Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Development Of Reservoir Type Ketoprofen Transdermal Patches Using Chemical Permeation Enhancers

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ABSTRACT

The purpose of the present study was to formulate reservoir type transdermal patches for Ketoprofen (KP) that may eliminate the potential adverse events that are associated with its oral delivery. Initially, the effect of different chemical permeation enhancers (Labrasol, Transcutol P, Lauroglycol 90 and Labrafil M 1944 CS at 5% level) on *in vitro* KP release from hydro-alcoholic gels was evaluated using Franz diffusion cells. Based on the results obtained from the permeation studies, suitable permeation enhancers were selected and the reservoir patches of KP were prepared by loading 2.5% w/w of KP in HPMC (E5) hydro-alcoholic gel with Cotran 9702 and Scotchpak 9733 as rate controlling and backing membranes respectively. Results from the permeation studies revealed that, among the permeation enhancers used, Lauroglycol 90 showed superior *in vitro* KP permeation rates i.e. 12.29 ± 0.29 µg/mL at the end of 24h, which is 2.58 folds higher compared to control. Overall, the *in vitro* KP release from the patches was in the order of Lauroglycol 90 >Labrafil M >Transcutol P >Labrasol. *In vitro* KP release from the reservoir patches was evaluated using USP Type V dissolution rate testing apparatus and the results revealed a significant enhancement in KP release ($p<0.05$) from patches containing Lauroglycol 90 (1.4 fold) and Labrafil M (1.1 fold) compared to control. Overall, the results from the present investigation can form basis to perform further *ex-vivo* studies that can be useful for the development of an optimised reservoir type transdermal system for KP.

Keywords: Ketoprofen, Transdermal reservoir patches, Chemical permeation enhancers, Hydro-alcoholic gels.

INTRODUCTION

Ketoprofen (KP), an arylcaboxylic acid derivate belonging to the class of non-steroidal anti-inflammatory drugs (NSAID) is one of the widely used therapeutic agent for the treatment of pain associated with musculoskeletal disorders [1]. Ketoprofen is known to have analgesic, anti-inflamatory and antipyretic properties and works by inhibiting cyclooxygenase (COX 1 and COX 2) enzymes. Inhibition of the COX enzymes results in the decreased production of inflammatory mediators (prostaglandins) thereby regulating the symptoms of pain [2].

Ketoprofen is commonly administered through oral route with doses ranging from 150-300mg for the management of arthritis and osteoarthritis as well as mild to moderate pain [3]. However, the oral administration of KP is associated with several adverse effects related to gastrointestinal track such as ulcerations, upper abdominal pain, vomiting and stomach bleeding [4]. Therefore, delivery of KP by routes alternative to oral route will overcome the adverse effects associated with the KP.

Transdermal route is one of the alternative routes that can be used overcome the adverse effects associated with oral delivery of KP[4]. Transdermal delivery offers controlled delivery of drugs through the skin into the systemic circulation, thereby maintain the constant plasma drug concentrations which results in improved drug therapy [5]. Also, the approach prevents the direct exposure of drug to the gastrointestinal track thereby avoiding the adverse effects such as ulcerations, bleeding in stomach, vomiting etc [4]. Therefore, development of transdermal delivery systems for KP may successfully overcome the gastrointestinal adverse effects associated with oral delivery along with providing the optimal therapeutic advantage.

However, despite of its advantages transdermal route suffers from drawbacks which are largely due to the barrier function of skin, particular the stratum corneum layer that is composed of flat dead cells filled with keratin fibres surrounded by lipid bilayers [6]. The drug molecules have to pass through the stratum corneum layer before reaching the systemic circulation. Due to the intrinsic barrier function of the skin the transdermal delivery is largely restricted to delivery of minimal number of drug molecules [4].

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

One of the strategies in overcoming the barrier function of skin is the use of chemical permeation enhancers [7]. These permeation enhancers aides in permeation of drug molecules by reversible disruption by of stratum corneum layer or by interaction with intercellular proteins or by changing the partition behaviour of the drug molecules [8]. Therefore, development of KP reservoir systems assisted with chemical permeation enhancers may aid in improved delivery of KP through the skin and thereby achieving optimal therapeutic efficacy.

Currently, drug in adhesive type transdermal patch of KP (Ketoplast, manufactured by Zuventus health care) is commercially available in the market. The patch has to be applied to a surface area of 70cm to achieve the desired therapeutic concentrations, which may not be feasible in terms of patient compliance. Use of chemical permeation enhancers may improve the KP permeation fluxes and in turn reduce the effective surface area of application. Literature survey revealed that a few works were reported on the development of drug in adhesive transdermal systems for KP using different permeation enhancers. Work reported by AbidHussainet al [9], focussed on development of novel KP transdermal patch using almond oil as penetration enhancer in various concentrations. Work reported by Ladda et al [10], focussed on the effect of single and combined permeation enhancers on skin permeation of KP from drug-in-adhesive patch. However, no works were reported till date on formulation of reservoir type transdermal systems of KP.

Therefore, the present investigation was aimed to design and formulate reservoir type transdermal drug delivery systems for KP and to investigate the effect of different chemical permeation enhancers on the *in vitro* KP release from reservoir systems.

MATERIALS AND METHODS

Ketoprofen was a gift sample from Glenmark Pharmaceutical Ltd, India. Hydroxy propyl methyl cellulose (HPMC E5) is obtained from Colorcon Asia Ltd., India. Lauroglycol 90, Labrafil M 1944 CS, Labrasol, Transcutol P were obtained from Gattefosse, India. Rate control membrane COTRAN^{TM} 9702 (Ethylene Vinyl Acetate), Backing membrane SCOTCHPAK^{TM} 9733 (Polyester and Ethylene Vinyl Acetate copolymer) were obtained from 3M Health care, USA. HPLC water, sodium chloride, ammonium acetate were purchased from Lobachemie Pvt. Ltd, Mumbai, India. All solvents and reagents were of HPLC grade.

Analytical method

A high-pressure liquid chromatography (HPLC-PDA) method was developed for the analysis of KP samples. A Shimadzu Prominence HPLC system equipped with DGU-20A3 degasser, LC-20AD binary pumps, SIL-20AHT auto sampler and SPD-M20A PDA detector was used. Data acquisition was carried out using LC solution software. The chromatographic analysis was performed on Inertsil ODS 3 column (150×4.6mm;5µ) and the quantification was carried out at a wavelength of 258nm. 10mM Ammonium acetate: Acetonitrile (60:40%v/v) at a flow rate of 1.0 mL/min was used as mobile phase composition.

Preparation of KP hydro-alcoholic gels

Ketoprofen gels (1g batch size) were prepared as per the formula given in Table 1. Initially, the required amount of HPMC E5 polymer was accurately weighed and dispersed in water. Further required quantity of ethanol was added and mixed. To the polymeric dispersion permeation enhancers (at 5% level) were added and mixed thoroughly. Finally, accurately weighed KP (25mg) was added to the polymeric dispersion and vortexed for 1 min to obtain KP hydro-alcoholic gels.

Table 1: Composition of KP hydro-alcoholic gels

Ingredients (mg)	Formulae (1g batch size)				
	F1	F2	F3	F4	F5
Ketoprofen	25	25	25	25	25

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

HPMC E5	20	20	20	20	20
Ethanol*	500	500	500	500	500
Lauroglycol90*	-	50	-	-	-
Labrasol*	-	-	50	-	-
Transcutol P*	-	-	-	50	-
Labrafil M 1944 CS*	-	-	-	-	50
Water*	455	405	405	405	405

***Volume added was calculated based on the densities**

KP content in hydro-alcoholic gels

KP content in prepared gels was estimated to evaluate the reproducibility of the preparation method and formulations. From the 1 g (1 mL) gel containing 25mg of KP, 40 µL (1mg of KP) gel was taken in 1 mL centrifuge tube and remaining volume was made up to mark with methanol. The samples were diluted suitably and analysed using RP-HPLC method. The estimations were carried out in triplicate.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Effect of different permeation enhancers on *in vitro* KP permeation from gels

The effect of various permeation enhancers on *in vitro* KP permeation from gels was evaluated using a vertical type Franz diffusion cell apparatus with a water circulation system, heater and an eight-stage magnetic stirrer. Diffusion cells with an effective diffusional area of 1.77 cm^2 and a receptor volume of 14mL were used and 0.9% w/v sodium chloride solution is used as a receptor fluid. Rate controlling membrane (COTRAN 9702) with inner side facing towards donor compartment was mounted between donor and receptor compartments. The apparatus is maintained at 32˚C and receptor medium was stirred at a speed of 600 rpm. Care was taken to prevent the air bubble entrapment underside of rate controlling membrane and in receptor solution. After equilibration, 0.7 mL of prepared KP gel with different permeation enhancers (LG 90, Labrasol, Transcutol P, Labrafil M 1944 CS) were applied on to the rate controlling membrane (RCM). Samples (0.5 mL) were withdrawn in predetermined time intervals for 24hr and replaced with same amount of fresh saline to maintain sink conditions. The samples were the analysed by HPLC-PDA method.

Preparation of KP reservoir patches

The KP reservoir patches were prepared using a heat sealable COTRAN 9702 as rate control membrane and SCOTCHPAK 9733 as backing membrane. Both the membranes were sealed using a metallic ring which was previously heated on a hot plate. To ensure a gap for filling the KP gel into the patch, a thin strip release liner (non-heat sealable) was placed between rate controlling and backing membranes (Figure 1). After filling the prepared KP gel (as shown in Figure 1) into the patch the gap that was leftover for filing the gel was resealed using the pre heated metallic ring. The composition of the reservoir patches was given in Table 2 and the prepared reservoir patches were shown in Figure 2.

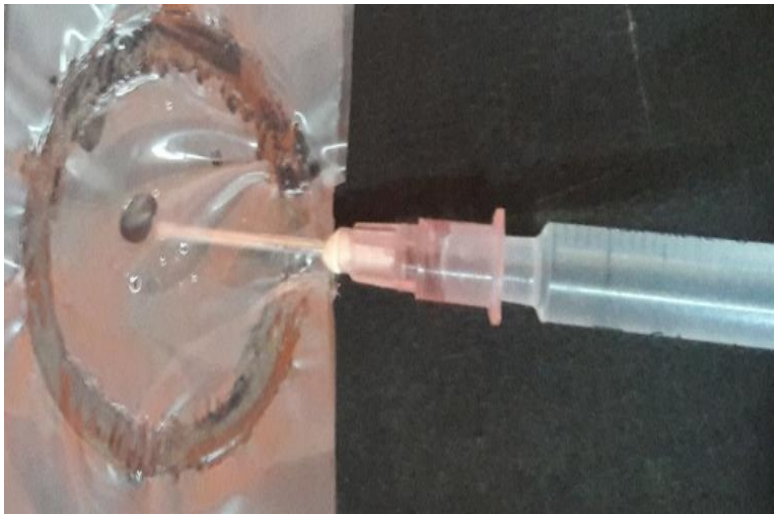

Figure 1: Filling of ketoprofen hydro-alcoholic gel into the reservoir patch

Table 2: Composition of reservoir patches

Formulation	Rate controlling membrane	Backing membrane	Permeation enhancer used in hydro-alcoholic

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

			gel
F6	Cotran 9702	SCOTHCHPAK 9733	Lauroglycol 90
F7	Cotran 9702	SCOTHCHPAK 9733	Labrafil M 1944 CS
F8	Cotran 9702	SCOTHCHPAK 9733	-

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

***In vitro* KP release studies**

In vitro drug release studies were performed using USP Type V Dissolution Rate Testing Apparatus using 400mL of 0.9% w/v saline was used as dissolution medium. A temperature of 32˚C and 50 rpm were maintained. The prepared reservoir patches were placed on a watch glass covered with nylon wire mesh and the patch was fitted tightly with rubber clamps with rate controlling membrane facing upwards. Then the watch glass was dropped into the dissolution flask (Figure 3). Samples (1ml) were withdrawn at predetermined time interval for 24hr and replaced with same amount of fresh saline to maintain sink conditions. The samples were analysed by HPLC-PDA method.

Figure 3: *In vitro* dissolution set up assembly

Statistical Analysis:
Results of experimental data were subjected to one-way ANOVA (using Fisher's LSD Post HOC test) using SYSTAT software (SYSTAT Software Inc., San Jose, USA). Results with '*p*' value of less than 0.05 were considered as of significant variance.

RESULTS AND DISCUSSION

KP content in gels

All the gel formulations showed uniform distribution of KP indicating the reproducibility of preparation method and formulations. KP content was found to be in range of 99.8 to 100.2 % with the gels prepared.

Effect of different permeation enhancers on *in vitro* KP permeation

In the present investigation, the effect of different permeation enhancers on *in vitro* KP release from the hydro-alcoholic gels was studied using a vertical type franz diffusion cell apparatus. The results demonstrate that addition of permeation enhancers resulted in significant increase in the KP permeation compared to the control (Figure 4). Also, the enhancement of KP permeation varied with the type of permeation enhancer used, with formulation containing Lauroglycol 90 (F2) showing superior enhancement in KP permeation followed by Labrafil M, Transcutol P and Labrasol.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

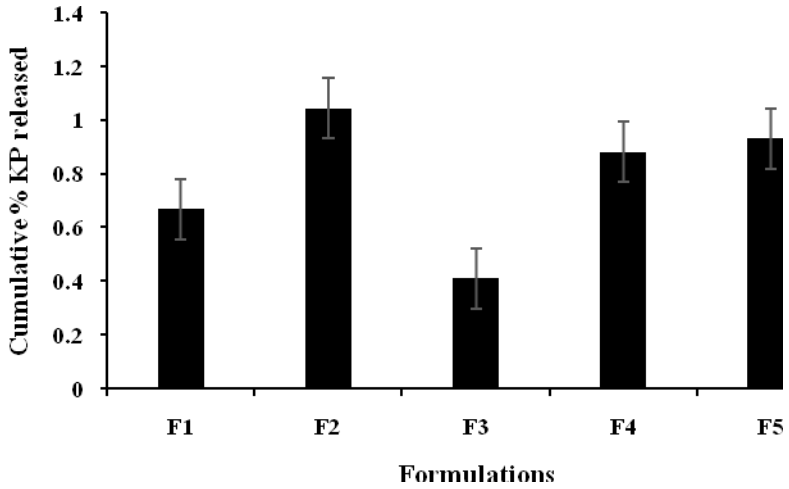

Figure 4: Effect of chemical permeation enhancers on *in vitro* ketoprofen permeation from hydro-alcoholic gels

The variation in the enhancement rates of KP with different permeation enhancers can be attributed to the differences in the enhancing mechanisms that were involved with each enhancer. With non-ionic surfactants like Labrafil M and Labrasol the permeation enhancement obtained can be attributed to the changes in the saturation concentration of the donor solution resulting in increase in concentration gradient across the membrane. The cumulative amounts of KP permeated at the end of 24hr were 7.62 ± 0.19 and 10.63 ± 0.179 µg/mL for formulations containing Labrasol (F3) and Labrafil M (F5) respectively which were about 1.6 and 2.23 fold higher compared to the cumulative amount that was obtained with the control (F1, 4.76 ± 0.08 µg/mL).

Among the two non-ionic surfactants used, Labrafil M showed moderately higher enhancement profiles compared to Labrasol. Reports from the literature, suggests that the permeation rate of KP will be higher in presence of lipophilic surfactants rather than that with hydrophilic surfactants [4]. Hence, Labrafil M being the lipophilic surfactant showed more KP permeation compared to Labrasol which is a hydrophilic surfactant.

The cumulative amount of KP permeated at the end of 24hr for formulation containing Transcutol P (F4) is 10.06 ±0.132µg/mL which is 2.11 fold higher compared to control. The higher KP permeation rates obtained with transcutol can be attributed to its effects on partition behaviour of the drug. Studies reported on permeation enhancement properties of transcutol suggests that the water absorbing property of transcutol causes changes in drug solubility resulting in alterations in partition the behaviour of the drug and thereby maximising the drug permeation across the membrane [11].

Formulation containing LG 90 (F2) showed superior KP permeation rates (12.29 ± 0.29 µg/mL at the end of 24hr) among the formulations prepared and is 2.58 times higher compared to control. The higher KP release can be attributed to its 15 carbon alky chain that is attached to the fatty acid moiety. Literature reports suggests that fatty acids with longer alkyl chains were found to enhance the permeation properties of the drug molecules compared to fatty acids with shorter alkyl chain lengths [10]. Overall, form the results it can be concluded that the addition of permeation enhancers significantly affected the KP release from the gels. LG 90 and Labrafil M with showed superior KP release were selected for further development of KP reservoir patches.

***In vitro* KP release from reservoir systems**

In the present investigation, i*n vitro* KP release from reservoir patches was studied using USP type V Dissolution Rate Testing Apparatus with 400mL of 0.9% w/v saline as dissolution medium. The comparative *in vitro* KP release profiles from the prepared reservoir patches were shown in Figure 5. The results indicate that the addition of permeation enhancers increased the KP release from patches. The cumulative percent KP release was found to be

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

2.92±0.04, 2.19±0.04 and 1.97 ±0.02 at 24hr with F6, F7 and F8 formulations respectively. A 1.4 fold and 1.1 fold increase in KP release was observed with LG 90 (F6) and Labrafil M (F7) when compared to control (F8).The KP release was found to be in order ofF6>F7>F8.Overall, from the results it can be concluded that LG 90 owing to its superior KP release rates was found to be the most promising chemical permeation enhancer for transdermal delivery of KP.

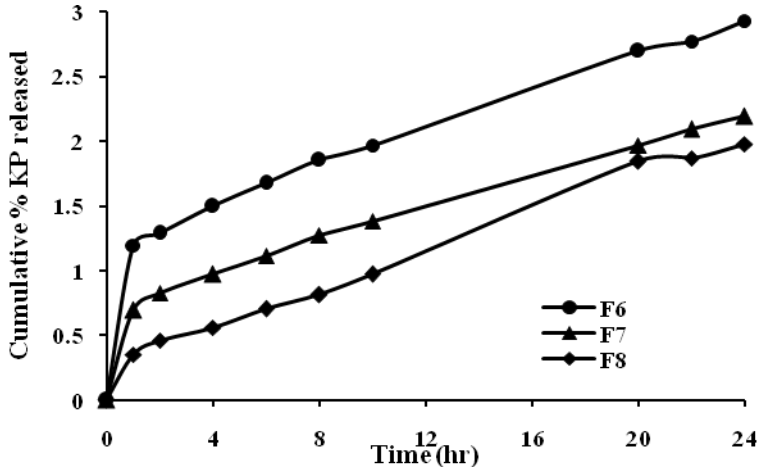

Figure 5: Comparative *in vitro* ketoprofen release from reservoir patches

CONCLUSION

In the present investigation an attempt was made to develop a reservoir type transdermal patch of KP that can address the adverse events associated with its oral therapy. Four types of chemical permeation enhancers (Labrasol, Transcutol P, Lauroglycol 90 and Labrafil M 1944 CS) were employed for a greater understanding on the effects of various enhancers on the transdermal permeation of KP from reservoir patch. It was observed that lauroglycol 90 was found to be the best suitable chemical permeation enhancer for transdermal delivery of KP. Overall, results from the present investigation can form the basis to perform further studies *(ex vivo)* that can be useful to achieve successful delivery of KP via transdermal reservoir patch.

ACKNOWLEDGEMENTS:

The authors are thankful to Glenmark pharmaceuticals, Mumbai, India for providing gift sample of KTP and also to the Siddhartha Academy of General and Technical Education, Vijayawada, for providing necessary facilities to carry out this research work.

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