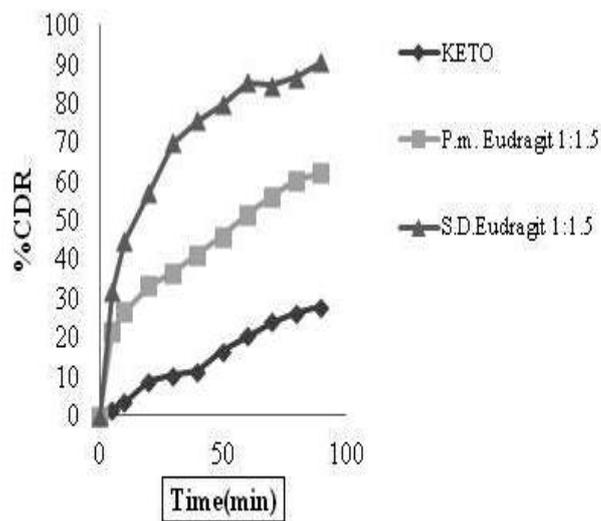


Dissolution Profile of Ketoprofen: Poloxamer, Physical mixture & Solid Dispersion (1:2)

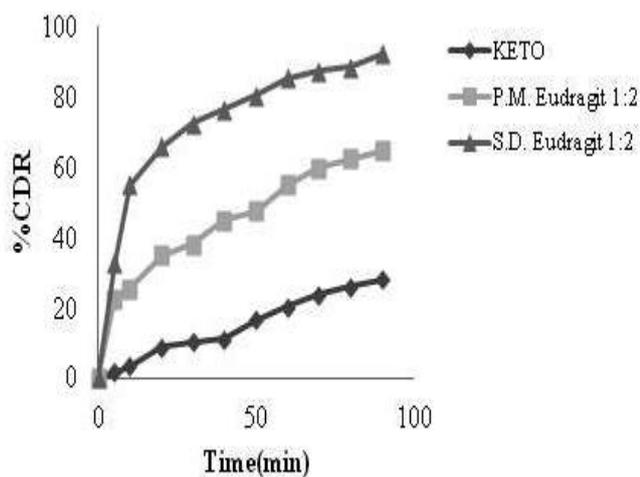
FIGURE 7 - Dissolution profile of Ketoprofen, physical mixture and solid dispersion with Polaxamer 188.



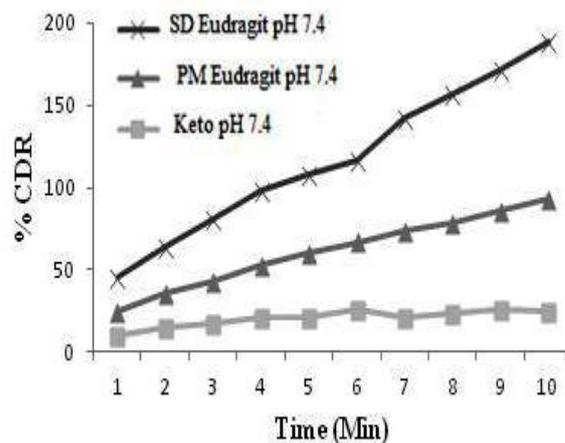
Dissolution Profile of Ketoprofen: Eudragit, Physical mixture & Solid Dispersion (1:1)



Dissolution Profile of Ketoprofen & Eudragit, Physical mixture & Solid Dispersion (1:1.5)

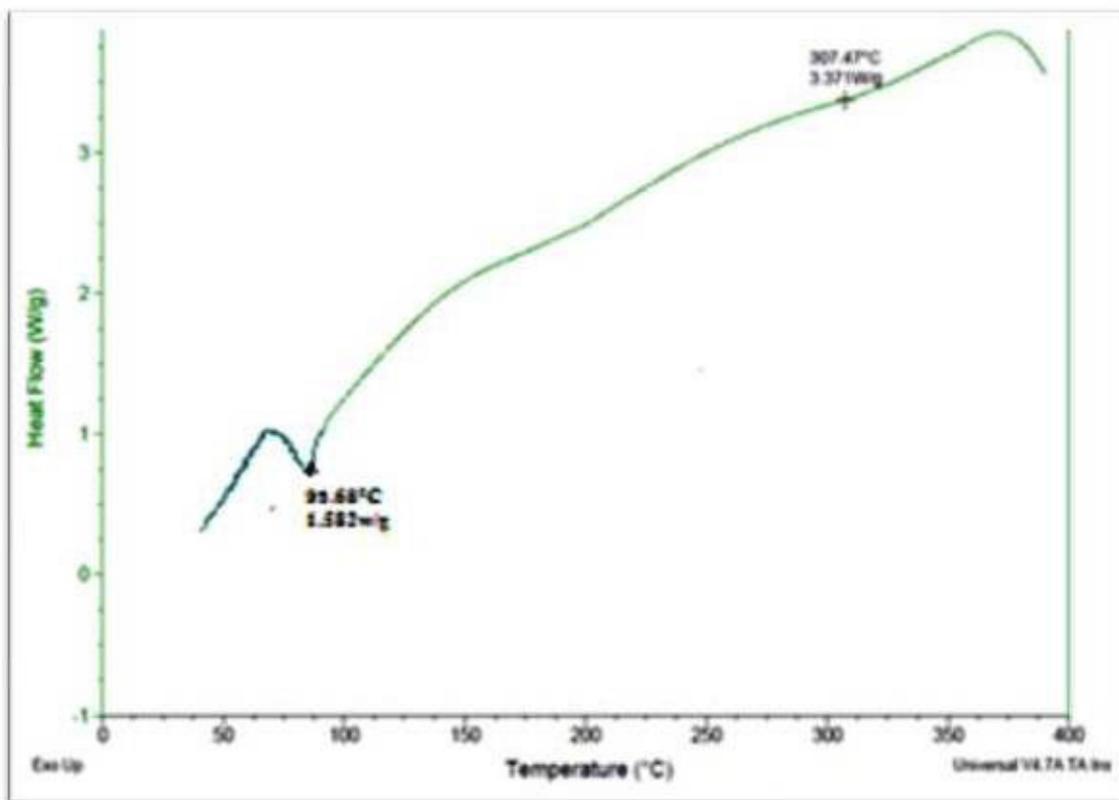
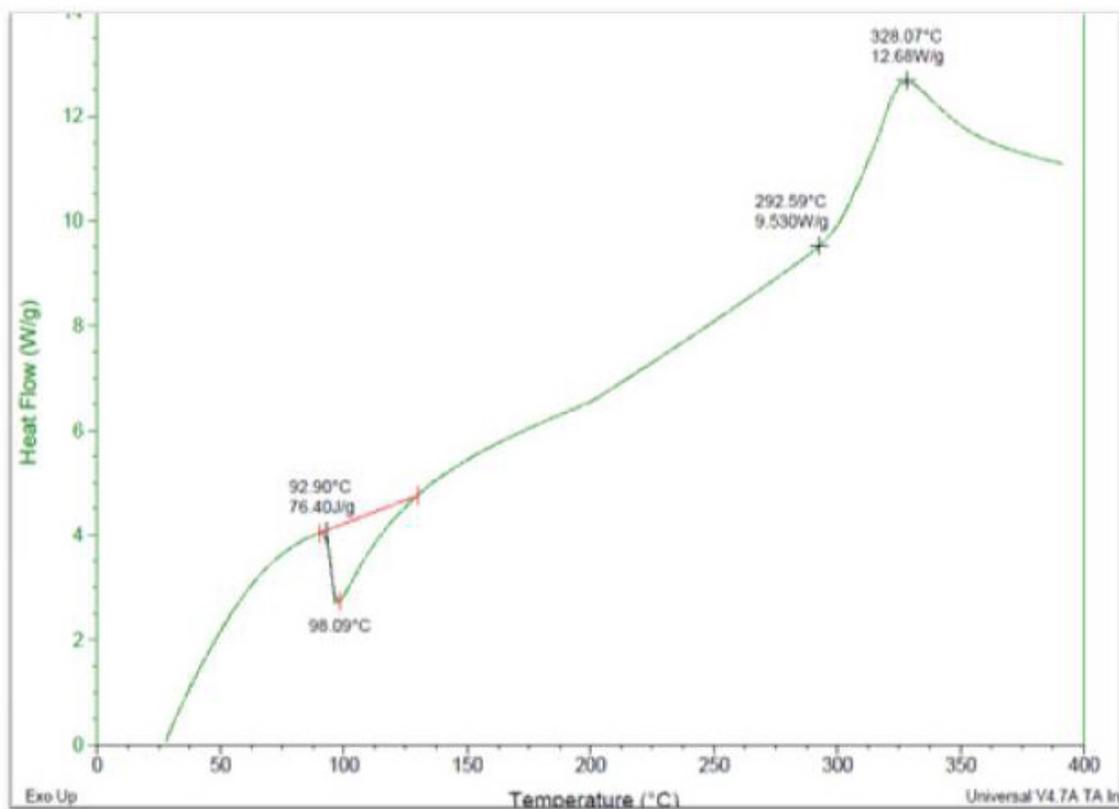


Dissolution Profile of Ketoprofen: Eudragit Physical mixture & Solid Dispersion (1:2)

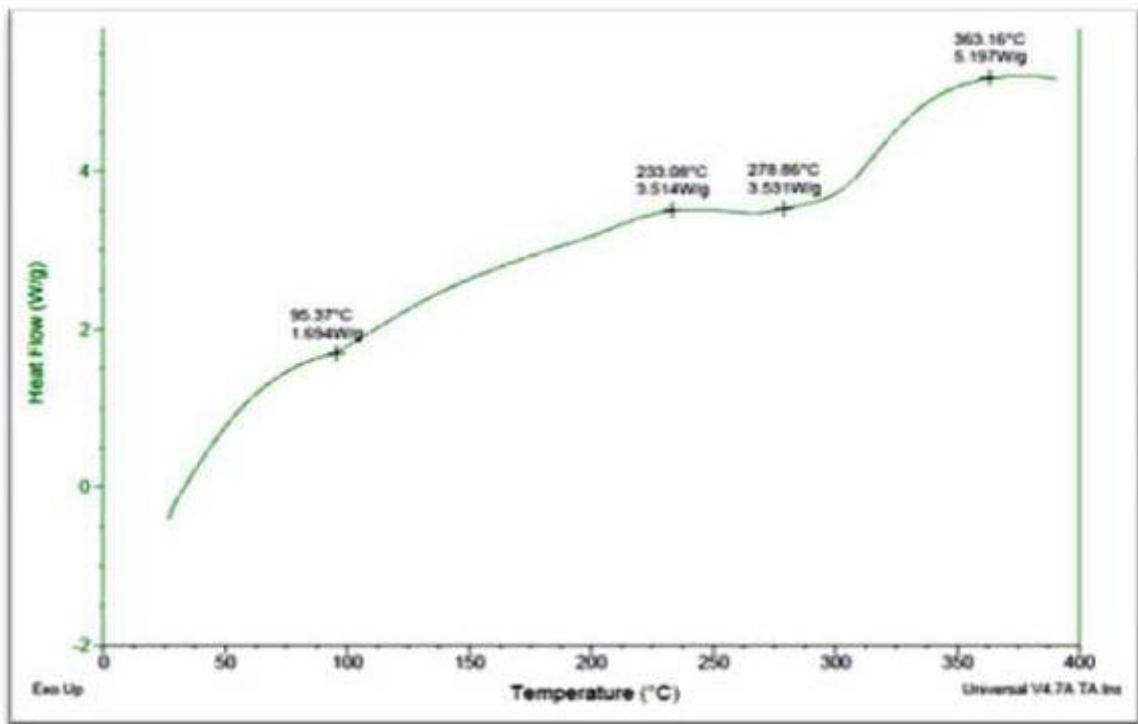
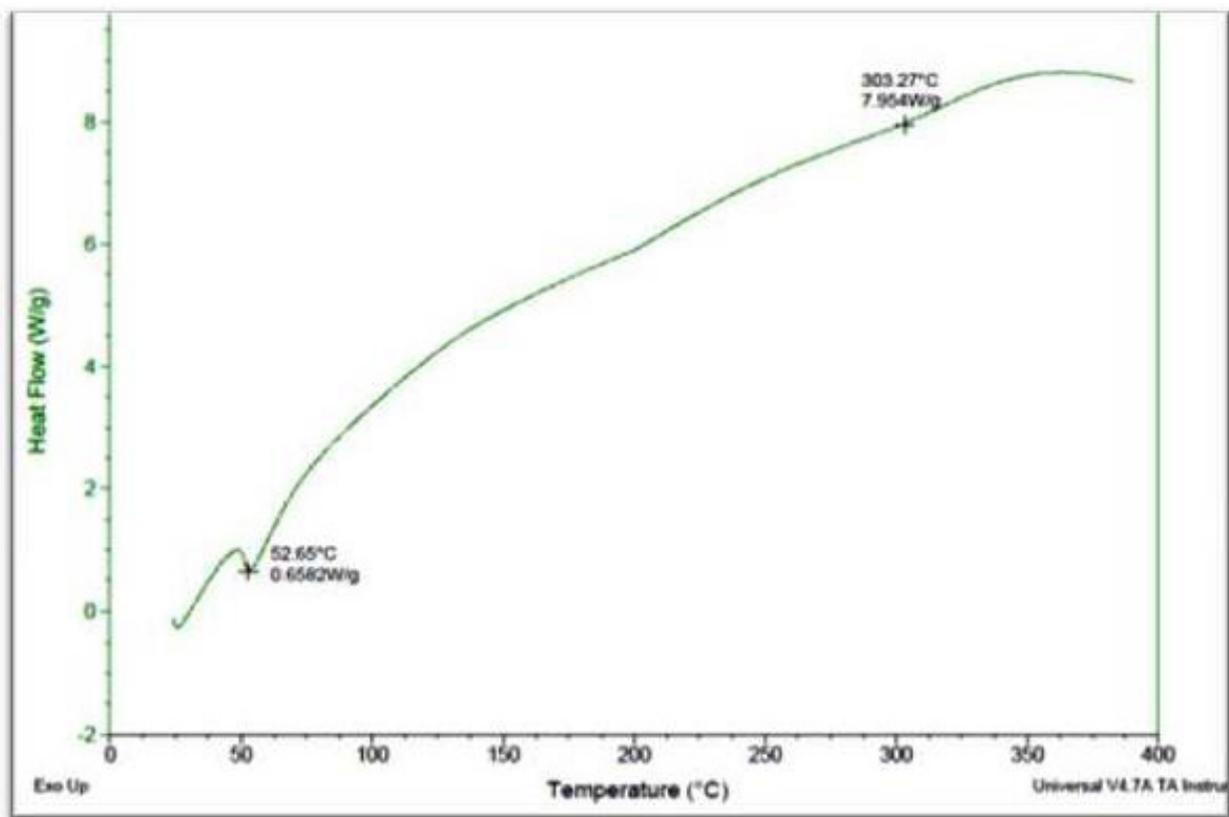


Dissolution Profile of Ketoprofen: Eudragit Physical mixture & Solid Dispersion (1:2) at pH 7.4

FIGURE 8 - Dissolution profile of Ketoprofen, physical mixture and solid dispersion with Eudragit S 100.



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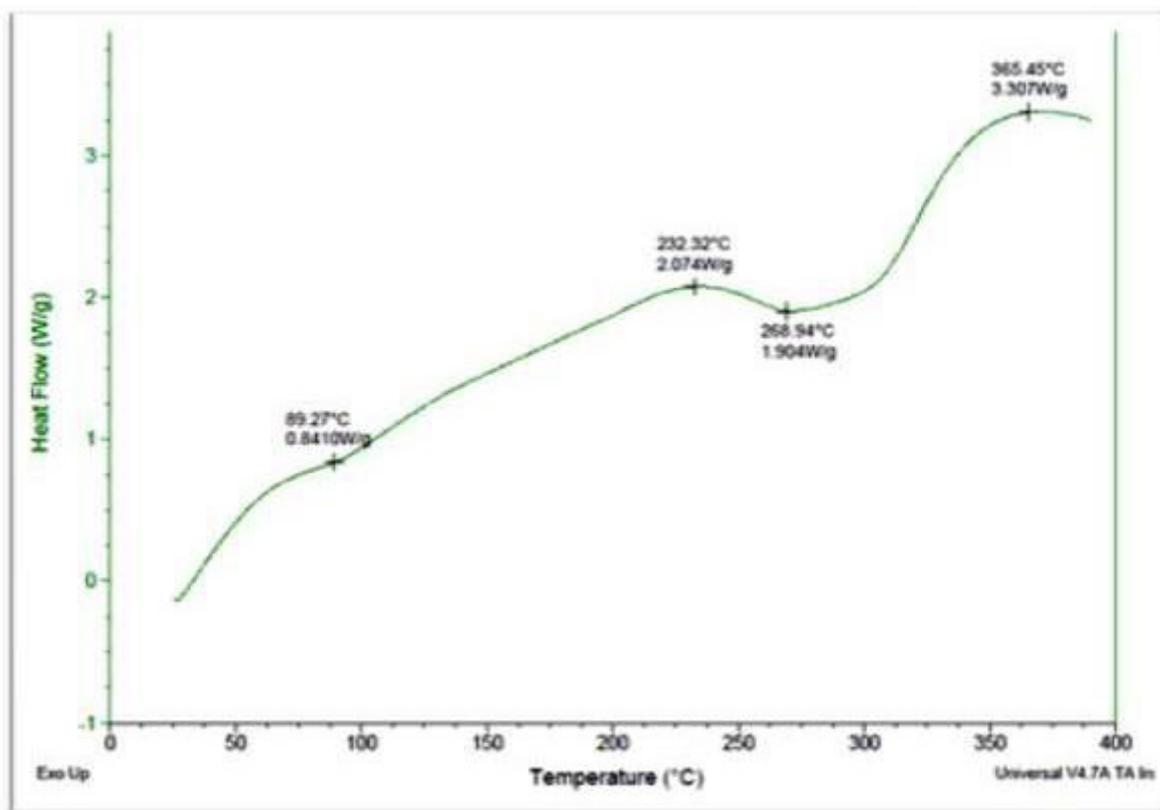


FIGURE 9 - (a) DSC of Ketoprofen at temp. 98.09 °C. (b) DSC of Physical Mixture of Batch P2p [Ketoprofen: Polo (1:1.5)] at temp. 95.68 °C. (c) DSC of Solid Dispersion of Batch P2 [Ketoprofen: Polo (1:1.5)] at temp. 52.65 °C. (d) DSC of Physical Mixture of Batch E1p [Ketoprofen: Eud (1:1)] at temp. 95.37°C. (e) DSC of Solid Dispersion of Batch E1 [Ketoprofen: Eud (1:1)] at temp. 89.27 °C.

X-Ray Diffraction (XRD)

The distinct, high, intense peaks were observed in X-Ray diffraction of pure Ketoprofen (Figure 10a) in the range of 5-50° 2 θ , indicating the highly crystalline nature of the drug. It showed distinct peaks approximately at 13, 15, 17 and 23° 2 θ . In X-ray diffraction pattern of physical mixture batch P2p (1:1.5) (Figure 10b) intense peaks were observed at 18 and 23° 2 θ , which did not show any change in crystallinity. The X-ray diffraction pattern of solid dispersion of batch P2 (1:1.5) (Figure 10c) showed intense peaks at 18 and 23° 2 θ . The X-ray diffraction pattern of physical mixture batch E1p (1:1) (Figure 10d) produced a single broad peak in the range of 8 to 23° 2 θ , whereas X-ray diffraction pattern of solid dispersion of batch E1 (1:1) (Figure 10e) produced two broad peaks in the range of 8 to 23° 2 θ and 25 to 38° 2 θ . Moreover, the 2 θ angle of these peaks remained practically unchanged. However, the X-ray diffraction of solid dispersion did not show any intense peak that is

characteristic of the crystal structure. It reflects that the drug was essentially converted from high crystalline to moderate form. The results also suggest that there may be a mild interaction between Ketoprofen and Poloxamer 188, Eudragit S 100 in solid dispersion which changes orientation during crystal growth phase. IR and DSC studies support the same hypothesis, which is confirmed by X-ray diffractometry

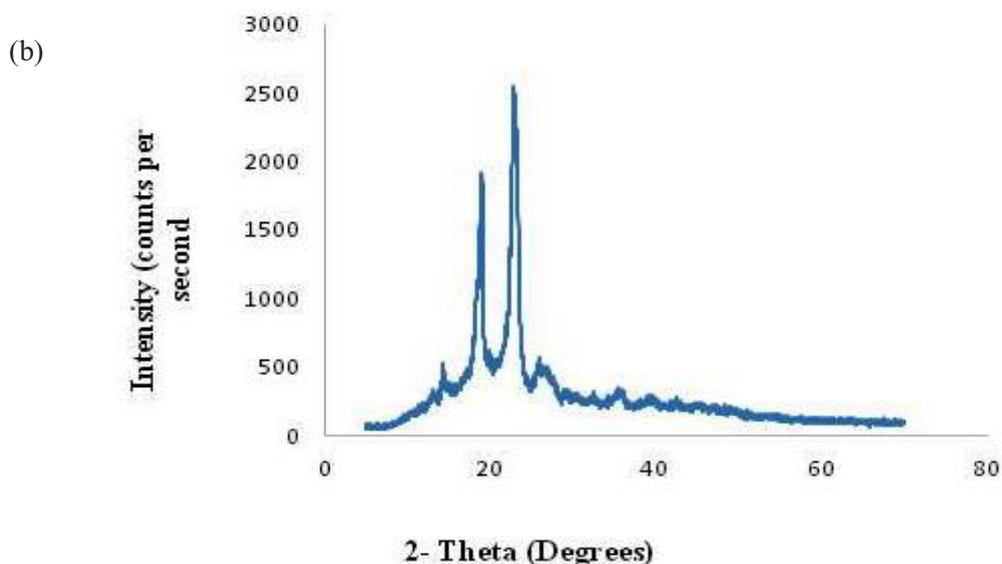
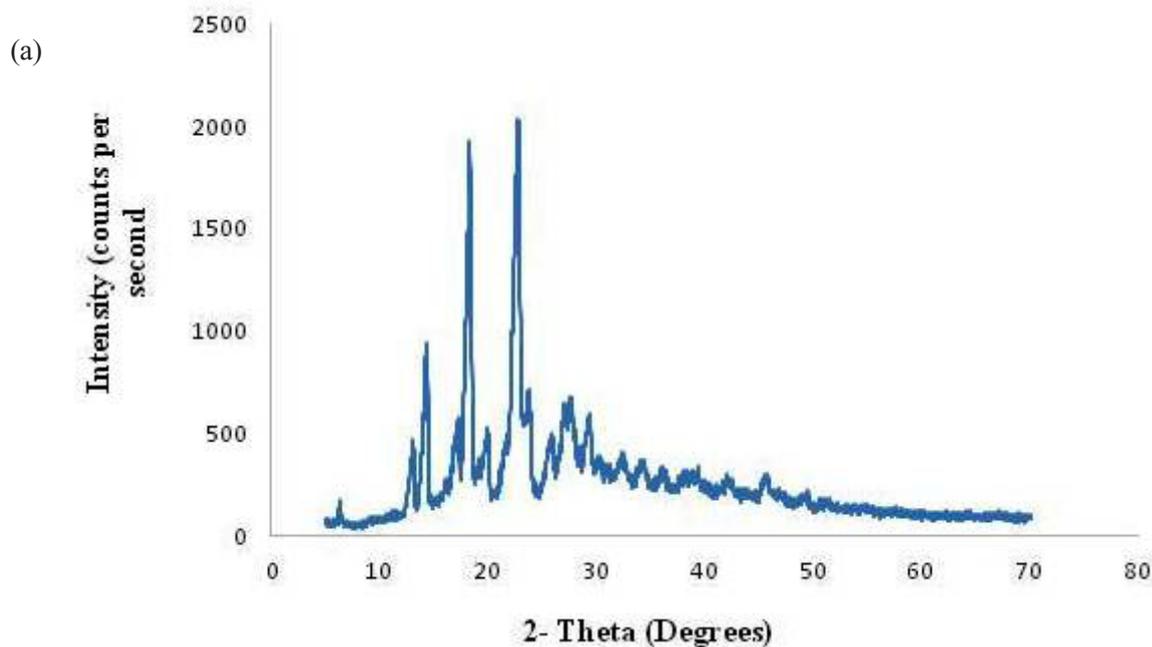
Scanning Electron Microscopy (SEM)

Figure 11 depicts SEM images of pure Ketoprofen the bar on the pictures indicates the degree of magnification 50 μm . The SEM of pure Ketoprofen showed irregular shape crystals of rough surfaces. SEM images of a physical mixture of batch P2p (1:1.5) showed slightly irregular shape. SEM images of a solid dispersion of batch P2 (1:1.5) at magnification 50 μm did not have any irregular shapes and crystalline nature of the drug, which can be because of entrapment of drug within the

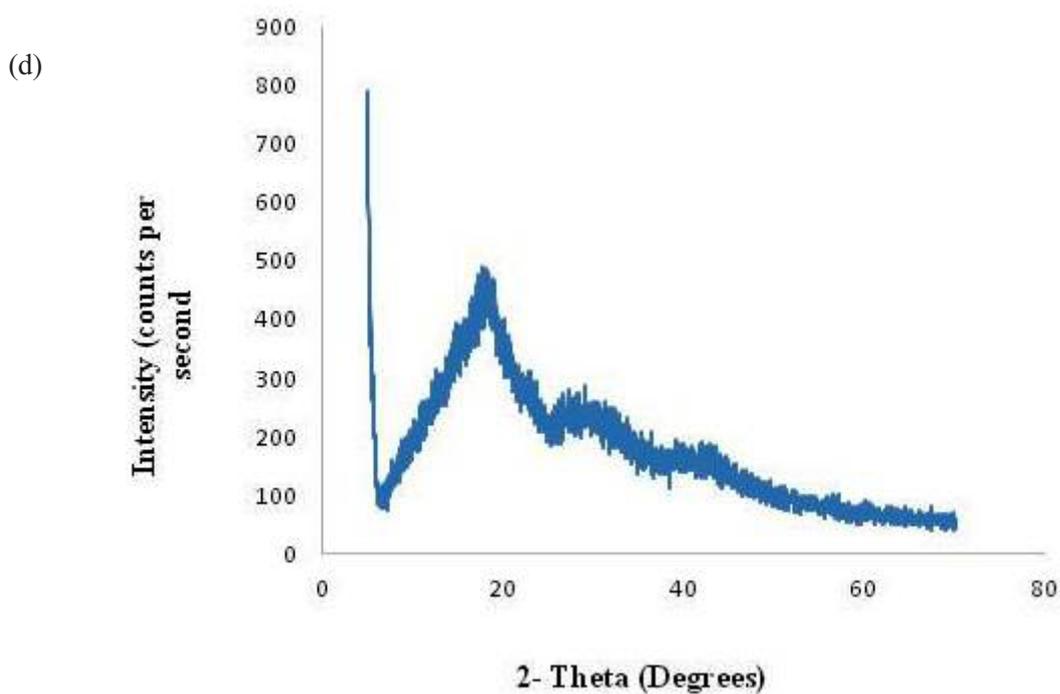
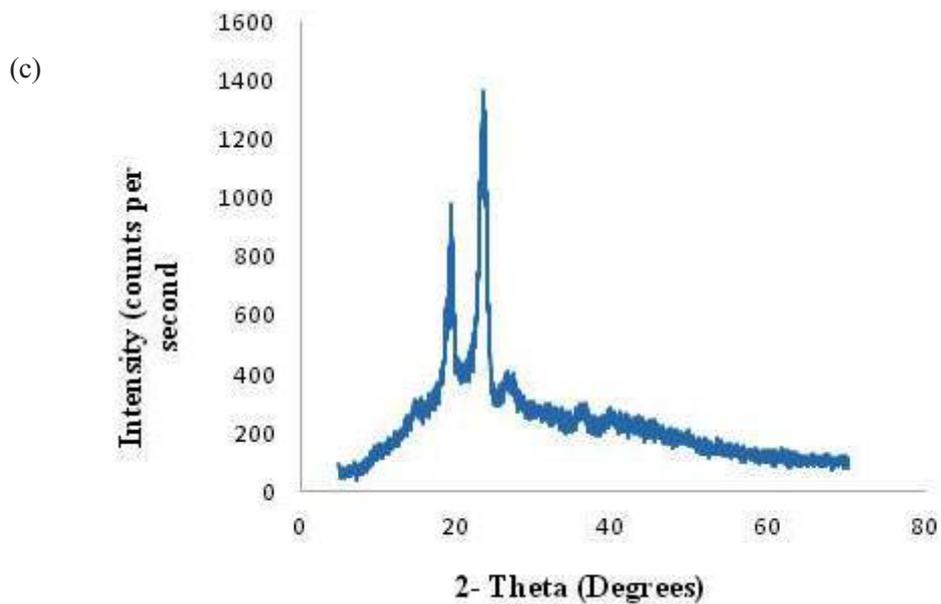
polymer i.e. Poloxamer 188. SEM of a physical mixture of batch E1p (1:1) showed slightly irregular shape at magnification 50 μm . SEM of a solid dispersion of batch E1 (1:1) showed non-crystalline nature of the drug, which can be because of entrapment of drug within the polymer i.e. Eudragit S 100.

The whole study of SEM showed a smooth surface of Ketoprofen with Poloxamer 188 and Eudragit S 100, by using solid dispersion there may be a complete coating

of Ketoprofen with polymer particles. Solid dispersion particles looked like irregularly shaped matrices which suggest that particle shape and surface topography is changed during formation of the solid dispersion. These findings demonstrate that reduction in particle size, increased surface area and close contact between drug and carrier may be required for the enhanced solubility of the drug.



(continuing)



(continuing)

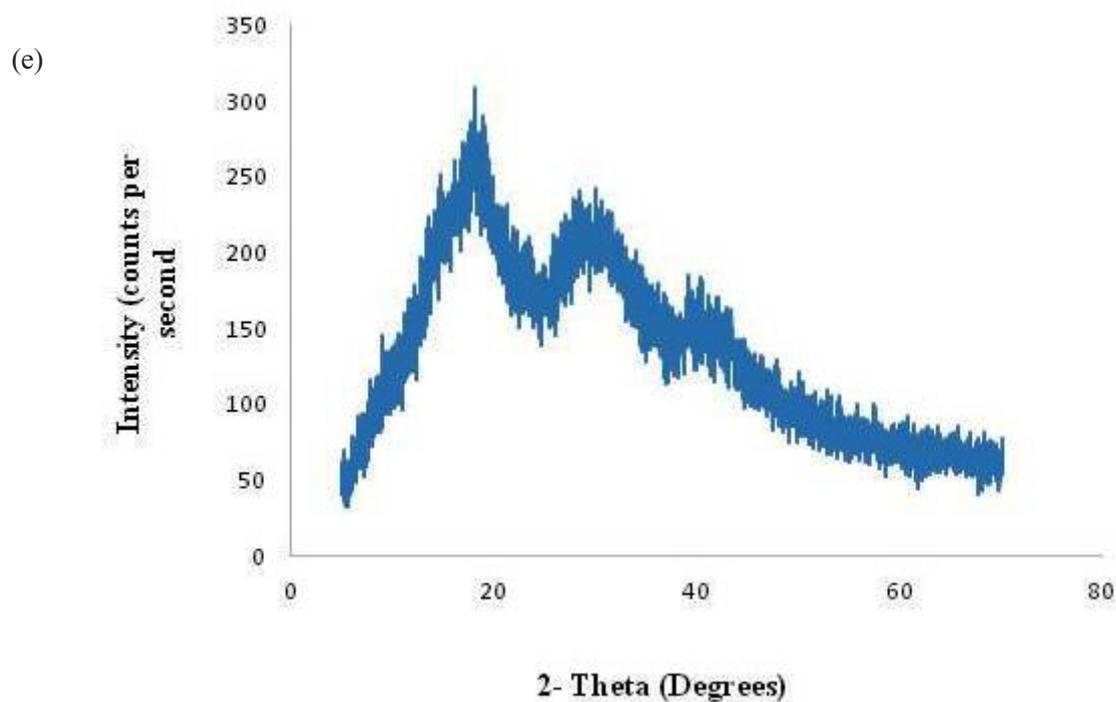


FIGURE 10 - (a) XRD of Ketoprofen. (b) XRD of Physical Mixture of Batch P2p [Ketoprofen: Polo (1:1.5)]. (c) XRD of Solid dispersion of Batch P2 [Ketoprofen: Polo (1:1.5)]. (d) XRD of Physical Mixture of Batch E1p [Ketoprofen: Eud (1:1)]. (e) XRD of Solid Dispersion of Batch E1 [Ketoprofen: Eud (1:1)].

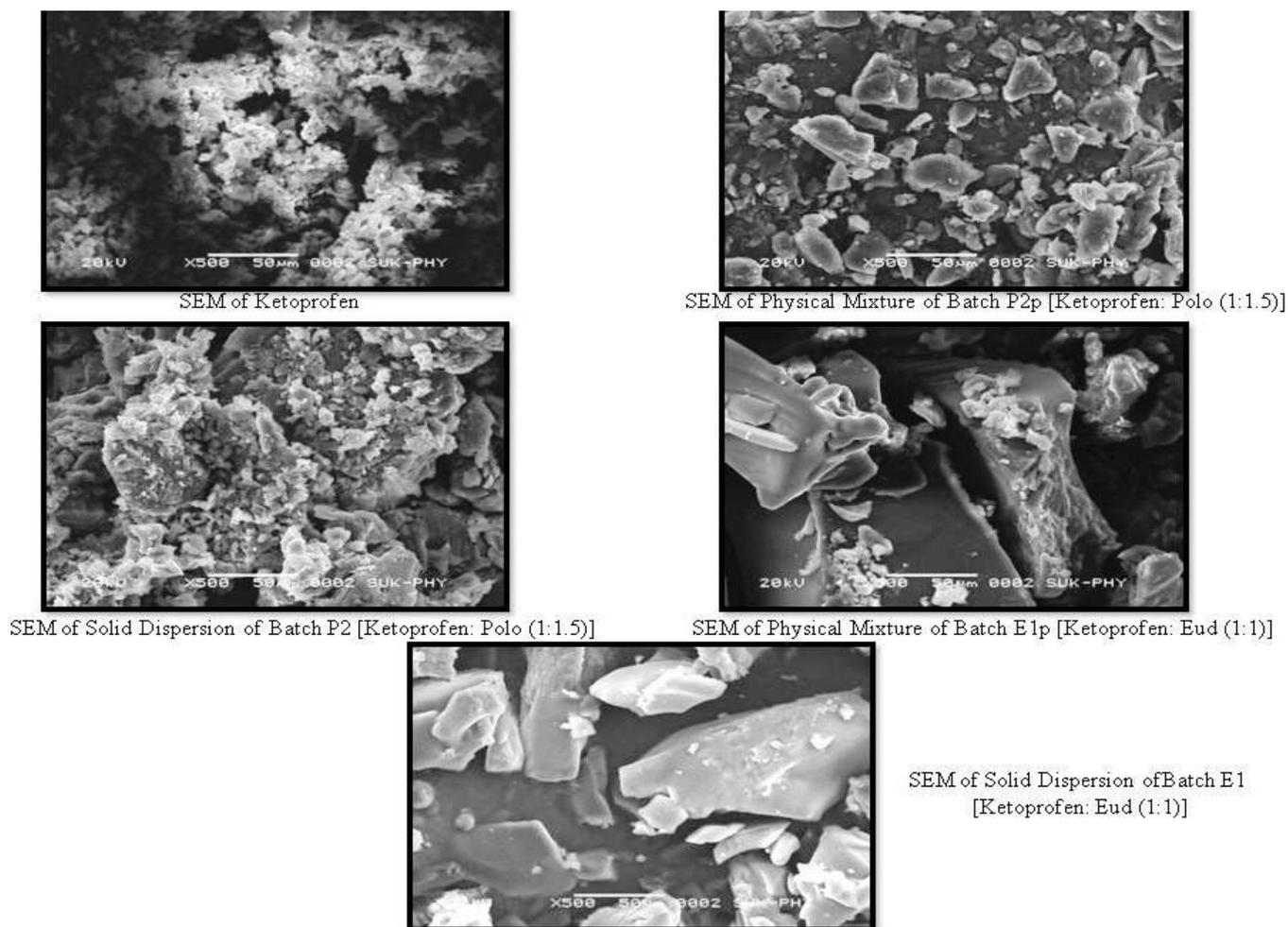


FIGURE 11 - SEMs of Ketoprofen, Physical mixtures and Solid dispersions.

Accelerate stability study

Effect of temperature: At 40 °C (Short Term)

It is recognized that amorphous drugs formulated in the form of a solid dispersion with its physical mixture tend to recrystallizes on storage. To check the effect of temperature & time, stability testing was performed according to ICH guidelines “stability testing of new drug substances and products Q1A (R2)” (ICH, 2003). The samples were stored at 40 °C /75% RH for 1 month in high-density polyethylene bottles. The results showed in a physical mixture of batch P2p (1:1.5) produced $39.56 \pm 0.123\%$ CDR and solid dispersion batch P2 (1:1.5) produced $20.78 \pm 0.124\%$ CDR. The batch E1P (1:1) produced $65.23 \pm 0.521\%$ CDR, while solid dispersion batch E1 produced $70.35 \pm 0.652\%$ CDR. The physical

mixture and solid dispersion showed changes in color and appearance in accelerated stability study.

From the result of the accelerated stability study, it can be concluded that the drug, physical mixtures and solid dispersions may undergo degradation.

CONCLUSION

Solid dispersion technique was used to improve physical characteristics and dissolution profile of Ketoprofen. Poloxamer 188 and Eudragite S 100 were used as a carrier to improve physicochemical characteristics and dissolution profile of ketoprofen. Solid dispersion technique was found to be effective in increasing the aqueous solubility of ketoprofen. *In vitro* dissolution studies showed that in the solid dispersion system gave faster dissolution rate than physical

mixtures. In accelerated stability study a significant change in various parameters like color, physical appearance, % CDR was observed, which indicates that these formulations are unstable.

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