

Enhanced Solubility and Drug Release of Ketoprofen Using Lyophilized Bovine Serum Albumin Solid Dispersion

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ABSTRACT

Solid dispersions have been proved to be an effective method for the improvement of solubility and bioavailability of poorly water-soluble drugs. The study was designed to demonstrate the potential of ketoprofen loaded BSA solid dispersions on the solubility & *in-vitro* release of ketoprofen.

Ketoprofen-BSA solid dispersions were prepared by the freeze-drying method. A 2-factor, 3-level central composite experimental design was used to study the effect of varying concentration of BSA and ketoprofen on drug solubility & *in-vitro* drug release.

The combined effect of concentration of BSA & ketoprofen on % release and solubility exhibited a linear relationship between independent and dependent variables, suggesting that higher level of BSA & ketoprofen favours the expedited release and solubility.

Bovine serum albumin may be explored as a carrier for the preparation of solid dispersion for the enhancement of solubility and *in-vitro* drug release of BCS class II drug ketoprofen.

Keywords: Bovine serum albumin, Ketoprofen, Solid dispersion, Lyophilization.

INTRODUCTION

Biopharmaceutical classification system (BCS) divided the active pharmaceutical ingredient into four classes (I, II, III, IV) based on their solubility in water and membrane permeability. In recent years class II drugs (having low solubility & high permeability) have appeared oft times as candidate compound for development in drug discovery stage¹. Various techniques including cyclodextrins complexes², nanoparticle technology³, self emulsifying drug deliv-

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ery systems (SEDDS)⁴, liposomes⁵, salt formation⁶, use of surfactant “micelization”⁷, amorphisation⁸ and solid dispersion etc., have been attempted to overcome the poor solubility issues. Nowadays, solid dispersion has become the synonym for the solubility enhancement of poorly water-soluble drugs. Solid dispersion of poorly soluble drugs in water soluble carriers to improve the solubility and dissolution was reported decades ago⁹. Since then, the solid dispersion is explored colossally. Solid dispersion as group of solid products made up of both hydrophilic matrix and hydrophobic drug. The matrix can be either amorphous or crystalline¹⁰. For the improvement of bioavailability and dissolution rate of poorly water-soluble drugs use of various hydrophilic carriers like polyethylene glycol (PEG)¹¹, hydroxypropylmethyl cellulose (HPMC)¹², polyvinylpyrrolidone (PVP)¹³, hydroxypropyl cellulose¹⁴, hydroxypropylmethyl cellulose phthalate¹⁵, gums¹⁶, sugar¹⁷, mannitol¹⁸, urea¹⁹, gelucires²⁰, eudragits²¹, chitosan²², sodium starch glycolate²³ and pregelatinized starch etc. has been investigated vastly²⁴.

Bovine serum albumin (BSA) also known as “Fraction V” is a serum albumin protein derived from cows is the most abundant protein in plasma that is also extensively used in pharmaceutical industry because of its low cost, ease of purification, biocompatibility and biodegradability and also due to its chemical similarity to human albumin²⁵. BSA plays the role of an “*in-vivo* solubilizing agent” that enables the solubilisation of a wide range of biomolecules and drugs in plasma (a hydrophilic medium)^{26,27}. Albumin has varied physiological functions like maintaining plasma osmotic pressure and neutralising free radicals^{28,29}. The solubility enhancement properties of albumin are generally due to its incredible ability to form reversible binding complexes with ligands mainly by hydrophobic and electrostatic interaction^{26,30}. This makes the bound molecule to flow in the blood at a higher concentration than its initial solubility. It possesses overall negative charge at physiological pH that endorses the binding of anionic molecules (weak acids) & hydrophobic molecules^{27,30}. Moreover, it also contains a no. of free amino and carboxyl groups amenable to form highly soluble salts with acidic or basic drugs, respectively. This exceptional capacity of albumin to dissolve poorly soluble drugs is explored in this piece of research.

The aim of present study is to predominantly investigate the use of BSA as a carrier for solubility enhancement of ketoprofen. Ketoprofen is a non-steroidal anti-inflammatory drug belonging to class II that is having aqueous solubility of 0.5µg/ml. Ketoprofen binds with albumin molecule as its chemical structure is adaptable to form salt bridges with albumin amino groups. In this study, solid dispersion is prepared by freeze-drying or lyophilization technique. Ketoprofen-BSA solid dispersions are characterized by Fourier transform infrared

spectroscopy (FT-IR), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) studies. In addition, the solubility and *in-vitro* release profile of ketoprofen are also evaluated.

METHODOLOGY

Materials

Ketoprofen was obtained as a gift sample from Infinity Laboratories, Behra (India). Bovine serum albumin (BSA), ethanol, sodium chloride, potassium chloride, di-sodium hydrogen orthophosphate, potassium di-hydrogen orthophosphate was procured from Hi-Media lab. Pvt. Ltd. All other chemicals & reagents used in the study were of analytical grade and used as received.

Preparation of freeze dried solid dispersion

Ketoprofen (0.1-0.5% w/v in aqueous ethanol) was added to BSA (0.1-2% w/v) that results in the formation of colloidal solution or colloidal suspension depending on the concentration of ketoprofen. The resulting solution/suspension was kept at -80°C for 4hrs and lyophilized for 48hrs in a lab scale lyophilizer.

Experimental design

A 2-factor, 3-level central composite experimental design was used to prepare solid dispersions. Based on preliminary trials, concentration of BSA (X_1) & concentration of ketoprofen (X_2) were selected as independent variables while solubility (Y_1) & *in-vitro* release (Y_2) were selected as the dependent variables (Table 1). The experimental design and statistical analysis of the data was carried out as per the design protocol by using Design Expert Software (Version 11).

Determination of drug content

The different solid dispersion (SD) batches and physical mixture (PM) equivalent to 10mg of ketoprofen were dissolved separately in 25 ml of phosphate buffer (pH 7.4). The solution was filtered and further diluted appropriately. Samples were filtered through 0.45µm milipore filters and analyzed by UV-visible spectrophotometer at 260nm.

Characterisation

Fourier Transform Infrared Spectroscopy (FT-IR)

Fourier Transform Infrared Spectroscopy was used to detect interaction between drug and carrier. FTIR spectral analysis of ketoprofen, BSA, PM and SD were done by FT-IR (FT-IR Spectrophotometer Perkin-Elmer BX II) in the range of 4000–400 cm^{-1} using KBr pellets.

X-ray diffraction analysis (XRD)

The X-ray diffractometry was carried out for phase identification of the materials. The XRD spectra of ketoprofen, BSA, PM and SD were carried out using an X-ray diffractometer (Miniflex 2, Rigaku, Japan) at room temperature and at 30kV. The scanning diffraction angle (2θ) ranged from 0° to 80° .

Differential scanning calorimetry (DSC)

Differential scanning calorimetric thermogram of ketoprofen, BSA, PM and SD were recorded using differential scanning calorimeter (SDT Q600 V20.9 Build 20 TA instrument, USA) in the temperature range of (25°C – 300°C) at a heating rate of $10^\circ\text{C}/\text{min}$ in nitrogen atmosphere.

Scanning electron microscopy (SEM)

The shape and surface morphology of SD were examined using scanning electron microscope (JSM-6100 scanning microscopy, Japan) The sample were coated with gold and mounted on aluminium stub containing double adhesive carbon tape. The photographs were taken at acceleration voltages of 10 kV.

Solubility

The solubility of ketoprofen drug was determined by taking pure drug, PM and solid dispersion equivalent to 10 mg ketoprofen in 10 ml of distilled water and was kept for 48hrs on shaker at room temperature (25°C). The obtained solution was filtered by $0.45\mu\text{m}$ milipore filter paper and the drug content was determined by taking absorbance using UV-Visible Spectrophotometer at 260 nm. The amount of ketoprofen was calculated using the calibration curve in water. The Gibbs free energy of transfer (ΔG) of ketoprofen from pure water to the aqueous solution of carrier was also calculated as

$$\Delta G = -2.303RT \log S_o/S_s$$

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 μ m milipore filters and analyzed by UV-visible 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 plots.

RESULTS AND DISCUSSION

The BSA-Ketoprofen solid dispersions were prepared using 2-factor, 3-level central composite experimental design using concentration of BSA (X_1) and ketoprofen (X_2) as independent variable. Solubility (Y_1) and % release (Y_2) were chosen as dependent or response variables.

Drug content of formulations

Ketoprofen assay data for content uniformity of the drug in different batches of SD and PM are given in Table 1. From the data it is clearly indicated that the drug content in the formulated batches of SD and PM was within the range of the theoretical amount, indicating the method used for formulation was suitable and reproducible in nature.

Fourier Transform Infrared Spectroscopy (FT-IR)

Figure 1 exhibits the FTIR spectra of ketoprofen, BSA, SD and PM in the frequency region from 4000 to 450 cm^{-1} . The spectra of ketoprofen showed characteristic absorption band at 2979.54 cm^{-1} due to -CH stretching. The peak appearing at 1653.74 cm^{-1} can be ascribed to -C=O stretching, while peak appearing at 1598.70 cm^{-1} is due to -C=C stretching. The absorption band at 1445.03 cm^{-1} and 866.30 cm^{-1} can be attributed to -C-C deformation and -CH deformation for substituted aromatic (out of plane), respectively. The spectra of Bovine serum albumin (BSA) present the characteristic absorption band of -NH bending vibration appearing at 3407.98 cm^{-1} , peak of -C=O stretching vibrations of the peptide bond (amide I band) appeared at 1651.51 cm^{-1} while peak appearing at 1546.85 cm^{-1} can be ascribed to -NH bending vibration / -CN stretching vibration (amide II band). The peak at 1239.16 cm^{-1} may be due to -CN stretching vibration / -NH bending vibration (amide III band). The spectra of SD revealed the characteristic peak appearing at 2962.52 cm^{-1} that can be ascribed to -CH stretching, the peak at 1654.55 cm^{-1} may be attributed to -C=O stretching while the peak at 1541.32 cm^{-1} is attributed to -C=C stretching and peaks appearing at 827.97 cm^{-1} , 703.55 cm^{-1} and 619.18 cm^{-1} are of fingerprint region. The spectra of PM revealed that the characteristic peak appearing at 2930.49 cm^{-1} can be ascribed to --CH stretching, the peak at 1656.27 cm^{-1} may be attributed to -C=O stretching, while the peak at 1534.82 cm^{-1} is attributed to -C=C stretching and peaks at 968.27 cm^{-1} , 827.92 cm^{-1} , 717.55 cm^{-1} and

618.92 cm^{-1} are of fingerprint region. The characteristic peaks of ketoprofen also seen in the SD and PM that indicate that ketoprofen is present in the solid dispersion and physical mixture.

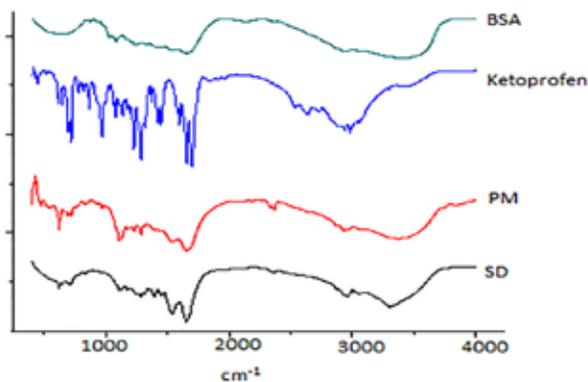


Figure 1. FT-IR spectra of ketoprofen, bovine serum albumin (BSA), physical mixture (PM) and solid dispersion (SD).

X-ray diffraction analysis (XRD)

The solid state of ketoprofen in the solid dispersion was examined using XRD (Figure 2). The XRD spectra of BSA is of typical amorphous material whereas the ketoprofen showed characteristics sharp peaks at 18.35°C and 23.069°C 2θ owing to its crystallinity. The X-Ray diffractogram of PM showed certain peaks corresponding to crystalline ketoprofen. However, XRD spectra of BSA-ketoprofen solid dispersion contain no sharp peaks thus unveiling amorphous characteristics of the final product.

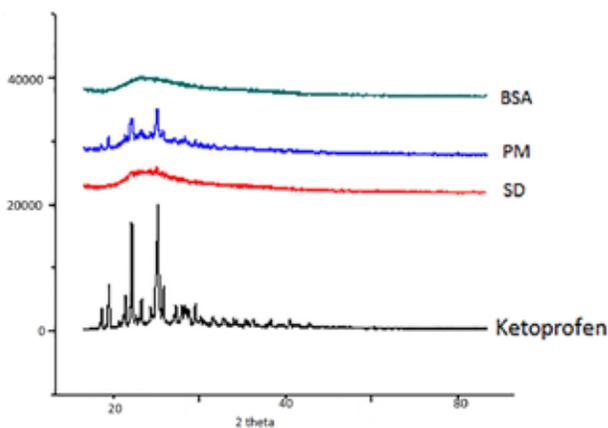


Figure 2. XRD spectra of bovine serum albumin (BSA), physical mixture (PM), solid dispersion (SD) and ketoprofen.

Differential scanning calorimetry (DSC)

Figure 3 displays the DSC thermogram of ketoprofen, solid dispersion (SD), physical mixture (PM) and bovine serum albumin (BSA). The thermogram of BSA appeared as broad peak at 94.26°C that is of typical amorphous material. The thermogram of ketoprofen showed a sharp peak at 93.08°C that corresponds to its melting point. A peak with decreased intensity at around 99.58°C is also seen in BSA-Ketoprofen physical mixture indicating the crystalline state of drug in the physical mixture. However, amorphous property of the solid dispersion can be inferred from the broad endotherm and disappearance of sharp peak in thermogram of SD.

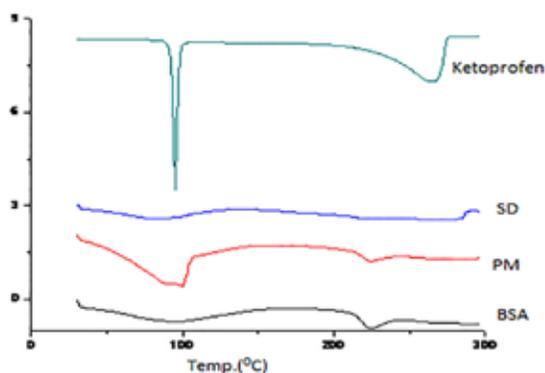


Figure 3. DSC thermogram of ketoprofen, solid dispersion (SD), physical mixture (PM) and bovine serum albumin (BSA)

Scanning electron microscopy (SEM)

Figure 4 exhibits the scanning electron micrograph showing surface morphology of solid dispersion. The SEM micrograph of SD shows irregular structure with porous and rough surface.

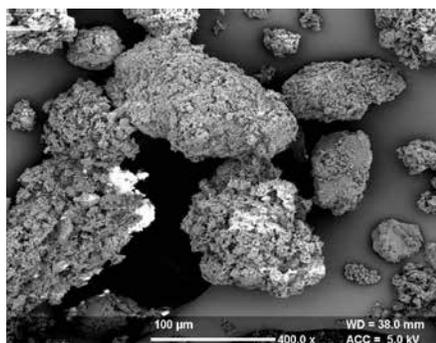


Figure 4. SEM photomicrographs of solid dispersion

Solubility

The different batches of SD were prepared containing BSA (1-2%) and ketoprofen (0.1-0.5%) as per the design protocol (Table 1). The pure ketoprofen dispensed a solubility of 18.79 µg/ml in water at room temperature whereas the physical mixture showed solubility of 34 µg/ml. The physical mixture presented solubility higher than the pure drug because of the BSA. However, the solid dispersion conferred solubility values ranging from 38-58 µg/ml. This increase may be due to formation of soluble complex between drug and BSA 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.

Batch	Conc. Of BSA (%) (X_1)	Conc. Of ketoprofen (%) (X_2)	Solubility (µg/ml) (Y_1)	% release in 60 min. (Y_2)	Drug content (%)	ΔG (KJ/Mol)
SD1	1	0.5	43±0.8	77.81±0.1	97.78±0.14	-1.8
SD2	1.5	0.3	51±0.25	89.67±0.1	98.17±0.08	-2.2
SD3	2	0.3	56±0.28	92.5±0.1	99±0.2	-2.4
SD4	1.5	0.3	51±0.25	85.44±0.21	97.89±0.61	-2.2
SD5	1.5	0.3	53±0.3	86.18±0.1	97.96±0.3	-2.3
SD6	1	0.3	40±0.1	76.33±0.23	97.39±0.2	-1.7
SD7	2	0.5	58±0.22	93.2±0.2	99.42±0.16	-2.5
SD8	1.5	0.3	5±0.6	88.37±0.17	98.05±0.1	-2.3
SD9	1.5	0.5	54±0.32	91.11±0.1	98.21±0.1	-2.3
SD10	1.5	0.1	47±0.71	80.11±0.3	97.56±0.25	-2.0
SD11	1	0.1	38±0.20	72.24±0.1	97±0.28	-1.5
SD12	2	0.1	48±0.16	85.21±0.28	97.88±0.22	-2.1
SD13	1.5	0.3	50±0.28	86.33±0.16	98.01±0.11	-2.2
PM	2	0.5	34±0.49	42±0.22	98.34±0.18	-1.3
Ketoprofen			18.79±0.29	26±0.17		

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 none transformation of the data. The adjusted polynomial equation obtained for the solubility (Y_1) shown in equation (i) with determination correlation (R^2) of 0.9740.

$$Y_1 = 51.62 + 6.83X_1 + 3.67X_2 + 1.25X_1X_2 - 3.6X_1^2 - 1.17X_2^2 \quad (i)$$

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 (> 0.9). Adequate precision that measures the signal to noise ratio 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 BSA & Ketoprofen 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 BSA & 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 BSA and ketoprofen (Fig. 5c) construed that the process is more favorable at higher level of BSA and ketoprofen 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.

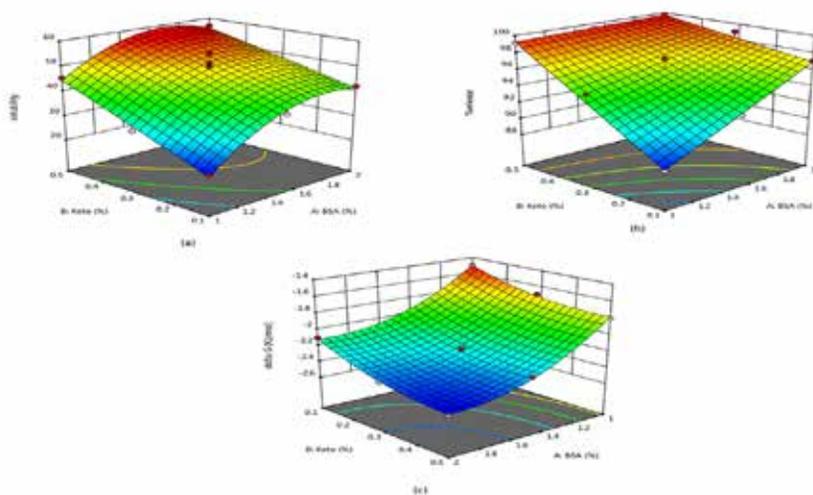


Figure 5. (a, b, c) Response surface plots showing effect of concentration of BSA & Ketoprofen on solubility (Y_1), *in-vitro* release (Y_2) and Gibb's free energy.

***In vitro* drug release**

Table 1 shows the *in vitro* drug release data at 60 min. From these results, it is observed that only 26% of ketoprofen was released in 1 hr from drug solution and 42% from the PM whereas different batches of SD show 72.24 to 98.2% release of ketoprofen in 1hr study. The higher percentage release of drug in case of SD as compared to pure drug and PM may be related to the solubility data. As previously mentioned that the BSA form the soluble complex with the drug and thus increasing drug wettability and leads to a better solubility and thus better rate of drug release.

The polynomial equation obtained for the dependent variable Y_2 (*in vitro* release) is shown in equation (ii)

$$Y_2 = 87.30 + 7.42X_1 + 4.09X_2 + 0.605X_1X_2 - 3.13X_1^2 - 1.93X_2^2 \quad (\text{ii})$$

Table 2 summarizing the results of ANOVA on response surface model (fitted best in quadratic 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 quadratic response surface model.

Table 2. Model summary statistic

Response factor	Model					Lack of fit	
	F-value	Prob.>F	R ²	Adeq. prec.	C.V. (%)	F-value	Prob.>F
Y_1	52.36	< 0.0001	0.9740	24.2411	2.58	0.7745	0.5659
Y_2	34.42	< 0.0001	0.9609	20.0699	1.99	0.8202	0.5467

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 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 BSA & ketoprofen on % release that exhibited a linear relationship between independent and dependent variables, suggested that higher level of BSA & ketoprofen 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

parameters suggested by the design were concentration of BSA (1.950%) & concentration of ketoprofen (0.480%) that provide SD with solubility of 58 µg/ml (predicted value 58.159 µg/ml) and % release 93.2% (predicted value 94.05%). 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 optimised batch of formulation.

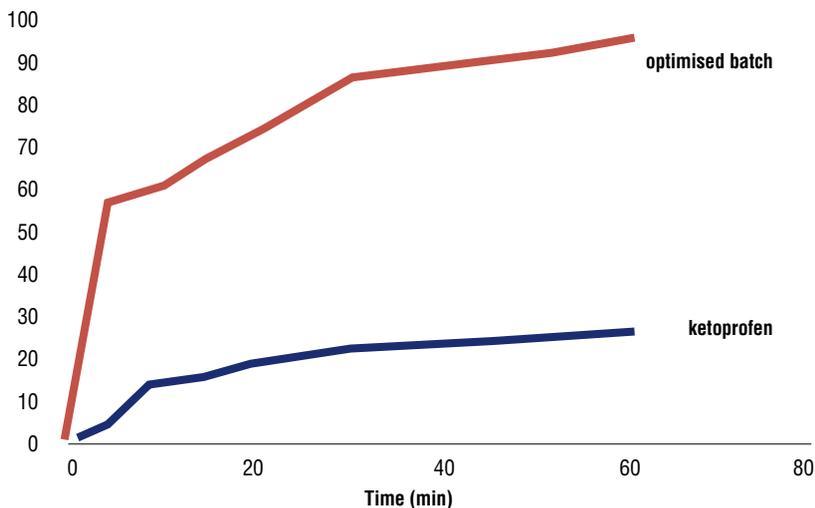


Figure 6. *In vitro* release profile of pure ketoprofen and solid dispersion (optimized batch).

CONCLUSION

The solid dispersion has been the synonym for the enhancement of solubility of poorly water-soluble drugs. In this study, Bovine serum albumin (BSA) is used as solubility enhancer of ketoprofen (a model drug). The solid dispersion containing BSA and ketoprofen was prepared using 2-factor-3-level central composite experimental design. The preparation of SD was characterized by FT-IR, XRD, DSC and SEM studies. The DSC and XRD studies demonstrated the amorphous nature of the solid dispersion. Thereby, solid dispersion exhibited a fast release and enhanced solubility as compared to pure drug and physical mixture. Thus, overall study rendered the suitability of lyophilized BSA solid dispersion in improving the solubility of poorly water-soluble drug.

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