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## Development and characterization of ketoprofen solid dispersion incorporated topical gels

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### ABSTRACT

The present work aims to increase the therapeutic effectiveness of ketoprofen by increasing its transdermal permeation, via solid dispersion incorporated in gel. 2-hydroxy propyl beta cyclodextrins (HP $\beta$ -CD) and  $\beta$ -cyclodextrin ( $\beta$ -CD) were used as carriers and carbopol 940 was the gelling agent. Eight solid dispersion formulations of ketoprofen were prepared using different drug: polymer ratios viz. 1:0.5, 1:1, 1:2, and 1:3 for 2-HP $\beta$ -CD and  $\beta$  cyclodextrin using the solvent evaporation method. The formulation of solid dispersion by solvent evaporation method is introduced to reduce the drug particle size and hence increase the dissolution rate. These dispersions were characterized with the help of FT-IR, DSC and X-ray diffraction studies. The optimized solid dispersion of ketoprofen was incorporated into gel and was compared with penetration enhancers. The formulations were analyzed to determine their pH, spreadability, viscosity, and in vitro drug release. The formulation with 1:0.5 SDK (drug: HP $\beta$ CD) was incorporated in carbopol gel, and produced 98.32 % drug release compared to solid dispersion of ketoprofen with menthol (SDKM5%), which produced 96.26% drug release. In ex vivo studies, SDK and SDKM5% formulations gave 94.37% and 92.26% drug release respectively within 24 h. The percent inhibitions of the edema formation by the gels were in the range of 19.63% to 69.65%, and the maximum inhibition was shown by the SDK formulation. Therefore, SDK formulation incorporated in gel produced better results than other formulations prepared with permeation enhancers. Stability studies conducted for SDK incorporated gel.

**Keywords:** Ketoprofen, Topical gel, Solid Dispersion, Partition Coefficient, Penetration, Anti inflammatory activity

### INTRODUCTION

Ketoprofen [2-(3-benzoylphenyl)-propionic acid] a potent non-steroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions, has pH dependent solubility and permeability [1]. Ketoprofen has similar pharmacological actions as other prototypical NSAIDs; that are thought to be associated with the inhibition of prostaglandin synthesis [2]. Dosing frequency is 50-100 mg twice a day. Its half life is 0.5 to 2 hrs. Ketoprofen is poorly aqueous soluble i.e. 0.5 $\mu$ g/ml. The problem associated with ketoprofen is its poor solubility in water which leads to poor dissolution rate and subsequent decrease in its gastrointestinal absorption [3]. In addition to absorption difficulties, oral formulations of ketoprofen can cause gastric mucosal damage, which may result in ulceration and bleeding [4].

Therefore, there is a need to develop topical dosage forms of ketoprofen to minimize the gastrointestinal side-effects of oral ketoprofen, and to provide relatively consistent drug levels at the application site for prolonged periods [5]. Transdermal and topical deliveries provides an increased bioavailability by avoiding first pass metabolism by the liver and a consistent delivery for an extended period [6]. Topical delivery vehicles (creams, gels) and transdermal delivery agents (dermal patches) can improve patient compliance due to decrease in the dosage frequency. However, ketoprofen poor permeability through human skin makes transdermal delivery difficult [7]. The stratum corneum, the external layer of the epidermis characterized by lipid-rich rich lamellae, serves as a formidable permeability barrier for transdermal absorption of ketoprofen. Although studies have explored the potential of oral formulations like inclusion complexes, prodrug, solid dispersion method, and microcapsule, there have been few attempts to enhance the bioavailability through topical and absorption, which could be an effective way to improve ketoprofen's solubility. The permeability problems at the skin surface may be obviated by the use of drug carriers, and penetration enhancers.

One way to increase the solubility of poorly soluble drugs is through the formation of solid dispersion. Numerous solid dispersion (SD) systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs [8]. There has been limited exploration of the efficacy of the SD method to create topical formulations of ketoprofen, as the method has mainly been used to create oral formulations. This study aims to apply the SD method using 2- hydroxy propyl beta cyclodextrins (2- HP $\beta$ -CD) and  $\beta$ -cyclodextrins ( $\beta$ -CDs) as carriers. The CDs, a family of cyclic oligosaccharides, form hydrophilic inclusion complexes with functional groups on lipophilic compounds in aqueous solution. The resulting complex masks the drug's hydrophobic sites within the inner cavity of the inclusion body, while the hydrophilic functional groups are exposed to the aqueous environment [9]. Therefore, cyclodextrin based drug delivery enhances aqueous solubility and bioavailability of a lipophilic drug without changing its intrinsic ability to permeate lipophilic membranes. In addition to being a potent solubilizer, 2- HP $\beta$ -CD has been shown to potentially enhance absorption during topically applied delivery by increasing the availability of dissolved drug molecules adjacent to the biological membrane surface, or by direct action on the stratum corneum.

The present study will aim to study both the release rate, and the absorption properties of topically administered ketoprofen with a novel approach using solid dispersion incorporated gels with 2-HP $\beta$ -CD and  $\beta$ -cyclodextrin as carriers, in the presence and absence of permeability enhancers.

## MATERIALS AND METHODS

### 2.1. Materials

Ketoprofen was received as a gift sample from Ranbaxy Lab Ltd, India.  $\beta$  cyclodextrin and 2-Hydroxy propyl  $\beta$  cyclodextrin was purchased from Hi Media Pvt. Ltd, India. Carbopol 940 & menthol was obtained as gift sample from LOBA Chemie Pvt. Ltd, Mumbai, India. All other chemicals used were of analytical grade and obtained commercially.

### 2.2. Methods

#### 2.2.1. Preparation of Solid Dispersion

An important prerequisite for the manufacture of a solid dispersion (SD) using the solvent method is that both the drug and the carrier should be sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Physical mixture of ketoprofen was prepared by using  $\beta$  cyclodextrin & 2-HP  $\beta$  CD carriers in 1:0.5, 1:1, 1:2, 1:3, 1:4 ratios. SD of ketoprofen was prepared using the solvent evaporation method by dissolving the drug and carrier in methanol with 15 minutes of continuous stirring, and then placed in desiccators for 4 days. The resultant solid dispersion was passed through a 44 mesh sieve and stored in a dessicator until used for further studies [10].

#### 2.2.2. Characterization of solid dispersions

The prepared solid dispersion were evaluated for drug carrier interaction using FT-IR (Perkins Elmer 1600 series) and differential scanning calorimetry (DSC – Pyris – 6) spectral studies. For DSC studies samples were sealed in aluminium pans and the DSC thermograms were recorded at a heating rate of 10°/min from 100 -300°C. FT-IR spectrum was carried out by KBr pellet method.

### 2.2.3. Preparation of solid dispersion incorporated gels

Weighed quantity of carbopol 940 soaked in 75 ml of water for 24 h. To this glycerine and DMSO was added with stirring. The solid dispersion containing 1% drug was dissolved in ethanol and this dry solution was added to above gel with continuous stirring (Table 1). The prepared gel was characterized for spreadability, extrudability, viscosity, pH and drug content.

### 2.2.4. Dissolution rate studies

Dissolution studies of solid dispersion of ketoprofen (SDK) were carried out using USP-I basket apparatus at 100 rpm for 1 hr using the 7.4 pH phosphate buffer media. The concentration of drug release was analysed using UV spectrophotometer at 258 nm.

### 2.2.5. *In vitro* diffusion studies

The diffusion studies were performed using a Keshary-chien diffusion cell. The cell was locally fabricated and had a 25 ml receptor compartment. The dialysis membrane was mounted between the donor and receptor compartments. The gel formulation was applied uniformly on the dialysis membrane and the compartments were clamped together. The receptor compartment was filled with the phosphate buffer (pH 7.4) and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. 1ml of samples was withdrawn from the receptor compartment at pre-determined time intervals and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically at 258 nm.

### 2.2.6. *In vitro* skin permeation

The rat epidermis was obtained from inbred adult male Wistar rats, which weighed between 130-150 gms, and were maintained under standard laboratory conditions ( $25 \pm 1^\circ\text{C}$  and  $60 \pm 5\%$  relative humidity with a 12-hour light/dark cycle). The epidermis was mounted onto Keshary-chien diffusion cell in such a way that the dermis side was in constant contact with receptor solution. The receptor compartment was filled with phosphate buffer (pH 7.4). The stratum corneum was facing the donor compartment which contained the gel formulation, and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead. 1 ml of sample was withdrawn at pre-determined time intervals (every one hour) from the receptor compartment and an equal volume of buffer was replaced. The samples were analyzed after appropriate dilution for drug content spectrophotometrically at 258 nm. Menthol was used as permeation enhancers. The rate of skin permeation by the drug was measured as the flux, which was calculated from the slope of the linear part of each permeation profile [11, 12].

### 2.2.7. Evaluation of anti-inflammatory activity

The anti-inflammatory activity of SDK was evaluated using the 42 male Wistar rats, described above. The rats were divided into seven groups with six rats in each group. The first three groups served as controls and the remaining as optimized samples containing 1% of Ketoprofen or SDK.

#### 2.2.7.1. Experimental animals

Adult male wistar rats, weighing between 130-150 g were maintained in standard laboratory conditions of laboratory conditions, at  $25 \pm 1^\circ\text{C}$  and  $55 \pm 5\%$  relative humidity with a 12-hour light/dark cycle. These rats are randomly divided into 7 groups, with six in each group.

#### 2.2.7.2. Measurement of Inflammatory Response

The first three groups served as controls, as described below: Group - I: un-inflamed, injected with saline; Group - II: control: inflamed, injected with carrageenan; Group - III: standard: inflamed, treated with the reference product. The other 4 groups were inflamed and treated with the following test ketoprofen formulations, SDK, SDKM5% (SDK incorporated in gel with menthol 5%), and blank. Carrageenan solution (1 %w/v, in normal saline) was used to induce inflammation.

Each rat was placed in an observation chamber for 10 min to minimize stress-related behaviours. 0.5 g of the gel formulations or the reference was gently rubbed onto the plantar surface of the left hind paw 50 times with the index finger. Thirty minutes later, pleurisy was induced by injecting 50  $\mu\text{l}$  of 1% w/v carrageenan solution subcutaneously into the sub-plantar surface of the left paw of the rat. Control un-inflamed animals received 50  $\mu\text{l}$  of normal saline subcutaneously, into the subplantar surface of the left paw. All rats were subsequently returned to the observation chamber. The inflammatory response was assessed by measuring the volume of the paw at 0, 1, 2, and 3 h after carrageenan administration, using a plethysmometer. The percentage of inhibition of edema was recorded.

## RESULTS AND DISCUSSION

In the present work ketoprofen was complex with highly water soluble carrier  $\beta$  cyclodextrin & 2-HP  $\beta$  CD carriers in 1:0.5, 1:1, 1:2, 1:3, and 1:4 ratios. Since several studies have shown that an excess of cyclodextrin carriers packaged with lipophilic drug reduces permeability through the stratum corneum, the SDK was optimized to achieve maximum aqueous drug solubility with the least amount of carriers [13, 14]. The solid dispersion was characterized by FTIR and DSC. FTIR and thermal behaviour of pure drug and selected drug carrier complexes depicted in **Figure 1 & 2**. IR studies indicated that there was no chemical interaction between drug and carrier took place during preparation of solid dispersion of Ketoconazole. The DSC thermo gram of pure ketoprofen and carrier complex shows sharp endotherm followed by exotherm which signifies that after melting ketoprofen decomposes, indicating some crystal of pure ketoprofen kept there in crystalline nature.

**Table 1: Compositions of the gel formulations (%w/w)**

Ingredients	Ketoprofen	SDK	KM (5%)	KM (10%)	SDKM (5%)	SDKM (10%)
Ketoprofen	1	-	1	1	-	-
SDK	-	1	-	-	1	1
Carbopol	4	4	4	4	4	4
Alcohol	5	5	5	5	5	5
Propylene glycol	10	10	10	10	10	10
Menthol	-	-	5	10	5	10
Triethanolamine	0.7	0.7	0.7	0.7	0.7	0.7
Sodium Chloride	0.2	0.2	0.2	0.2	0.2	0.2
Water (ml)	14	14	14	14	14	14

*Note: Ketoprofen-plain ketoprofen gel; SDK- solid dispersion of ketoprofen; KM- ketoprofen with menthol; SDKM- solid dispersion of ketoprofen with menthol*

**Table 2: Percentage drug release profiles of ketoprofen with HP  $\beta$  CD as carrier in 7.4 pH phosphate buffer**

Time (min)	Plain Drug (1% w/w)	1:0.5 (HP $\beta$ CD)	1:1 (HP $\beta$ CD)	1:2 (HP $\beta$ CD)	1:3 (HP $\beta$ CD)
0	0	0	0	0	0
5	9.29	18.32	35.23	41.47	49.55
10	9.46	24.35	48.87	57.59	61.23
15	10.32	39.44	56.12	69.43	73.25
30	11.02	48.21	64.47	77.15	79.68
45	11.85	56.47	77.19	83.32	93.25
60	12.69	68.22	86.26	94.55	99.65

**Table 3: Comparative in vitro release profile of ibuprofen with solid dispersion incorporated in gel and with permeation enhancers**

Time (min)	Ketoprofen	SDK	KM (5%)	KM (10%)	SDKM (5%)	SDKM (10%)
0	0	0	0	0	0	0
15	0.3	2.3	1.12	1.56	2.6	1.81
30	1.62	7.85	3.22	3.78	7.86	6.21
60	2.56	18.26	8.21	10.23	18.45	15.32
120	4.23	41.32	18.31	20.45	37.45	28.74
180	7.68	54.12	27.23	28.32	54.26	39.12
240	9.89	63.21	36.21	34.58	66.25	45.25
300	12.35	76.41	46.23	47.23	75.15	55.78
360	15.32	82.54	57.17	55.18	82.21	68.21
420	17.89	91.14	67.45	58.29	88.74	73.25
480	19.23	98.32	78.81	62.21	96.26	77.15

We also found that the percentage drug released by solid dispersion of Ketoconazole with HP $\beta$ -CD (1:3) was higher when compared to the formulations containing pure drug and SDK with  $\beta$ -CD (**Table 2**). **Table 4** showed that SDK and SDKM5% formulations gave 94.37% and 92.36% of drug release for 24 hrs respectively

This may be due to an increased wettability of the drug by using such hydrophilic carriers and an increased amount of the drug being available for dissolution as cyclodextrins have been found to enhance the permeation by increasing the aqueous solubility of Ketoconazole [15]. Since HP $\beta$ -CD is more hydrophilic than  $\beta$ -CD and has an aqueous solubility in excess of 50% (w/v), it forms stronger inclusion complexes to allow Ketoconazole to readily penetrate into the skin [16]. Because of enhanced/ greater release solid dispersion prepared with 1:3 drug carrier ratios was selected as ideal batch for incorporation into gels.

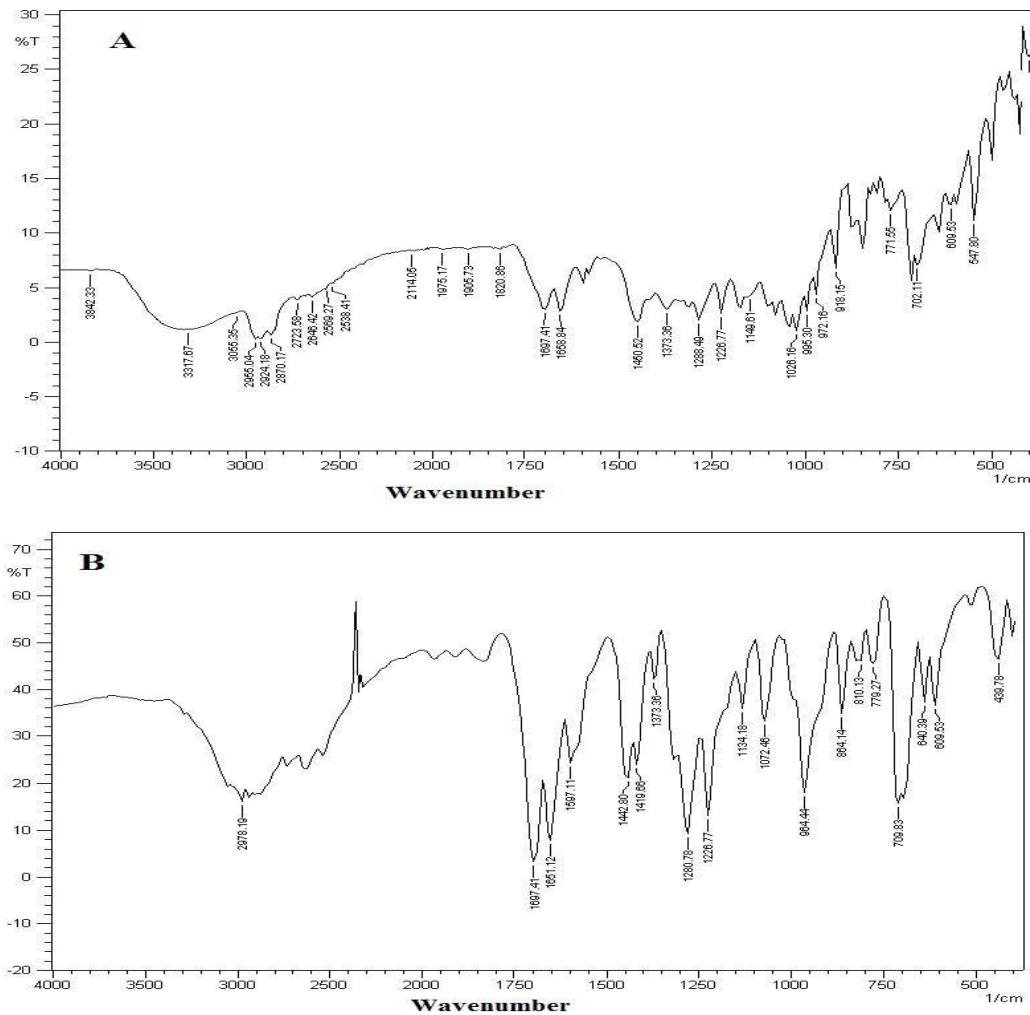


Figure 1: FT-IR spectra of pure drug (A) and drug carrier complex (B)

Table 4: Ex vivo drug release of Ketoprofen gel optimized formulations

Time (h)	Ketoprofen	SDK	SDKM (5%)
0	0	0	0
0.15	0.16	1.88	1.64
0.5	0.32	3.98	2.08
1	1.29	8.46	5.27
2	1.87	17.46	11.58
4	3.63	46.27	38.94
8	9.89	68.22	58.16
12	12.35	78.19	69.29
16	16.12	81.14	79.27
20	20.19	87.29	84.14
24	24.23	94.37	92.26

All the prepared gels were subjected to evaluation for pH, content uniformity and viscosity. The pH of all formulation was more than 6.0, which lies in the normal skin pH. The drug content was in the range of 92.41% to 98.64% indicating uniform dispersion of ketoprofen in the gels. All formulated gel showed an increase in the viscosity as the amount of carrier was increased. The *in vitro* percent drug release of ketoprofen through rat skin was found to be more for solid dispersion gels as compared to plain drug gel. This was due to more solubility, highest

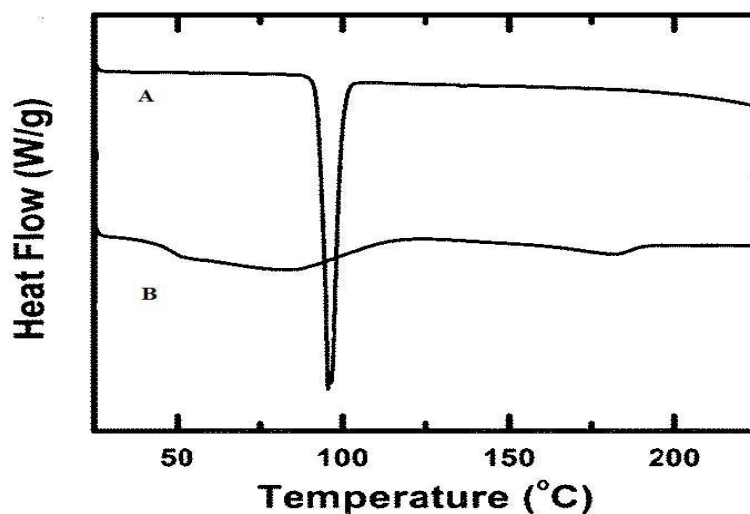
dissolution of solid dispersion as compared to pure ketoprofen. Additionally, it is interesting to note that the SDK formulation without permeation enhancers yielded a higher release rate compared to SDK in the presence of permeation enhancers such as menthol. Such chemical enhancers can be used to improve the bioavailability of topically applied formulations by decreasing the viscosity of the lipids in the stratum corneum. However, they can also alter the intrinsic physiological properties of the skin which may explain their reduced effect on the drug release rate compared to that of SDIB in the absence of enhancers. Therefore, the use of SDK alone (without enhancers) may improve bioavailability of topically administered ketoprofen without affecting the integrity of skin.

The flux was used to gauge the permeation of ketoprofen through the skin. Highest flux was obtained for the SDK formulation in comparison to the ketoprofen pure drug and SDK with penetration enhancers. The molecular size and hydrophilic nature of HP $\beta$ CD-ketoprofen complex produced maximum flux by maximizing the amount of free ketoprofen available for permeation. The SDK produced a release of 98.32% at the end of 8<sup>th</sup> hour. Since this study requires fast release with a quick onset of action, HP $\beta$ CD was used to obtain maximum transdermal permeation to result in an expedited pain relief. In vitro drug release of ketoprofen gel with permeation enhancers such as menthol produced 78.81% drug release within 8 hrs respectively (**Table 3**).

We also found that the SDK formulation has the most potent anti-inflammatory effect as it minimized skin edema compared to all other formulations. The percentage inhibitions of the edema formation by the gels were in the range of 19.63% to 69.65% and the maximum inhibition was shown by the SDK formulation (**Table 5**). Here, the inhibition of edema was used to ensure retention of the functional efficacy of SDK formulation.

**Table 5: Percentage protection against edema formation**

Formulation	30 mins	60 mins	120 mins	180 mins
Ketoprofen	4.5%	7.98%	15.23%	19.63%
SDK	24.12%	33.62%	42.23%	69.65%
SDKM (5%)	17.23%	27.65%	35.62%	47.33%



**Figure 2: DSC studies of pure drug (A) and drug carrier complex (B)**

### CONCLUSION

There is an increased need for topical forms of ketoprofen due to the gastrointestinal and liver problems, which can manifest in patients taking oral forms of the drug, since topical drug delivery system bypasses the GI system, and first pass metabolism by the liver. The disadvantages like first pass metabolism, poor absorption though skin can be overcome by topical drug delivery system. Ketoprofen possessing similar disadvantage was manipulated and additionally, SDK is a better alternative to improve the solubility and penetration through the skin

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