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Research Article

STUDY ON *INVITRO* PERMEATION ENHANCEMENT OF KETOPROFEN BY FORMATION OF SOLID DISPERSION

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ABSTRACT
Solid dispersions of ketoprofen were prepared by using different water soluble carriers like β-cyclodextrin, PEG 6000, polyvinyl pyrolidone and urea in appropriate concentration to enhance the transdermal flux. The prepared solid dispersions were characterized by IR spectroscopy & DSC suggested no interaction of drug with carriers. The solid dispersions were evaluated for solubility, *Invitro* dissolution and *Invitro* permeation through rat skin. The solubility of ketoprofen was enhanced 3-7 times in order of solid dispersion, urea<PV<PEG 6000<β-cyclodextrin and also was increased with increase in the concentration of carriers. The dissolution of all ketoprofen solid dispersions was 67.45% to 95.41% more as compare to the pure drug (24.46%) after 120 min. The percentage drug dissolution was increased for the different carrier as urea<PVP<PEG 6000<β-cyclodextrin and also as the concentration of carriers increase the dissolution was also increased. The *in vitro* dissolution was correlated with the solubility study. The flux obtained for all solid dispersion was 3-8 times more as compare to pure drug due to enhanced solubility and dissolution of ketoprofen in donor compartment. The highest flux was obtained with β-cyclodextrin (446.31mcg/cm^2/h) and PEG 6000 (432.22mcg/cm^2/h). Hence the permeation flux of ketoprofen could be enhanced by formation of solid dispersion for effective topical preparations.
KEYWORDS: Ketoprofen; solubility; *Invitro* dissolution; *in vitro* permeation; flux

INTRODUCTION

Transdermal delivery of drugs through the skin for local or systemic action provides a convenient route of administration for a variety of clinical indications. For transdermal delivery of drugs, stratum corneum is the main barrier layer for permeation of drug. To circumvent the stratum corneum and to increase the flux through skin, different approaches of penetration enhancement are used like formulation-based enhancement techniques in which transdermal drug flux can be improved by increasing the concentration of the drug in the vehicle.[1] Consequently, increase in the maximum solubility of the drug can result in a higher flux and this concept is supported by many studies employing supersaturated systems[2,3] which can be obtained by a variety of techniques such as solid dispersion[4]. The formation of solid dispersion is an effective method for increasing the dissolution rate of poorly soluble drugs which often results in generation of supersaturated states, hence improving percuteneous absorption[5]. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, urea, mannitol, polyvinyl pyrrolidone (PVP), polyethylene glycols (PEG), and ß-Cyclodextrin used as carriers for solid dispersions[6]. Cyclodextrin have reported to modified transdermal drug penetration of many compound by complexation and accelerate drug release by enhancing the proportion of diffusible substance. Cyclodextrin and their complexes act as a true carrier, by keeping the poorly soluble drug molecule in solution and helps in penetration[7]. Lopenz Renata et al[8] have studied the influence of complexation of dexamethasone acetate with βCD and HPβCD on the vitro permeation through hairless mouse skin and found that amount of drug increases 2 and 3-times for βCD and HβCD. Zi Peng et al[9] have studied the ability of HPβCD to influence the percutaneous absorption of capsaicin (CP) through rat skin and concluded that flux of drug increased with increasing concentration of HPβCD from 0 to 2.2% w/v. Polyvinyl pyrolidon (PVP) is well tolerated physiologically, readily soluble in water and has been used for increasing the solubility, dissolution and permeability. El-Badry M and Fathy M[10] have prepared solid dispersions of meloxicam using polyvinyl pyrrolidone K-30 by freeze drying and solvent evaporation method, study revealed that permeation rate through mouse skin was significantly enhanced. Urea is a hydrating agent, form solid dispersion, improve the solubility and dissolution of poorly soluble drugs and

promotes transdermal permeation by facilitating the hydration of stratum corneum. Okonogi S et al[11] have prepared solid dispersion system of sparingly water soluble drug ofloxacin with urea and mannitol and observed that dissolution rate markedly increased in the solid dispersion with an increase in urea concentration. Ketoprofen, a potent NSAID is a preferential inhibitor of cyclooxygenase -2 and has analgesic and anti-inflammatory activity, widely used in the treatment of rheumatoid arthritis, osteoarthritis and other joint disease. The poor aqueous solubility and wettability of ketoprofen leads to difficulty in formulating oral and topical formulation. The literature survey reveals that the solubility of ketoprofen can be enhanced by solid dispersion using cyclodextrins and PEG[12, 13].

Hence in the present study, solid dispersions of ketoprofen were prepared using β-cyclodextrin, PEG 6000, polyvinyl pyrolidone and urea to increase solubility and dissolution there by enhancing ketoprofen flux through rat skin.

MATERIALS AND METHODS

Ketoprofen was kindly provided as gift sample from M/s.Ciron drugs & pharmaceuticals Pvt. Ltd., Mumbai, India. β-cyclodextrin and PVP was obtained from Hi-Media Laboratories Pvt. Ltd, India and PEG 6000 and urea from SD Fine Chem. Ltd. Mumbai. All other chemicals used were of analytical grade.

Development of solid dispersion

The binary system of ketoprofen and cyclodextrins (β-CD) were prepared in 1:1 and 1:2 molar ratios in water: ethanol (1:1 v/v) solution by kneading method[6]. Solid dispersion of ketoprofen were prepared with PEG 6000 in weight ratios of 1:7 and 1:9 and PVP & urea in weight ratios 1:3 & 1:5 by solvent evaporation method using methanol. The slurry obtained in all above methods were dried, crushed and sieved. The drug: polymer ratio and method of preparation is shown in Table 1.

Characterization of solid dispersion

a) FTIR spectroscopy

FT-IR spectra of ketoprofen and the selected solid dispersions were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets by gently mixing the sample with potassium bromide in1:100 and the sample was scanned from 4,000 to 400 cm-1.

b) Differential scanning calorimetry

Thermal analysis of selected ketoprofen solid dispersion was performed by differential scanning calorimetric method using a Shimadzu TGA-50 DSC instrument (Shimadzu Corporation, Japan). Samples equivalent to approximately 8 mg Ketoprofen were placed in aluminum pans and heated from 25 to 200˚C with a heating rate of 10˚C/min.

Evaluation of ketoprofen solid dispersion

a) Content uniformity

An accurately weighed amount of each preparation was dissolved in small volume of methanol and further diluted in phosphate buffer pH 7.2. The content of ketoprofen was determined spectrophotometrically at 254 nm using Shimadzu-1700 UV visible spectrophotometer.

b) Solubility study

Excess amount of sample was added to 3 ml of phosphate buffer pH 7.2, sonicated for one hour and agitated in a shaker with a temperature maintained at 37ºC for 72 hours. The suspension was filtered and analyzed spectrophotometrically (Shimadzu 1700 UV-Visible spectrophotometer) at 254 nm.

c) *Invitro* dissolution study

The study was conducted in USP Dissolution apparatus using 900 ml phosphate buffer pH 7.2 as dissolution medium maintained at 37±0.5ºC temperature and 50 rpm. A weighed amount of the sample (equivalent to 8 mg ketoprofen) was tied by using muslin cloth. At appropriate interval 5 ml sample was withdrawn, filtered and the concentration of ketoprofen was determined spectrophotometrically at 254 nm. Dissolution study was carried out for 120 min.

d) *Invitro* permeation study

The permeation study was conducted using rat abdominal skin after approval from Animal Ethics Committee (No.346/CPCSEA). Male rats weighing 140-160 g were used to obtained freshly excised fully thickness skin. Animals were sacrificed by ether and hair from abdominal region was removed by means of electric shaving machine taking care not to damage the epidermal layer. The subcutaneous fat was removed carefully without any damage to epidermis. Skin (0.025cm) was stretched over the end of an open-ended glass tube and tube was immersed in 200 ml beaker containing 100 ml pH 7.2 phosphate buffer and kept in vertical position so that the membrane touches (1-2 mm deep) the surface of the buffer solution. The surface area available for the diffusion was 1.76 cm². The diffusion tube (donor) and beaker (receptor) were maintained at 37ºC using hot plate magnetic stirrer and at 50 rpm. An aliquot of 3 ml saturated solution of pure drug and ketoprofen solid dispersion in phosphate buffer pH 7.2 was placed in the diffusion tube. At predetermined time interval 5ml sample were removed from receptor and replaced with fresh phosphate buffer solution, analyzed spectrophotometrically at 254 nm. The study was

conducted for 6 hrs and the flux was calculated from plot of amount permeated versus time.

RESULTS AND DISCUSSION

In the present study solid dispersions of ketoprofen were prepare by using different highly water soluble carriers like β-cyclodextrin, PEG 6000, PVP and urea. The solid complex of ketoprofen with β-cyclodextrin was prepared in molar ratios of 1:1 and 1:2 by kneading method. The solid dispersions of ketoprofen with PEG 6000 was prepared in 1:7 and 1:9 in weight ratios by solvent evaporation. For the preparation of ketoprofen solid dispersions, the weight ratios used for PVP and urea was 1:3 and 1:5 by employing solvent evaporation method.

The selected solid dispersions were characterized by FTIR spectroscopy and DSC and obtained spectra is depicted in fig. 1 and 2. IR study indicated that there was only physical entrapment of ketoprofen with carrier molecules. The DSC thermogram of selected drug solid dispersion showed sharp endotherm followed by exotherm which signifies that after melting ketoprofen decomposes, indicating some crystal of pure ketoprofen kept there in crystalline nature.

The ketoprofen content in all solid dispersions was in permissible range from 95.14% to 99.02% (Table 2) which indicated that drug was uniformly dispersed throughout the formulation. The solubility study of solid dispersions was carried out in both distilled water and in phosphate buffer pH 7.2 and results are present in Table 2. The solubility of pure untreated ketoprofen was less as compare to its solid dispersion. The solubility of ketoprofen solid dispersion was increased for all the solid dispersions in order of urea<PVP<PEG 6000<β-cyclodextrin. The solubility of ketoprofen was increased with increase in the concentration of carriers for all the solid dispersions. Among the carriers used β-cyclodextrin and PEG 6000 showed highest solubility in range of 2.50 to 2.88 mg/ml as compare to PVP and urea which showed low solubility in range of 1.56 to 1.88 mg/ml.

All the ketoprofen solid dispersions and pure drug were subjected to *Invitro* dissolution study in phosphate buffer pH 7.2 and the results are illustrated in fig. 3. The dissolution of all ketoprofen solid dispersions was more (67.45% to 95.41%) as compare to the pure drug (24.46%) after 120 min. The percentage drug dissolution was increased for the different carrier as urea<PVP<PEG 6000<β-cyclodextrin and also as the concentration of carriers increased the dissolution was also increased. The *in vitro* dissolution was correlated with the solubility study. The ketoprofen solid dispersions containing β-cyclodextrin showed highest drug dissolution (95.41%) which was attributed to fact that the β-cyclodextrin form inclusion complex with lipophillic ketoprofen and also the surface area of the particle increased[12]. The PEG 6000 showed more than 90% of drug dissolution because of increase in solubility of ketoprofen due to the entrapment of the drug in the helical interstitial space of PEG molecules and also reducing the particle size[13]. The PVP ketoprofen solid dispersion showed the rapid dissolution of more than 80% within 120 min, due to the fact that solubility of ketoprofen was enhanced by incorporation of ketoprofen in liner chain of PVP which retards the crystallization of poorly water soluble drug. The dissolution of ketoprofen was in the range of 67.45% to 77.93% for solid dispersion of urea, the reason for increased dissolution was attributed to the wettability of the drug particle and also reducing the surface tension.

Invitro permeation of ketoprofen through rat skin was performed by taking saturated solution of ketoprofen solid dispersion in phosphate buffer pH 7.2 for a period of 6 hrs. The flux (mcg/cm^2/h) was calculated from the linear portion of straight line obtained by plotting amount of drug permeated Vs time as shown in fig. 4. All the percutaneous permeation parameters like flux (J_{ss}), lag time (t_l), permeability coefficient (K_P), diffusion coefficient (D) and release rate constant (k) were calculated and represented in Table 3. The flux obtained for all solid dispersion was more (136.58 to 446.31 mcg/cm^2/h) as compare to pure drug (51.03mcg/cm^2/h) which was due to enhanced solubility and dissolution of ketoprofen in donor compartment. The flux was directly related to concentration of drug in vehicle. The solid dispersions increased the amount of dissolved drug in donor compartment due to the supersaturation and hence the flux was increased as represent in fig 5. The highest flux was obtained with β-cyclodextrin (446.31 mcg/cm^2/h) which was due to the fact that the cyclodextrin enhanced the drug solubility and thermodynamic activity in the vehicle which leads to increased permeability of drug[8,14]. The flux obtained for PEG 6000 dispersion was 432.22mcg/cm^2/h and for PVP dispersion was 160.09 mcg/cm^2/h, which was more as compare to pure drug due to high solubility and dissolution. The flux obtained for urea dispersion was 155.43 mcg/cm^2/h, which was less as compare to all the carriers used, the reason was that urea enhanced the solubility and also act as permeation enhancer but retain the drug more in stratum corneum which contributes for low flux value. The overall *in vitro* permeation of ketoprofen was perfectally correlated with the solubility and dissolution.

CONCLUSION

The solubility and dissolution was significantly ($p<0.05$) enhanced by using solid dispersions of ketoprofen which in turn enhanced the permeation flux. Hence solid dispersion of ketoprofen as a formulation technique, could be used to enhanced percuteneous permeation through rat.

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Table 1: Formula for ketoprofen solid dispersion with method of preparation

Code	Composition	Ratio	Method of preparation
F1	Ketoprofen + ß-cyclodextrin	1:1	Kneading method
F2	Ketoprofen + ß-cyclodextrin	1:2	Kneading method
F3	Ketoprofen + PEG 6000	1:7	Solvent evaporation method
F4	Ketoprofen + PEG 6000	1:9	Solvent evaporation method
F5	Ketoprofen + PVP K-30	1:3	Solvent evaporation method
F6	Ketoprofen + PVP K-30	1:5	Solvent evaporation method
F7	Ketoprofen + urea	1:3	Solvent evaporation method
F8	Ketoprofen + urea	1:5	Solvent evaporation method

Table 2: Evaluation of Ketoprofen solid dispersions

Formulation Code	Appearance	Drug Content (%)	Solubility (mg/ml)	
			Water	Phosphate buffer pH 7.2
K	White	-	0.02±0.11	0.40±0.26
F1	White	98.38±0.15	0.49±0.23	2.72±0.23
F2	White	96.56±0.25	1.04±0.34	2.88±0.35
F3	White	96.82±0.14	0.91±0.18	2.50±0.17
F4	White	98.77±0.25	0.94±0.15	2.61±0.37
F5	Creamy White	94.95±0.25	1.00±0.22	1.63±0.21
F6	Creamy White	95.79±0.36	1.09±0.21	1.88±0.38
F7	White	93.78±0.35	0.54±0.20	1.58±0.45
F8	White	96.11±0.65	0.57±0.33	1.82±0.41

(mean±SD, n=3)

Table 3: Percuteneous permeation parameters of ketoprofen solid dispersions

Formula code	Flux, J_{SS} (µg/cm²/hr)	*Enhancement factor	Permeability coefficient, K_P (cm/hrx10^{-2})	Diffusion coefficient, D (cm²/hrx10^{-4})	Release rate constant,k (µg/cm²/$h^{0.5}$)
K	51.03	1.0	0.63	-0.42	227.73
F1	436.04	8.54	5.45	2.94	1876.46
F2	446.31	8.74	5.57	2.93	1918.32
F3	424.34	8.31	5.30	2.86	1827.52
F4	432.22	8.46	5.40	2.90	1861.65
F5	142.57	2.79	1.78	4.86	604.51
F6	160.69	3.14	2.00	3.05	671.63
F7	138.06	2.70	1.72	4.96	586.02
F8	155.43	3.04	1.94	3.01	652.26

$$\text{*Enhancement factor} = \frac{\text{Flux with carrier}}{\text{Flux without carrier}}$$

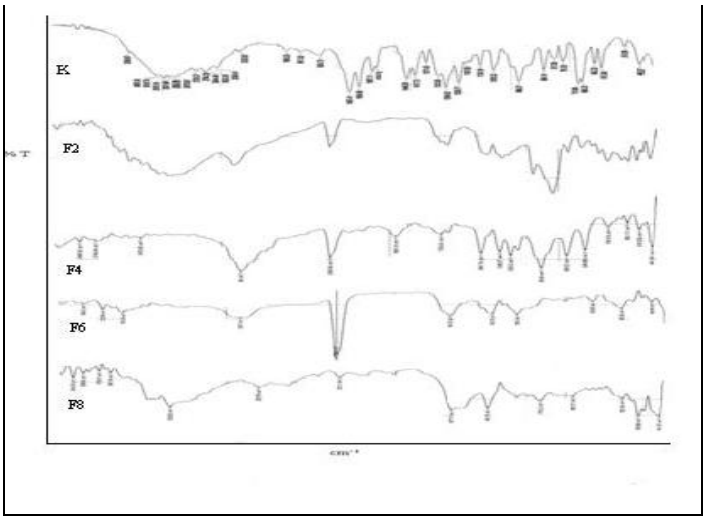

Figure 1: IR Spectra of Pure Drug (K) and selected ketoprofen solid dispersions F2, F4, F6 and F8

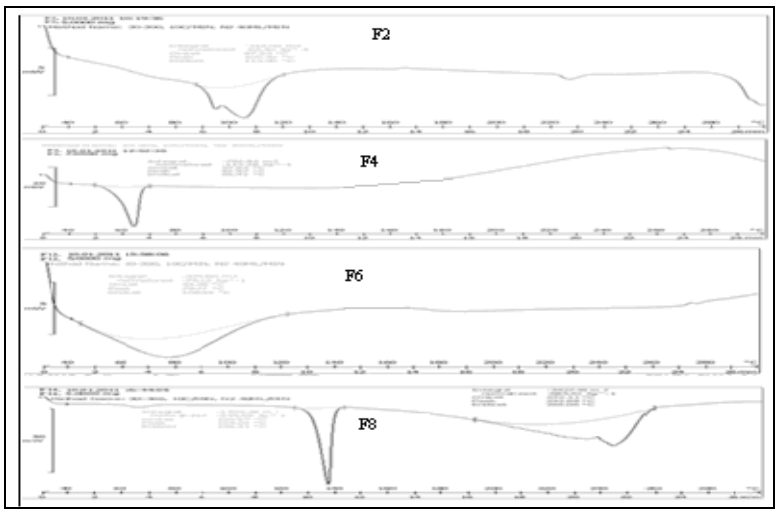

Figure 2: DSC Thermogram of selected ketoprofen solid dispersion F2, F4, F6 and F8

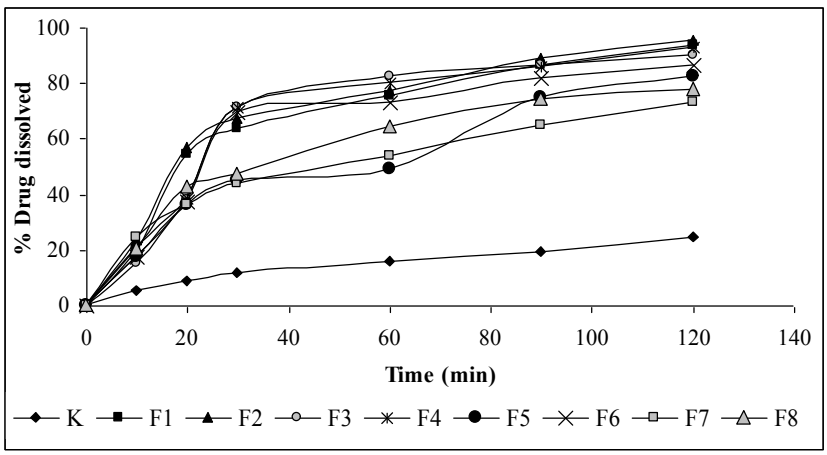

Figure 3: *In vitro* Dissolution of pure Ketoprofen and Ketoprofen solid dispersions

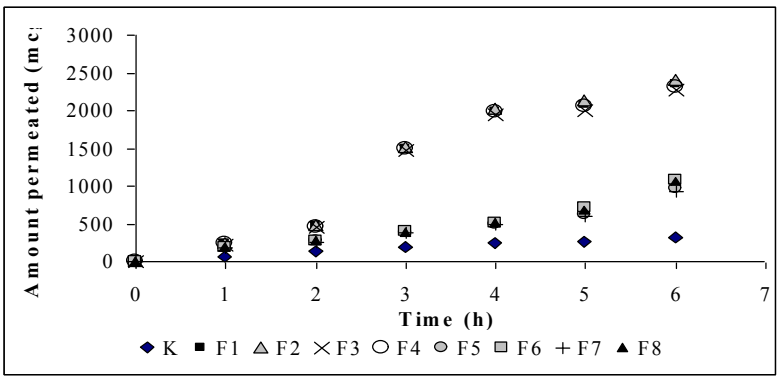

Figure 4: *In vitro* permeation of ketoprofen from pure drug (K) and solid dispersion solution through rat skin

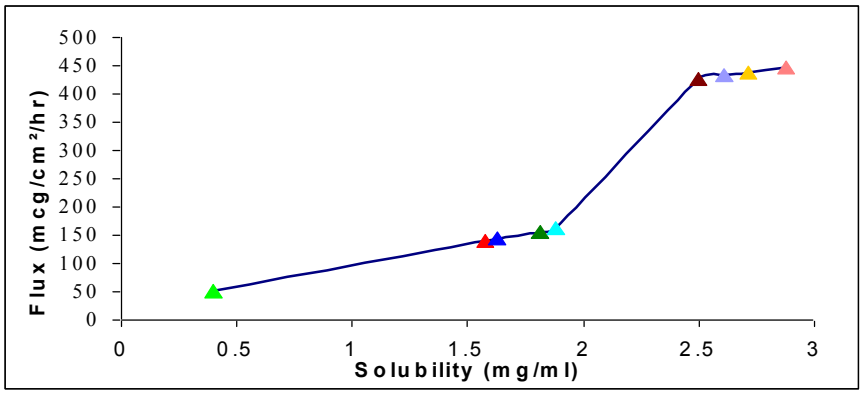

Figure 5: Effect of solubility on flux of ketoprofen pure drug and ketoprofen solid dispersions

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