

Development, Characterisation and Evaluation of PVP K-30/PEG Solid Dispersion Containing Ketoprofen

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ABSTRACT

The present study is designed with the objective to enhance the aqueous solubility of ketoprofen. For the said purpose solid dispersion employing PVP K-30 and PEG 6000 is prepared by hot melt method. The preparation of solid dispersion (SD) was optimized using 2-factor, 3 level central composite design. The preparation of SD was characterized by FTIR, DSC, XRD and SEM studies. Further, solubility, Gibb's energy and *in vitro* release study was determined for different batches of the formulation as suggested by the design expert. The solubility of different batches of SD was found to be between 36.2 to 53.0 µg/ml whereas pure drug and physical mixture possess the solubility of 14.4 and 23.8 µg/mL, respectively. The *in vitro* release is found to be 76.74 to 95.32% and PM shows 75.4 % release and pure drug shows 23.5 % release. Thus, the ketoprofen-loaded solid dispersion would be useful for delivering poorly water-soluble ketoprofen with enhanced dissolution, solubility and no crystalline changes.

Keywords: Ketoprofen, solid dispersion, dissolution rate, solubility study.

INTRODUCTION

Poor aqueous solubility of pharmaceutically active ingredients has been a challenge to the researchers. More than 40 % of newly developed drugs candidates are poorly water soluble¹. This low aqueous solubility further lowers the absorption in GI tract and thus reduced bioavailability is observed. Therefore, the development of new techniques to enhance drug solubility remains one of the major research areas in drug discovery and development process². A scan of literature has revealed that numerous attempts has been made to improve the

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solubility and dissolution of drugs that include cyclodextrins complexes³, drug micronization in to amorphous form⁴, prodrug formation⁵, solid dispersion⁶⁻¹², salt formation¹³, solubilization of drug in solvents, nanoparticles technology¹⁴, physical modification, nanosuspension¹⁵⁻¹⁹, modification of crystal habit such as polymorphous, pseudo polymorphous, self-emulsifying drug delivery systems (SEDDS)²⁰, liposomes²¹⁻²⁵ and use of surfactant “ micelization” ²⁶ etc. Out of numerous techniques explored so far solid dispersion have been proved to be the most promising strategy to improve the solubility of poorly water-soluble drugs. In solid dispersion compounds are mixed / dispersed in solid state in a suitable carrier or matrix to deliver the insoluble compounds²⁷. Solid dispersions preparation by hot melt or fusion method is preferred because of it is simple and is useful for the compounds that do not undergo significant thermal degradation. Further toxicity and environmental issues that are associated with use of organic solvents make the technique more preferable²⁸.

Ketoprofen, categorized as BCS class II drug, is a safe propionic acid derivative non-steroidal anti-inflammatory drug. However, its poor water solubility (0.13 mg/ml at 25° C) limits its absorption and dissolution rate that results in delayed onset of action. Therefore, its incorporation in water soluble matrix solid dispersion have been considered as an effective method for improving its dissolution rate and solubility. A number of efforts have been made to incorporate ketoprofen into solid dispersion using mannitol, urea, PVP K-30²⁹, PVP K-30 and D-mannitol³⁰, bovine serum albumin¹², Macrogal and Kollagen³¹ and PEG 6000³². On scouring the literature, it is observed that PVP and PEG are most popularly used polymers for the preparation of solid dispersion³³. Low melting point of PEG (50-60°C) and rapid solidification offers it to be used in forming solid dispersion²⁵ while the PVP K-30 is high melting point (150-180°C) and small its molecular weight render it to be a suitable carrier in achieving high dissolution³⁴.

The present study is designed to obtain solid dispersion of ketoprofen with PEG 6000 and PVP K-30 using hot melt or fusion method with the objective to enhance solubility and dissolution of the drug. The preparation of solid dispersion was optimized by using 3 factor 2 level central composite experimental design. The optimized batch was characterized by FTIR, SEM, DSC, XRD spectra and evaluated for its *in-vitro* release behavior and solubility.

METHODOLOGY

Materials

Ketoprofen was obtained as a gift sample from Infinity Laboratories Pvt. Ltd

(Behra, India). Polyvinyl pyrrolidone (PVP) K30 (kollidon K30) and polyethylene glycol 6000(PEG 6000) (PEG 6000) was supplied by Symmetry laboratories, Faridabad. All other reagents and chemicals used in the study were of analytical grade and used as received.

Methods

Preparation of solid dispersion

SDs of ketoprofen were prepared by using hot melt technique by mixing required quantities of ketoprofen(100 mg) ,PVP K-30 and PEG 6000 as displayed in Table 1. The ingredients were added in decreasing order of their melting point and the resulting homogeneous preparation was cooled and stored in a desiccator for 24 h. Subsequently, the dispersion was ground using a mortar and sieved through a #100 sieve.

Physical mixtures (PM) was prepared by thoroughly mixing presieved equal weight ratio of ketoprofen, PEG 6000 and PVP K-30 using pestle and mortar until a homogeneous mixture was obtained.

Experimental design

The preparation of solid dispersion using PVP K-30 and PEG 6000 was optimized using 2-factor, 3 level central composite design. The concentration of PEG 6000 (X_1) and concentration of PVP K-30 (X_2) were selected as the formulation variables while the % drug release, solubility ($\mu\text{g/ml}$) and Gibb's energy (kg/mol) were chosen as response variables. Each independent variable was investigated at three levels (i.e. -1, 0, and 1). The experimental design and statistical analysis of the data was done by using Design Expert software (version 11.0).

Determination of drug content

The different batches of solid dispersions and physical mixture (PM) containing ketoprofen equivalent to 10mg were dissolved separately in 25 ml of phosphate buffer (pH 7.4). Samples were filtered through 0.45 μm milipore filters and after appropriate dilution were analyzed by UV visible spectrophotometer at 260nm. The drug content was determined using calibration curve.

Characterization of solid dispersion

Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopy is employed to characterize the possible interactions between the drug and the carrier in the solid state. FTIR spectra of powder samples of ketoprofen, PEG 6000, physical mixture and solid dispersion were ob-

tained using a spectrophotometer (FTIR-8300, Shimadzu co., Kyoto, Japan) by using potassium bromide (KBr) pellet method in the scanning range of 400-4000 cm^{-1} .

Powder X-ray diffraction (PXRD)

PXRD is the most important tool to determine the structure of the compound. Powder XRD patterns were traced employing X-ray diffractometer (Philips PW 1830, the Netherlands) for the samples of ketoprofen, PVP K-30, PEG 6000, physical mixture and solid dispersion using Ni filtered Cuka radiation of wavelength 1.5404 Å, a voltage of 35 kV, a current of 30 mA and receiving slit of 0.1 mm. The sample were analyzed over 2θ range of 5-50°.

Scanning electron microscopy (SEM)

The particle shape and morphology of the sample was investigated using SEM (JEPL, JSM-6100). The samples for SEM were mounted on sample holder with double-sided adhesive tape after vacuum coated with gold.

Differential scanning Calorimetry (DSC)

DSC analysis of samples ketoprofen, PVP K-30, PEG 6000, physical mixture and solid dispersion was carried out using DSC (Q10 V9.9 Build 303, US). Each sample was heated at the scanning rate of 10°C /min, from 30 to 200°C.

Solubility studies

Ketoprofen pure drug, PM and solid dispersion containing ketoprofen equivalent to 10 mg was dispersed in 10 ml of distilled water and kept on shaker for 48hrs at room temperature (25°C) to determine the solubility of ketoprofen. The obtained solution was filtered by 0.45 μm milipore filter paper and the drug content was determined by taking absorbance at 260 nm using *uv-vis* spectrophotometer. The amount of drug was calculated using the calibration curve in water. The Gibbs free energy of transfer (ΔG) of drug from water to the aqueous solution of carrier was calculated as equation 1.

$$\Delta G = -2.303RT \log S_o/S_s \quad (1)$$

where S_o/S_s is the ratio of solubility of ketoprofen in aqueous solution of carrier to that of the same medium without carrier.

In vitro drug release

In vitro dissolution studies were performed using the USP type II dissolution apparatus. Dissolution studies of pure drug (ketoprofen), PM and solid dispersions containing ketoprofen equivalent to 10mg were conducted in 300ml

phosphate buffer (pH 7.4) at $37 \pm 0.5^\circ\text{C}$ with constant stirring rate of 50 rpm. The powders were dispersed over the dissolution medium. Aliquots of sample (5ml) was withdrawn at different time intervals and replaced with an equal amount of the dissolution medium to maintain a constant volume. Samples were filtered through $0.45\mu\text{m}$ milipore filters and analyzed by uv-vis spectrophotometer at 260nm. The mechanism of drug release from the solid dispersion was determined by fitting the release data to several models like zero order, first- order, Higuchi and Korsmeyer–Peppas model.

RESULTS AND DISCUSSION

Drug content of formulations

The content of ketoprofen in different batches of SD was determined by carrying out the assay of drug by *uv-vis* spectroscopy is displayed in Table-1. The drug content was found to be between 82.8 to 97.9 % whereas for PM containing equal amount of ingredients has drug content of 84.4%. From the data it is clearly indicated that the drug content in the formulated batches of SD and PM is quite handsome indicating that drug is for entrapped/present in a sufficient amount.

Fourier Transform Infrared Spectroscopy (FT-IR)

Characteristic IR absorption peaks of ketoprofen were detected at 2979.23 cm^{-1} due to $-\text{CH}$ stretching, 1694 cm^{-1} ($-\text{C}=\text{O}$ stretching of acid), 1654 cm^{-1} ($-\text{C}=\text{O}$ stretching of ketone), $1598, 1583, 1457\text{ cm}^{-1}$ ($-\text{C}=\text{O}$ stretching of aromatic ring), 1420 cm^{-1} ($-\text{C}-\text{H}$ deformation of CH_3 asymmetrical) and 1370 cm^{-1} ($-\text{C}-\text{H}$ deformation of CH_3 symmetrical) respectively¹².

Important vibrations detected in the spectrum of PEG are the $-\text{C}-\text{H}$ stretching at 2889 cm^{-1} and the $-\text{C}-\text{O}$ (ether) stretching at 1112 cm^{-1} . The $-\text{OH}$ group is indicated by a strong band around 2890 cm^{-1} . The region from $2700-3000\text{ cm}^{-1}$ in the spectra of pure ketoprofen, PEG 6000, PM and SD exhibited peaks assigned to aliphatic $-\text{C}-\text{H}$ stretching³⁵.

IR spectra of SD was found to be almost similar with that of PM because characteristic peaks representing specific functional group were detected. Especially the peak at 2888 cm^{-1} resulting from $-\text{C}-\text{H}$ stretching vibration was observed in both SD and PM of ketoprofen³⁶. So the characteristic peaks of ketoprofen also seen in SD and PM that indicate that ketoprofen is present in the SD and PM.

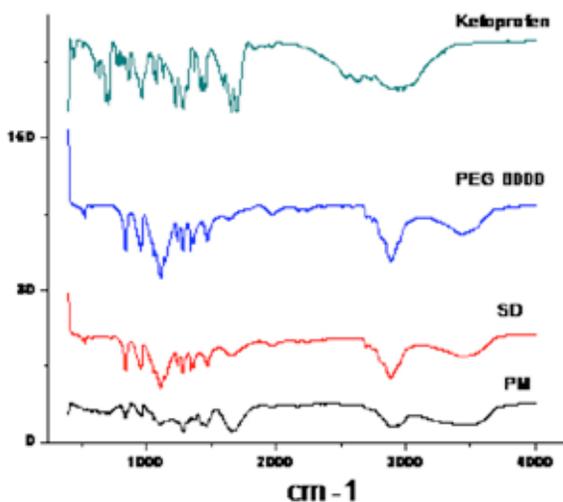


Figure 1. FTIR spectra of pure ketoprofen, PEG 6000, SD and physical mixture.

Power X-ray diffraction (PXRD)

The powder XRD of pure ketoprofen, physical mixtures, polymers PEG 6000, PVP K-30 and solid dispersion are shown in figure 2. The presence of numerous distinct peaks in the X-ray-diffraction spectrum of ketoprofen indicates that ketoprofen is present as a crystalline material with characteristics sharp peaks appearing at a diffraction angle of 2θ at 18.608, 22.976 and 27.23 etc. XRD spectra of PVP K-30 showed no intrinsic peaks at the diffraction angles examined, which is typical of amorphous sample. PEG 6000 exhibited a distinct pattern with diffraction peaks at 2θ of 19.12, 23.504, revealing its crystalline nature. As expected, all major characteristic crystalline peaks for the drug were also observed in the SD and PM. These results indicated that ketoprofen was present in an unchanged crystalline state in the SD³⁷⁻³⁹.

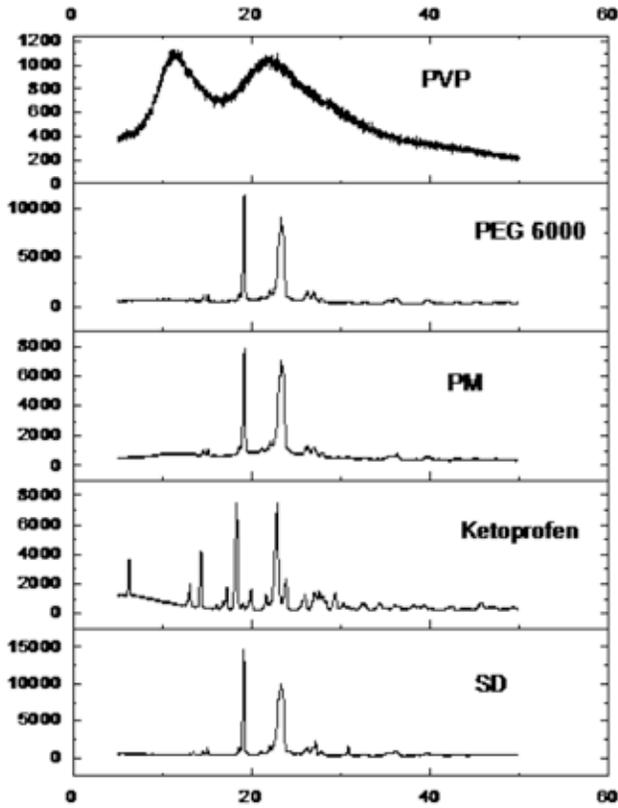


Figure 2. Powder X-ray-diffraction of PVP K30, PEG 6000, physical mixture (PM), pure ketoprofen and solid dispersion (SD).

Scanning electron microscopy (SEM)

SEM photomicrographs of solid dispersion shown in figure 3. On observing the SEM image of solid dispersion, the surface is observed as rough and flaky.

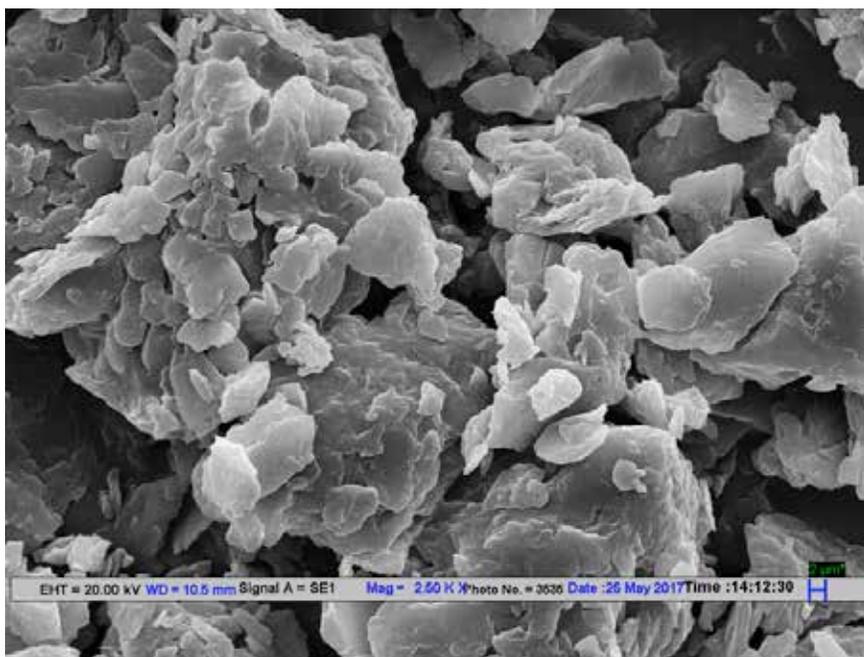


Figure 3. SEM photomicrograph of solid dispersion.

Differential scanning calorimetry (DSC)

DSC curves obtained for pure ketoprofen, physical mixture and solid dispersion are shown in figure.4. The thermogram of ketoprofen showed an endotherm onset of heating at 91.97 °C and end of melting point is 97.59 °C with heat of fusion (ΔH) 93.0185 J/g, corresponding to its melting point and indicating its crystalline nature. Interestingly, a sharp peak corresponding to the drug was also observed in both the PM and the SD, which in contrast to the thermogram seen with most SDs. It indicates the absence of strong interactions between the drug and the carriers during preparation of the SD. It also suggests that ketoprofen was present in an unchanged crystalline state in the SD. Thus, similar to the XRD findings, these result indicated that ketoprofen was present in an unchanged crystalline state in the SD⁴⁰. Our results suggest that the enhanced solubility of ketoprofen was not due to the transformation of the crystalline form into an amorphous state, but instead were due to the attachment of the carriers to the surface of poorly water-soluble ketoprofen, converting the hydrophobic drug to hydrophilic form in this solid dispersion.

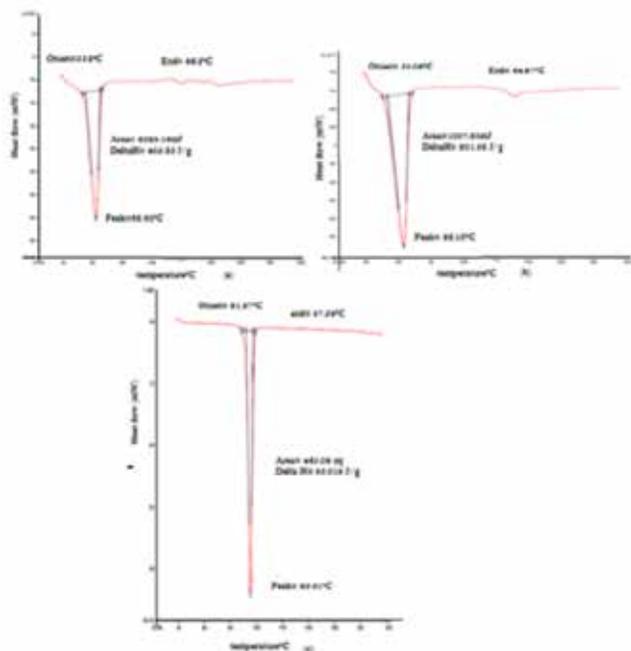


Figure 4. DSC Thermogram of SD (a), PM (b) and ketoprofen (c).

Solubility studies

The different batches of SD were prepared containing PEG 6000, PVP K-30 and ketoprofen as per the design protocol (Table 1). The pure ketoprofen dispensed a solubility of 14.4 µg/ml in water at room temperature whereas the physical mixture showed solubility of 23.8 µg/ml. The physical mixture presented solubility higher than the pure drug because of the polymers (PEG 6000 and PVP K-30) are present. However, the solid dispersion conferred solubility values ranging from 36.2-53.0 µg/ml. This increase may be due to formation of soluble complex between drug and polymers whereas the lower solubility in case of physical mixture as compared to SD may be explained on the basis of results obtained from DSC and XRD studies revealing that ketoprofen is still present in crystalline state.

Table 1. Solubility, in-vitro release, drug content and Gibb's free energy of different batches.

Batches	Conc. Of PEG 6000 (mg) (X_1)	Conc. Of PVP K-30 (mg) (X_2)	Solubility ($\mu\text{g/ml}$) (Y_1)	% release in 60 min. (Y_2)	Drug content (%)	Gibb's energy (KJ/mol)
SD1	1000	1000	36.2	77.89	86.4	-3
SD2	4000	1000	47.9	89.2	82.8	-4.3
SD3	1000	2000	36.9	78.76	95.3	-3.4
SD4	4000	2000	53.0	95.32	97.9	-5.7
SD5	1000	1500	35.7	76.74	88.9	-2.9
SD6	4000	1500	51.6	90.98	86.4	-4.2
SD7	2500	1000	40.8	81.34	86.4	-3.6
SD8	2500	2000	52.8	92.36	96.8	-4.9
SD9	2500	1500	45.8	87.4	86.2	-3.9
SD10	2500	1500	42.5	84.39	87.6	-3.1
SD11	2500	1500	42.9	86.74	87.8	-3.34
SD12	2500	1500	43.5	84.5	86.5	-3.2
SD13	2500	1500	44.7	86.12	88.0	-3.8
Ketoprofen			14.4	23.5		

Table 1 shows the results of solubility of different batches of solid dispersions prepared as per the design protocol. The responses generated were fitted into various polynomial models using experimental design. The response solubility was fitted best into quadratic model with square root transformation of the data. The adjusted polynomial equation obtained for the solubility (Y_1) shown in equation (1) with determination correlation (R^2) of 0.842.

$$Y_1 = 6.63 + 0.5330 X_1 + 0.2160 X_2 \quad (1)$$

Table 2 summarizes the results of ANOVA on the response surface model. The polynomial model was found to be significant ($p < 0.05$) with non-significant lack of fit ($p > 0.05$). The good correlation between the experimental and predicted response is indicated by higher value of R^2 (> 0.8). Adequate precision that measures the signal to noise ratio (17.58) was much above the required value of 4, indicating adequate signal and model fit to navigate the design space. Fig. 5 (a) display the combined effect of concentration of PEG 6000

& PVP K-30 on solubility. It can be inferred from the plots that there exists a curvilinear relationship between independent and dependent variables. It is inferred from the plot that higher level of polymers & ketoprofen results in increase in solubility.

To attain stability a natural tendency to acquire minimum Gibbs energy is always there. The plot of Gibbs free energy against varying concentration of polymers (PEG 6000 & PVP K-30) and ketoprofen (Fig. 5c) construed that the process is more favorable at higher level of polymers possessing minimum value of ΔG . Further, all the values of ΔG are negative (Table 1) at all levels of carrier demonstrating spontaneity of drug solubilization process.

$$\Delta G = -3.51 - 0.8167X_1 - 0.5083X_2 - 0.2500X_1X_2 + 0.0431X_1^2 - 0.6819X_2^2$$

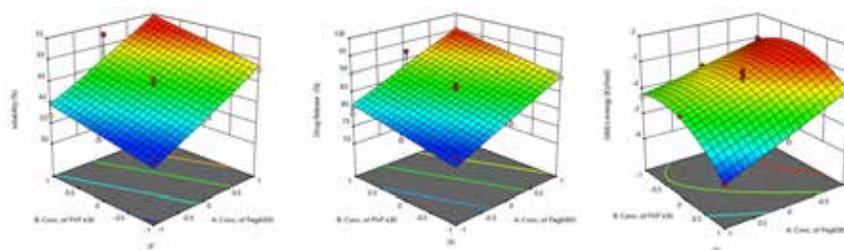


Figure 5. (a,b,c) Response surface plots showing effect of concentration of PEG 6000 & PVP

K-30 on solubility (Y_1), *in-vitro* release (Y_2) and Gibbs free energy.

***In vitro* drug release**

Table 1 shows the *in vitro* drug release data at 60 min. From these results, it is observed that only 23.5% of ketoprofen was released in 1 hour from drug solution and 75.4% from the PM whereas different batches of SD show 76.74 to 95.32% release of ketoprofen in 1hr study. The polynomial equation obtained for the dependent variable Y_2 (*in vitro* release) is shown in equation (2).

$$Y_2 = 85.52 + 7.02X_1 + 3.00X_2 \quad (2)$$

Table 2 summarizing the results of ANOVA on response surface model (fitted best in cubic model after none transformation of the data). The responses generated were fitted into various polynomials models using the experimental design. It was observed that response *in vitro* release (Y_2) fitted best into cubic response surface model.

Table 2. Model summary statistic

Model						Lack of Fit	
Response factor (Y)	F-value	Prob.>F	R ²	Adeq. Prec.	C.V (%)	F-value	Prob.>F
Y1	33.27	<0.0001	0.84	17.95	2.69	4.41	0.086
Y2	40.89	<0.0001	0.86	20.17	2.42	3.28	0.135

The polynomial model was found to be significant ($p < 0.05$) with non-significant lack of fit ($p > 0.05$). The higher value of R^2 (> 0.9) pertinent good correlation between the experimental and predicted response. Adequate precision that estimates the signal to noise ratio (20.17) was much above the required value of 4, indicating adequate signal and model fit to navigate the design space. Figure 5 (b) display the combined effect of concentration of PEG 6000 & PVP K-30 on % release that exhibited a linear relationship between independent and dependent variables, suggested that higher level of PEG 6000 & PVP K-30 favours the expedited release. The numerical optimization tool using desirability approach was employed to prepare solid dispersion. The optimization of independent variables was done with constraints of maximum solubility and maximum % release.

The optimization of independent variables was done with constraints of maximum solubility and maximum % release. The parameters suggested by the design were concentration of PEG 6000 (0.993%) & concentration of PVP K-30 (0.985%) that provide SD with solubility of 54 $\mu\text{g}/\text{ml}$ (predicted value 54.23 $\mu\text{g}/\text{ml}$) and % release 95.43% (predicted value 95.87 %). The closer agreement between predicted and observed values indicated the high prognostic ability of the model. Figure 6 displays the in vitro release profile of ketoprofen as pure drug and from the optimized batch of formulation.

A numerical optimization tool of design expert software was used further for calculating the optimal concentration of PVP K-30 and PEG 6000 for preparation of solid dispersion. The optimal calculates parameters were found to be concentration of PEG 6000(4000 mg) and concentration of PVP K-30(2000 mg) which provided us with the drug release is 95.32 %.

The optimized batch of ketoprofen containing solid dispersion of PVP K-30 and PEG 6000 was found to batch no. 4 (optimized batch) and drug release is 95.32 % of the drug.

It is clearly observed that the dissolution rate of pure ketoprofen is low because 23.5% of drug dissolved in 60 min. The resultant study showed that the dis-

solution of drug from physical mixture was improved (75.4 %) but the Solid dispersion from resulted in a marked increase of ketoprofen dissolution (95.32 %) compare to physical mixture at the end of 1 hr. Typical mechanism for improvement of dissolution characteristics of drug via solid dispersion are particle size reduction, and improved wettability and dispersibility of ketoprofen due to surface tension lower effect of PVP K-30.

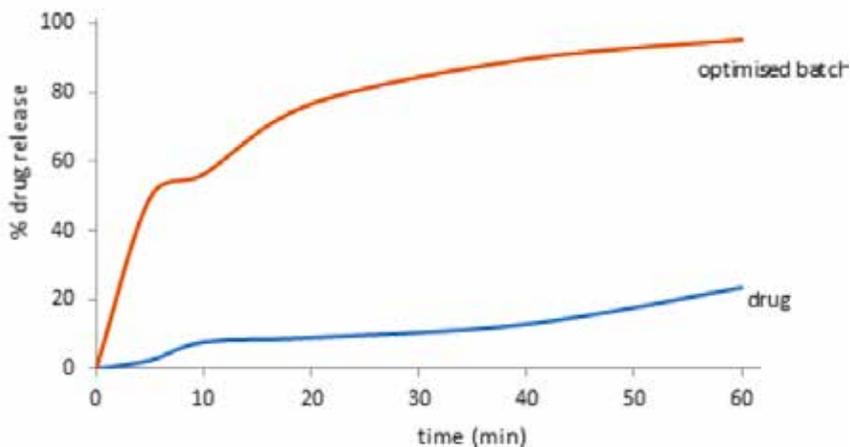


Figure 6. *In vitro* release profile of drug (pure ketoprofen) and solid dispersion (optimized batch).

The release of ketoprofen from solid dispersion was fitted into various kinetic models to estimate their release kinetics and mechanism of release. The results of release rate data for the formulation fitted best into Higuchi model ($R^2 = 0.917$, $n=1.02$) of release kinetic. Further, the value of 'n' >1.0 indicates that the release of ketoprofen from solid dispersion occurs by super-case-2 transport that is the release occurred by relaxation or erosion of polymer after swelling in biological fluid.

Hot melt method is a fast and simple technique for preparing solid dispersion. The solubility and dissolution rate of ketoprofen from solid dispersion with PVP K-30 and PEG 6000 was markedly increased in comparison to pure ketoprofen and physical mixture. As it is revealed from the DSC and PXRD spectra that ketoprofen is in present in crystalline form but the dissolution rate has been increased. Our results suggest that the enhanced solubility of ketoprofen was not due to the transformation of the crystalline form into an amorphous state, but due to the attachment of the carriers to the surface of poorly water-

soluble ketoprofen, converting the hydrophobic drug to hydrophilic form in the solid dispersion. The higher dissolution rate of ketoprofen in SD was therefore attributed to improved wetting of crystal surface mainly due to presence of PEG 6000 and PVP K-30 particles, which provoked the solubilization effect. In conclusion, this surface-attached ketoprofen-loaded SD would be of use for delivering poorly water-soluble ketoprofen with enhanced solubility and dissolution, but without crystalline changes.

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