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Research Article

SOLUBILITY AND DISSOLUTION IMPROVEMENT OF KETOPROFEN BY SOLID DISPERSION IN POLYMER AND SURFACTANT USING SOLVENT EVAPORATION METHOD

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ABSTRACT

Ketoprofen is a propionic acid derivative non-steroidal anti-inflammatory drug. It is widely used in the management and treatment of patients with rheumatic disease, but its poor water solubility can give rise to formulation problems and reduce its therapeutic efficiency and bioavailability. The present project was designed to improve solubility and dissolution of ketoprofen. Various solid dispersions formulas of ketoprofen were prepared by solvent evaporation method using mannitol, Urea, PVP K30, and Tween 80 as carriers to enhance solubility of compound. These formulations were evaluated for drug content, phase solubility, and *in vitro* dissolution. Evaluation by Deferential Scanning Calorimetry (DSC) and Fourier Transformer Infra Red (FTIR) revealed no chemical interaction between the drug and its carriers. All formulas showed marked improvement in solubility behavior and drug release in the following order PVP K-30> urea>mannitol. Formulation (F12) containing ketoprofen: PVP K-30: Tween 80 ratio of 1:3:1 showed best release (95.0%) compared to 23.20 % for the pure drug at 5 minutes. In conclusion, solid dispersion of ketoprofen in polymer with surfactant properties (formulation-F12) can be utilized to improve solubility and release of ketoprofen oral solid dosage form.

Keywords: Ketoprofen, Solid dispersion, Solubility, Dissolution

INTRODUCTION

Ketoprofen is a potent and safe propionic acid derivative non-steroidal anti-inflammatory drug (NSAID) with good analgesic properties widely used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gouty arthritis. However, it has poor water solubility (0.13 mg mL^{-1} at 25°C) which may predispose to formulation problems and limit its therapeutic applications and bioavailability [1]. Many methods have been investigated for enhancing the dissolution properties of poor water soluble drugs and possibly their bioavailability; solid dispersion in water-soluble carriers has attracted considerable interest in this respect and has often been successfully applied [2,3]. Solid dispersions of many poorly water soluble drugs by incorporating them into a water-soluble polymer matrix have been considered as an effective method for improving drug dissolution rate and their saturation solubility in the gastrointestinal fluid [4]. Solid-dispersion strategy has been also experimented also for formulation of ketoprofen, and various carriers have been tested [5,6]. However, at present, no marketed products of ketoprofen produced by this approach are available, probably because of the unsatisfactory performance of the studied systems [7,8]. Polyvinyl pyrolidon (PVP) is well tolerated physiologically, readily soluble in water and has been used for increasing the solubility and dissolution of poorly soluble drugs [9]. While urea is a hydrating agent capable to form solid dispersion and improves solubility and dissolution of poorly soluble drugs [10], mannitol is one of the common hydrophilic carriers used in the preparation of solid dispersions [11,12]. Recent investigations have shown that formulation of ternary solid dispersions by using suitable carrier combinations or by adding an appropriate third component, such as a hydrophilic surfactant, can give rise to a further improvement in drug dissolution properties with respect to the corresponding binary systems [13,14]. Accordingly, the present was designed to enhance solubility and dissolution of ketoprofen using solid dispersion in polymer alone or in combination with Tween 80 as surfactant.

MATERIALS AND METHODS

Preparation of solid dispersions of Ketoprofen

Accurately weighed quantities of ketoprofen (KP) (3B pharmachem, Wuhan international, China) and the carriers PVP-K30 (Sinopharma Chem. Reagents, China), mannitol and urea (BDH, Pool, England), or Tween-80 (Merck, Schuchardt, Germany) in different proportions, as shown in table 1, were dissolved in methanol, followed by evaporation of solvent using rotary evaporator (Buchi, Switzerland) thermostated at 40°C. The solidified mass obtained in each case was scraped, crushed, pulverized, and passed through an 80-mesh sieve. All the solid dispersions were preserved in well-closed glass containers in desiccators under vacuum (about 20 mmHg) at 18-20°C for 2 days.

Table 1: Formulas composition of ketoprofen solid dispersions

Formula	Ratio of drug: polymer: surfactant (weight proportion)				
	Ketoprofen	Mannitol	Urea	PVP-k30	Tween-80
F1	1	1	-	-	-
F2	1	2	-	-	-
F3	1	3	-	-	-
F4	1	-	1	-	-
F5	1	-	2	-	-
F6	1	-	3	-	-
F7	1	-	-	1	-
F8	1	-	-	2	-
F9	1	-	-	3	-
F10	1	-	-	4	-
F11	1	-	-	6	-
F12	1	-	-	3	1

Solubility studies

Solubility studies of KP were carried out to evaluate the possible solubilizing effect of the carrier by adding an excess of drug (20 mg) to 10 ml of aqueous solutions containing increasing concentrations of carrier (1:0,1:1, 1:2,1:3, 1:4,1:6 and 1:8) in sealed glass containers maintained under stirring (Rotary shaker, GFL, Germany) at constant temperature (20°C) until equilibrium (2 days). Also the prepared solid dispersions were subjected to solubility study; drug concentration was determined spectrophtometrically at 260 nm (Cecil CE 7200, England).

Dissolution studies

Dissolution experiments were performed using USP paddle (Pharmatest, Germany) method by dispersed powder technique in 900 ml of artificial gastric medium (0.1N HCl) thermostated at 37±0.5°C [15], with a paddle rotation speed of 50 rpm. Powdered samples of each preparation equivalent to 50mg of KP were added to the dissolution medium. At appropriate time intervals, 5 ml of the mixture was withdrawn and filtered, and assayed for KP content by UV spectrophotometer at 260 nm. Percent dissolution efficiency (%DE) was computed to compare the relative performance of various carriers in solid dispersion formulations [16]. The magnitude of %DE (%DE t min) for each formulation was computed as the percent ratio of area under the dissolution curve up to the time (t) to that of the area of the rectangle described by 100% dissolution at the same time.

Differential Scanning Calorimetry (DSC)

Thermal analyses were performed using differential scanning calorimeter (DSC-6, Perkin-Elmer, USA) under nitrogen flow of 20 ml/min; approximately 2 mg of KP, PVP, and solid dispersion was placed in a sealed aluminum pan and heated at a scanning rate of 10°C/min from 30°C to 220°C.

Kinetic modeling of drug release

To analyze mechanism of KP release from the selected formula, the *in vitro* release data were fitted into various release kinetic models: first order, zero order, Higuchi, and Korsmeyer and Peppas models; the model with the highest correlation coefficient was considered to be the best model. First order kinetic (log M_t=log M_o+k_1 t/2.303), Zero order kinetic ($Mt=M_o+K_ot$), Higuchi model ($M_t/M\infty=k_Ht^{1/2}$), Korsmeyer-Peppas model (Power Law-$M_t/M\infty=K_{KP}$ t^n, log [$M_t/M\infty$]=log K_{KP}+n log t), where M_t is the amount of drug released in time *t*, M_0 the initial amount of drug, M_∞ is the cumulative amount of drug released at infinite time, *K* is respective release constant and *n* is the release exponent, which characterizes the mechanism of drug release. Korsmeyer and Peppas equation superposes two apparently independent mechanisms of drug transport, Fickian diffusion and a case-II transport for the description of drug release from a swelling polymer [17-21].

Statistical analysis

One way analysis of variance and the Student's t-test were used to determine the presence of any significant differences (P<0.05) among the test groups.

RESULTS AND DISCUSSION

Solubility studies revealed a linear increase of drug solubility in the presence of increasing concentrations of carrier (Figures 1, 2, and 3) as described by A_L type solubility diagram [22,23].

Similar results have been recorded about many drugs using hydrophilic polymers, due to formation of soluble complexes and/or co-solvent effect of carrier [13]. This can be explained on the bases of formation of intermolecular hydrogen bonds between drug and polymer. The effectiveness of the tested polymers varied in the order PVP>Urea>Mannitol (Figure 4).

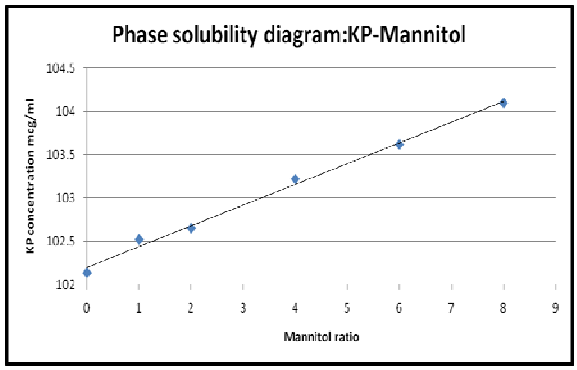

Fig. 1: Ketoprofen (KP) Phase-solubility diagrams in aqueous solutions at 20 °C in the presence of mannitol

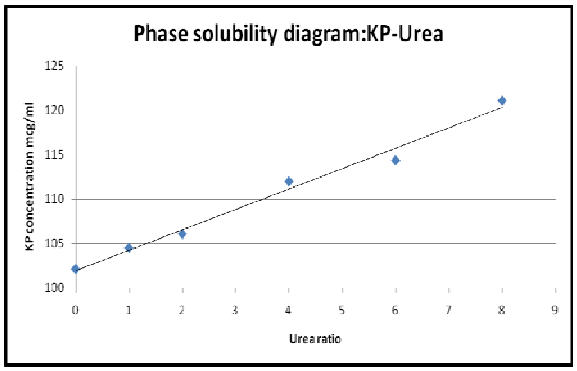

Fig. 2: Ketoprofen (KP) phase-solubility diagrams in aqueous solutions at 20 °C in the presence of urea

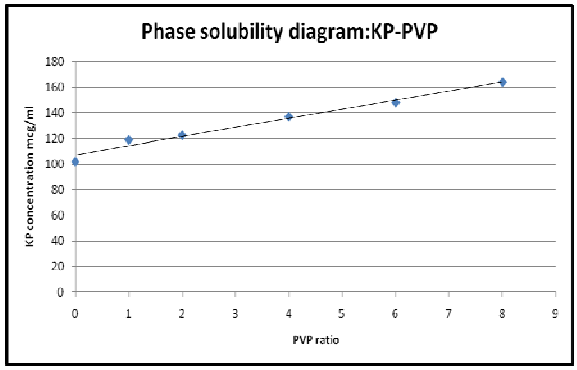

Fig. 3: Ketoprofen (KP) phase-solubility diagrams in aqueous solutions at 20 °C in the presence of PVP

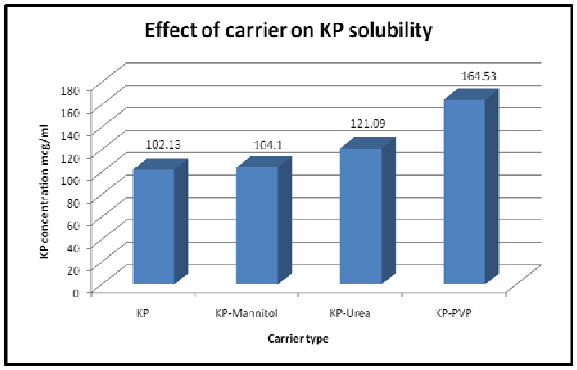

Fig. 4: Solubility of Ketoprofen (KP) in aqueous solutions at 20 °C in ratio of drug: carrier 1:8 as physical mixture

The ratio of the molar solubility of ketoprofen in carrier solution (Ss) and the molar solubility of the drug in solution (Sw) can be considered as a partitioning ratio. Therefore, the Gibbs free energy of transfer (ΔG_t) from the solution to the carrier solution can be calculated as: ΔG_t = -RTln (Ss/Sw). Table 2 represents the thermodynamic parameters associated with the solubility of ketoprofen in the presence of different carriers. The Gibbs free energy values provide the information whether the reaction condition is favorable or unfavorable for drug solubilisation in the carrier. Negative Gibbs free energy values indicate favorable conditions; as shown in table 2, Gibbs free energy values were negative indicating the spontaneous nature of the drug solubilisation. The values decreased by increasing carrier concentration, demonstrating that the reaction more favorable as the concentration of carrier increased. The presence of PVP markedly increased the solubility of the drug. The results of aqueous solubility studies of KP from the prepared solid dispersions formulas are compatible with the results of phase solubility of drug; where the carrier, as physical mixture; produce the same rank of effect PVP>Urea>Mannitol.

Table 2: The values of Gibbs free energy of transfer for the solubility process of ketoprofen -carrier physical mixture

Ratio of drug: polymer physical mixture (weight proportion)				ΔG_t cal
Ketoprofen	**Mannitol**	**Urea**	**PVP30K**	
1	1	-	-	-799.361
1	2	-	-	-800.099
1	4	-	-	-803.323
1	6	-	-	-805.575
1	8	-	-	-808.265
1	-	1	-	-810.5
1	-	2	-	-819.2
1	-	4	-	-850.9
1	-	6	-	-863
1	-	8	-	-896.3
1	-	-	1	-886.684
1	-	-	2	-903.83
1	-	-	4	-969.341
1	-	-	6	-1014.45
1	-	-	8	-1074.77

Moreover, the addition of surfactant to the system (F12) further increases the solubility of KP (Figure 5). Figures 6 and table 3 showed the results of dissolution studies in terms of percent drug dissolved and dissolution efficiency of pure KP and from solid dispersions include PVP as polymer alone or with Tween 80 significantly improve drug dissolution properties obtained from the solid dispersion in PVP than the corresponding pure KP, and also significant improvement in dissolution properties was reported after incorporation of surfactant with PVP in formula (F12).

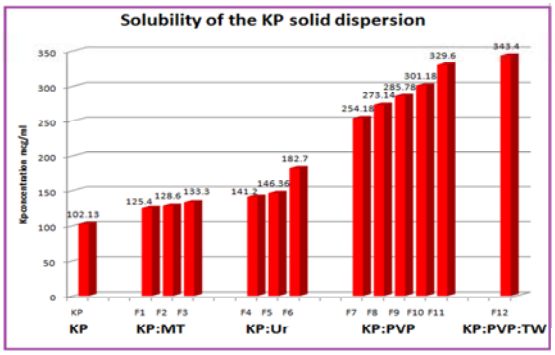

Fig. 5: Solubility of Ketoprofen (KP) in aqueous solutions at 20 °C from prepared solid dispersion

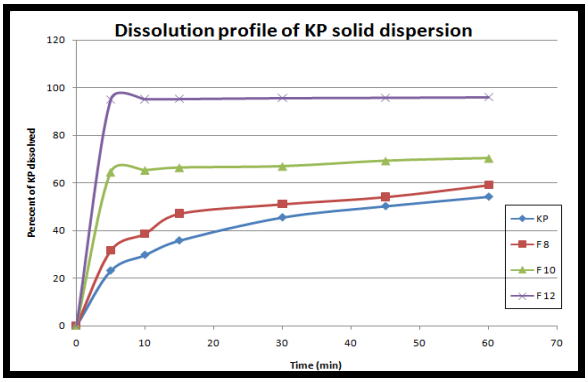

Fig. 6: Dissolution profiles of Ketoprofen (KP) alone and from prepared solid dispersions

Table 3: Dissolution Parameters of Ketoprofen (KP) alone or from its prepared solid dispersions in percent dissolved (PD) and dissolution efficiency (DE) at 10, 30, and 60 minutes

Sample	PD10	PD30	PD60	DE10	DE30	DE60
KP	29.80	45.61	54.30	19.05	32.19	41.16
F8	38.76	51.16	59.16	25.52	40.23	47.45
F10	65.35	67.00	70.40	48.61	60.53	64.76
F12	95.13	95.60	95.95	71.28	87.33	91.55

Many trials to improve solubility and dissolution of KP by solid dispersion were done utilizing binary and ternary systems [24]; moreover, Alatas *et al* used PEG 4000 in the system [25], while Sherikar *et al* used solvent diffusion method for this purpose [26] but they couldn't achieve satisfactory results using simple methods like the one followed in the present work. Various mechanisms including reduction of particle size of incorporated drug, partial transformation of the crystalline drug to the amorphous state,

formation of solid solution and complexes, reduction of aggregation and agglomeration, improved wetting of drug, and solubilisation of the drug by the carrier of the diffusion layer may explain the improvement in aqueous solubility/dissolution properties of the prepared solid dispersions [27]. Accordingly, formula F12 was chosen as best formula since it produces the higher solubility and dissolution effeciency, thus it was subjected to further analysis including kinetic of drug release and DSC studies. Table 4 lists the regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data. Linear regression analysis and model fitting showed that drug release from selected formula (F12) followed models in the order of Korsemeyer–Peppas>Hixson–Crowell cube root law> Higuchi>first-order>zero order. The solid dispersion tended to exhibit Fickian diffusion characteristics, as the corresponding values of *n* were lower than the standard value for declaring Fickian release behavior; these results point out the prevalence of diffusional mechanistic phenomena.

Table 4: Kinetic analysis of drug release from selected solid dispersion formula.

Mechanism	Zero-order		First-order		Higuchi		Hixson-Crowel		Korsemeyer	
	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2
Selected formula	0.767	0.225	0.011	0.273	9.316	0.479	0.001	0.973	0.047	0.999

The thermal curves of the pure drug, polymer, and of the selected solid dispersion formula (F12) are shown in figures 7, 8, and 9 respectively. The thermal curve of KP indicates its crystalline nature, exhibiting only one endothermic peak (93.71°C) and of the polymer (broad peak at 70 °C). Tween 80 was liquid at room temperature, therefore it was not possible to record a DSC trace under the experimental conditions used [28]. The thermal behavior of KP in ternary systems indicated that Tween 80 did not play a role in the thermal behavior of KP, and shows significant decrease of the endothermic peak of KP This may be due to the interaction between KP and PVP in solid dispersion which confirms the decrease in crystalline nature of the drug.

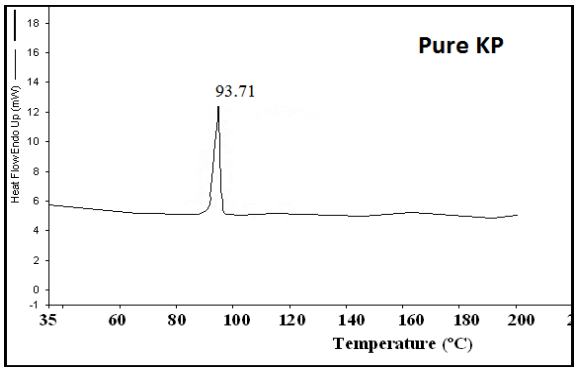

Fig. 7: DSC thermogram of pure ketoprofen (KP)

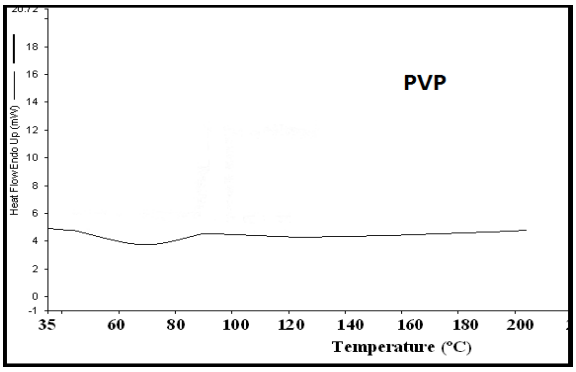

Fig. 8: DSC thermogram of pure polyvinylpyrrilidone (PVP)

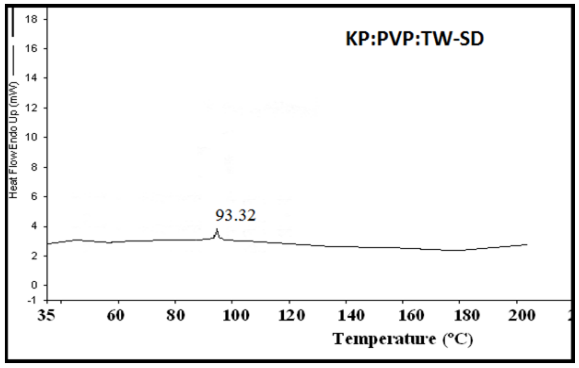

Fig. 9: DSC thermogram of prepared solid dispersion KP:PVP:TW (1:3:1)

CONCLUSION

The binary solid dispersion of ketoprofen in PVP was effective in improving its dissolution properties. However, addition of a surfactant when preparing the KP-PVP solid dispersions improved ketoprofen dissolution properties compared with the simple binary product. The most effective system was the KP: PVP: TW (1:3:1) ternary system, which allowed achievement of 95% dissolved drug after only 5 minutes compared with the binary system.

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