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Research Article

Potential of Cyclodextrin Complexation and Liposomes in Topical Delivery of Ketorolac: *In Vitro* and *In Vivo* Evaluation

M. S. Nagarsenker,[1,2] L. Amin,[1] and Abhijit A. Date[1]

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Abstract. The objective of this investigation was to evaluate the effect of delivery strategies such as cyclodextrin complexation and liposomes on the topical delivery of ketorolac acid (KTRA) and ketorolac tromethamine. Ketorolac acid–hydroxypropyl-β-cyclodextrin solid dispersions (KTRA-CD) were prepared by kneading method. The liposomes containing ketorolac tromethamine (KTRM) and KTRA-CD were prepared. The *in vitro* permeation of KTRM solution, KTRA solution, KTRA-CD, and liposomes containing KTRM or KTRA-CD through guinea pig skin was evaluated. The anti-inflammatory activity of the topically applied KTRA-CD gel (containing 1% *w/w* KTRA) was compared to that of orally delivered KTRM solution. The KTRA-CD demonstrated significantly higher transdermal transport of ketorolac as compared to all other systems whereas liposomes significantly reduced the transport of ketorolac. The anti-inflammatory activity of the topically applied KTRA-CD gel was similar to that of the orally administered KTRM. Thus, cyclodextrin complexation enabled effective transdermal delivery of the ketorolac.

KEY WORDS: hydroxypropyl-β-cyclodextrin; ketorolac acid; ketorolac tromethamine; liposomes; transdermal delivery.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used as analgesics and in the treatment of locomotor pathologies and of local inflammation. Limited efficacy or adverse effects like gastrointestinal bleeding associated with oral delivery of NSAIDs has prompted researchers to investigate the feasibility of alternative drug delivery systems, such as the dermal and/or transdermal route, for the administration of these drugs.

Ketorolac, a pyrrolizine carboxylic acid derivative structurally related to indomethacin, is a nonsteroidal agent with potent analgesic and moderate anti-inflammatory activity. Clinical studies have shown that the single dose of ketorolac is more effective than that of morphine, meperidine, and pentazocine in moderate to severe postoperative pain (1). Furthermore, unlike narcotic analgesics, ketorolac does not alter gastric motility or hemodynamic variables or adversely affect respiration, nor it is associated with adverse central nervous system effects, abuse, or addiction potential; therefore, ketorolac is a relatively more favorable therapeutic agent for the management of moderate to severe pain (2,3).

Ketorolac is currently available as ketorolac tromethamine (KTRM) which is administered intramuscularly and orally in divided multiple doses for short-term management of postoperative pain (30 mg q.i.d. by intramuscular injection and 10 mg q.i.d. as oral tablets). Oral bioavailability of KTRM is reported to be 90% with a very low first pass metabolism. However, the drug is reported to cause severe gastrointestinal side effects such as gastrointestinal bleeding, perforation, peptic ulceration, and acute renal failure (3,4). Therefore, parenteral administration of KTRM is the preferred route of administration for moderate to severe pain management. Regardless of the route of administration, the biological half-life of the KTRM ranges from 4 to 6 h (3). Because of such a short half-life, frequent dosing is required to alleviate pain. To avoid an invasive drug delivery (i.e., intramuscular injection) and to eliminate frequent dosing regimens, there is a need for an alternative noninvasive mode of delivery for ketorolac. Due to these reasons, dermal and transdermal delivery of ketorolac is an attractive alternative to existing therapeutic strategies.

Additionally, high analgesic activity and low molecular weight of ketorolac makes it a good candidate for transdermal delivery. In view of this, researchers have attempted several delivery strategies such as use of permeation enhancers (5), use of proniosomes (6), synthesis of prodrugs (7), iontophoresis (8,9), and ultrasound (10) to develop a transdermal delivery system of either KTRM or ketorolac acid (KTRA). However, to date, potential of cyclodextrins and liposomes has not been evaluated for the dermal/transdermal delivery of either KTRM or KTRA, which is presented in this investigation.

Cyclodextrins are known to influence the percutaneous absorption of therapeutic agents by both a solubilizing action on the drug thus increasing its availability at the absorption site and by an interaction with the free lipids present in the

[1] Department of Pharmaceutics, Bombay College of Pharmacy, Kalina, Santacruz (East), Mumbai, 400098, India.
[2] To whom correspondence should be addressed. (e-mail: mangal_nag511@yahoo.co.in)

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stratum corneum resulting in improvement of transdermal penetration of therapeutic agents (11,12). Liposomes are known to improve the dermal localization of therapeutic agents and can act as a depot enabling the controlled release of therapeutic agent. Moreover, they can also be tailored to yield transdermal delivery of the therapeutic agents by suitable modifications (13). The present study investigates the potential of cyclodextrins and liposomes in the topical delivery of ketorolac. In the present investigation, we evaluated the potential of liposomes and/or cyclodextrins in the topical delivery of KTRM and KTRA by means of *in vitro* and *in vivo* studies.

MATERIALS AND METHODS

Materials

Ketorolac tromethamine (Sun Pharma Exports, Dadra, India), hydroxypropyl-β-cyclodextrin (HPBCD; Cerestar, USA), Phospholipon 90 (PL90) and Phospholipon 90H (PL90H; Phospholipid GmBH, Germany), and Noveon AA1 (Noveon Chemicals, Mumbai, India) were received as a gift sample. Cholesterol and chloroform (AR grade) were purchased from Qualigens, Mumbai, India. All the materials were used as received without any purification.

Preparation of Ketorolac Acid

KTRA was obtained by acidifying a solution of ketorolac tromethamine with 0.5 N hydrochloric acid. Ketorolac, precipitated as a free acid at pH 4, was washed free of tromethamine and the resultant KTRA suspension was checked for the absence of trometamol by the method given as an identification test for tromethamine in the USP monograph of KTRM (14). The KTRA was dried in a vacuum oven and used for the further studies.

Preparation of Solid Dispersion of KTRA with Hydroxypropyl-β-Cyclodextrin

Physical mixture of KTRA and HPBCD in the molar ratio of 1:2 was prepared by mixing the two in geometric proportions with a spatula (14). The mixture was kneaded using alcohol-distilled water (1:1) to obtain a dough like mass which was then dried in a vacuum oven at 45°C for 1 h and sieved through 85# (180 μ) to obtain a free-flowing powder (14).

Preparation of Liposomal Dispersions of KTRM and KTRA–HPBCD

Liposomal dispersions were prepared by the conventional lipid film hydration method using a mixture of PL90 (at the concentration of 50 μM or 38.75 mg), PL90H (at the concentration of 135 μM or 104.9 mg), and cholesterol (at the concentration of 62.27 μM or 24.1 mg) as solutions in chloroform which were placed in a round bottom flask containing glass beads (average diameter=4 mm). Chloroform was evaporated at 55–60°C under vacuum of −760 mm of Hg, for 15 min on a rotary evaporator (Superfit, Mumbai, India). The thin dry film deposited over the inner surface of the flask was hydrated with 5 ml phosphate buffer (pH 6.6) containing KTRM (25 mg) or KTRA–HPBCD complex (KTRA-CD; amount equivalent to 25 mg of KTRA) at 55–60°C. The flask was shaken for 15 min to dislodge the lipid film and to form vesicles.

Characterization of KTRA–HPBCD Complexes

The KTRA–HPBCD complex was characterized by using differential scanning calorimetry (DSC), infrared (IR), and X-ray diffraction (XRD) to ascertain the formation of complex.

Particle Size Analysis of Liposomal Dispersions

The particle size of the liposomal dispersion containing KTRM (KTRM-L) and KTRA-CD (KTRA-CD-L) was measured by dynamic light scattering analysis (Mastersizer, Malvern Instruments, Malvern, UK) using a He–Ne laser radiation at a wavelength of 632.8 nm. About 3 ml of liposomal dispersion was suitably diluted in 1,000 ml of distilled water at 25°C, in order to avoid multiscattering phenomena. Samples were placed in quartz cells and analyzed through a 45-mm focus lens by means of a computer controlled image system. The measurements were carried out at 25°C and at a scattering angle of 90°. The experiments were performed in triplicate and each sample was analyzed three times.

Encapsulation Efficiency of Liposomal Dispersions

Liposomal dispersions (5 ml) were centrifuged at 25,000 rpm for the 30 min using Beckman Ultracentrifuge (Wipro, Mumbai, India). The supernatant was analyzed for unencapsulated drug (KTRM or KTRA) at 321 nm by using a validated UV-spectrophotometric method after suitable dilution.

The entrapment efficiency was calculated by the following equation:

$$\%\mathrm{EE} = \left[\frac{M_{\text{initial drug}} - M_{\text{free drug}}}{M_{\text{initial drug}}}\right] \times 100 \qquad (1)$$

where $M_{\text{initial drug}}$ is the mass of initial drug used in the experiment and the $M_{\text{free drug}}$ is the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

UV Analysis of KTRM and KTRA

Standard solution of KTRM and KTRA (100 μg/ml) was prepared by dissolving accurately weighed quantity of the drug in methanol and working standards were prepared by dilution of this standard solution with pH 6.6 phosphate buffer. The absorbance of the resulting solutions was recorded at 321 nm in a 10-mm quartz cell on a Shimadzu UV-1650 UV–VIS double beam spectrophotometer (Shimadzu, Japan). All the experiments were performed in triplicate.

Preparation of the Various Samples for Permeability Studies

For the permeation studies, the KTRA–HPBCD complex was dissolved in the pH 6.6 buffer to yield a KTRA

concentration of 4.8 mg/ml. The KTRM and KTRA containing liposomal dispersions (pH 6.6) were prepared as per the method described earlier such that the final KTRA concentration was 4.8 mg/ml. KTRM solution was prepared in pH 6.6 buffer (concentration equivalent to 4.8 mg/ml of KTRA). Saturated solution of KTRA (3 mg/ml) was prepared in pH 6.6 buffer. All these samples (1 ml) were used for the *in vitro* permeation study. The pH of all the samples used for the permeation study was 6.6.

In Vitro Skin Permeation Study

In vitro permeation of KTRM or KTRA from various samples was evaluated using full thickness abdominal skin excised from adult guinea pigs weighing in the range of 300–400 g. The visceral side of the freshly excised skin was cleaned free of any adhering subcutaneous tissue. The hair on the epidermal surface of the skin was cut with the help of a pair of scissors, as close to skin as possible without damaging the skin. The skin samples were mounted on modified Franz diffusion cells with a surface of 5 cm^2 and a receptor volume of 8 ml such that the dermal side of the skin was exposed to the receptor fluid and the stratum corneum remained in contact with the donor compartment. Phosphate buffer (pH 6.6) was filled in the receptor compartment and stirred continuously with the help of a magnetic stirrer. The medium was maintained at 37°C with the help of a water jacket of the receptor compartment receiving water at the temperature of 37°C from circulating water bath. On the epidermal side of the skin, 1 ml of the test sample was spread evenly and both the donor and receptor compartments were clamped together. The donor compartment was covered with the aluminum foil tightly so as to avoid evaporation of water from the formulation during the study. The receptor medium was withdrawn completely and replaced with fresh medium at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 h. Samples were diluted suitably and analyzed spectrophotometrically for the content of KTRM or KTRA at 321 nm. The aliquots obtained after subjecting blank formulations (without drug) to permeation studies were used as a reference for the determination of KTRM and KTRA to negate any possible interference from the skin components or formulation components. Cumulative amount of KTRM or KTRA permeated through skin was plotted as a function of time. The total quantity of the drug (Q) that diffused to the receptor compartment in time (t) during the steady state and the flux at the steady state, J_s [μg/(cm^2 h)], was calculated using the linear portion of the correlation between the accumulated quantity of the drug that diffused through the skin by unit area and time. All the experiments were performed in triplicate.

Preparation of KTRA–HPBCD Containing Gel

For the preparation of gel, KTRA–HPBCD complex was dissolved in distilled water to yield a KTRA concentration of 10 mg/ml. To 50 ml of this solution, 0.5 g of gelling agent (Noveon AA1) was dispersed under stirring by using an overhead stirrer. The stirring was continued until the gelling agent was completely dispersed. The pH of the dispersion was adjusted to 6.5 using a 0.05% *w/w* triethanolamine solution. The final concentration of the KTRA in the gel was 1% *w/w*.

Statistical Analysis

Data obtained from skin permeation experiments were expressed as mean±standard error (three independent samples). The flux values and amount of the drug permeated at the end of 10 h from various were analyzed utilizing analysis of variance (GraphPad InStat Demo Version). Differences were considered statistically significant at $P<0.05$.

Evaluation of Anti-inflammatory Activity

Anti-inflammatory activity of topically applied KTRA–HPBCD containing gel (KTRA-CD gel) and orally administered KTRM was determined in swiss albino mice (20–25 g) using carrageenan-induced paw edema model. Animal care and handling throughout the experimental procedure were performed in accordance to the Committee for the Purpose of Control and Supervision of Experiments on Animals guidelines. The experimental protocol was approved by the Animal Ethical Committee of Bombay College of Pharmacy. The overnight fasted animals were divided into three groups of six rats each as follows

Group 1: Control (no treatment)
Group 2: Oral administration of KTRM solution equivalent to 80 mg/kg KTRA
Group 3: Topical administration of KTRA-CD gel at the KTRA dose of 80 mg/kg

After 30 min of drug administration, mice of all three groups were challenged by a subcutaneous injection of 0.1 ml of a 1% *w/v* carrageenan solution, into the plantar site of the left hind paw. The paw volumes were measured using Ugo basile 7140 Plethysmometer, just before and after 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h of carrageenan administration. The percent inhibition of edema at any time for each rat was calculated as

$$\%\ \text{inhibition} = 100 \times [1 - (A - x)/(B - y)] \qquad (2)$$

where A is paw volume after administration of carrageenan at time t, and x is paw volume before administration of carrageenan. B is the mean paw volume of control rats after administration of carrageenan at time t and y is mean paw volume of control rats before administration of carrageenan.

The percent edema inhibition observed with the KTRA-CD gel and KTRM oral solution was compared using two-tailed paired t test (GraphPad InStat Demo Version). Differences were considered statistically significant at $P<0.05$.

RESULTS AND DISCUSSION

Preparation and Characterization of KTRA–HPBCD Solid Dispersions

The KTRA–HPBCD solid dispersion was prepared by kneading technique as reported in our earlier investigation. The DSC, IR, and XRD studies indicated that there was a considerable interaction between KTRA and HPBCD and the KTRA was rendered amorphous in the solid dispersion. The results are same as reported in our earlier publication (14).

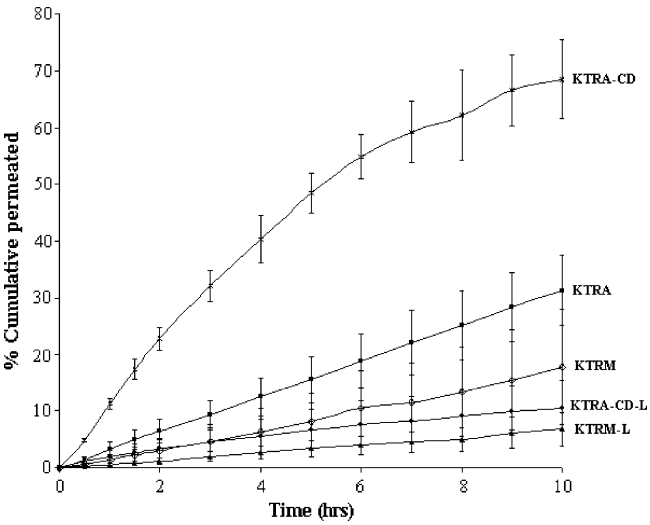

Fig. 1. *In vitro* permeation profile of KTRM or KTRA through guinea pig skin observed with various systems (data expressed as mean±SD; $n=3$). *KTRM* ketorolac tromethamine solution, *KTRA* ketorolac acid saturated solution, *KTRA-CD* KTRA–hydroxypropyl-β-cyclodextrin solution, *KTRM-L and KTRA-CD-L* liposomes containing KTRM and KTRA-CD, respectively. KTRA-CD showed significantly higher permeation profile as compared to the other systems ($P<0.05$)

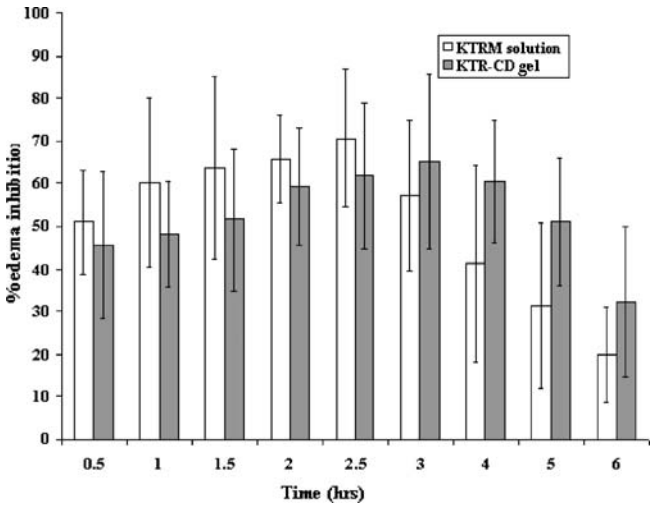

Fig. 2. Anti-inflammatory activity of topically applied KTRA-CD gel and orally delivered KTRM solution. Data expressed as mean±SD ($n=6$). Anti-inflammatory activity of the topically applied KTRA-CD gel was similar to that of oral KTRM solution ($P>0.05$)

UV Analysis of KTRM and KTRA

The assay was linear in the concentration range 1–15 μg/ml for KTRM ($Y=0.0579X+0.003$; $r^2=0.999$; % coefficient of variation (CV)=1.12) and 1–10 μg/ml for KTRA ($Y=0.0774X+0.001$; $r^2=0.997$; % CV=1.2). The method was used to determine the encapsulation efficiency as well as the percutaneous absorption of the KTRM and KTRA.

Evaluation of Liposomal Dispersions of KTRM and KTRA–HPBCD

Liposomes containing KTRM and KTRA–HPBCD could successfully be formulated using lipid film hydration method. KTRM liposomes showed particle size in the range of 0.39 to 9.74 μ with the mean particle size of 3.82±0.19 μ whereas KTRA–HPBCD liposomes showed particle size in the range of 0.9 to 11.2 μ with the mean particle size of 4.91±0.05 μ. The encapsulation efficiency of the KTRM liposomes was 10.32±1.5% and that of KTRA–HPBCD liposomes was 10.64±1.43%. The loading of KTRM was in liposomes was 1.48% *w/w* of the lipids whereas the loading of KTRA in liposomes was 1.52% *w/w* of the lipids.

In Vitro Skin Permeation Studies

The mean percentage cumulative permeation of the drug from various systems is shown in Fig. 1 and the values of flux and permeability coefficients are reported in Table I. It is evident from the Fig. 1 and Table I that the KTRA has high permeability from the skin as compared to that of the KTRM though the differences were not significant. However, it is noteworthy that the KTRA concentration used for the permeation study was 1.5-fold lesser than that of the KTRM despite of which the permeability and the flux values were higher for KTRA. The reason for the higher permeability could be due to the higher lipophilicity of the KTRA (data not shown) as compared to that of KTRM. In addition to lipophilicity, the amount of the drug present in unionized form also governs the permeation of the drug molecule. The

Table I. Mean values of Cumulative KTRM or KTRA Permeated at the End of 10 h, Flux Values, and Permeability Coefficients of Various Formulations

Formulation	KTRM or KTRA permeated at the end of 10 h (% of applied dose)	Flux value (μg/cm^{2}h)	Permeability coefficient (cm/h)
Ketorolac tromethamine solution	17.81±10.81	17.86±9.91	$(3.72\pm1.2)\times10^{-3}$
Saturated solution of ketorolac acid	31.24±6.22	26.66±10.08	$(8.88\pm3.36)\times10^{-3}$
KTRM liposomes	6.84±2.94	4.71±0.94*	$(0.98\pm0.11)\times10^{-3}$
KTRA–HPBCD liposomes	10.53±4.876	4.96±2.70**	$(1.03\pm0.51)\times10^{-3}$
KTRA–HPBCD solution	68.51±6.99	65.48±7.55**	$(13.64\pm1.57)\times10^{-3}$

Data expressed as mean±SD ($n=3$)
*$P<0.05$ (significantly different than KTRM solution); **$P<0.05$ (significantly different than KTRA solution)

KTRM has a pKa of 3.45 whereas the KTRA has pKa of 4.95. The pH of both the solutions was 6.6. Hence, at pH 6.6, most of the KTRM would be present in the ionized form which results in lower permeation or the flux value (Table I). On the other hand, the extent of ionization of KTRA at pH 6.6 would be much smaller than that of KTRM. Hence, KTRA has shown more permeability and flux value as compared to that of KTRM. The complexation of the KTRA with the HPBCD significantly increased the permeation of KTRA from the skin as compared to all the other systems employed in the investigation ($P<0.05$). At the end of 10 h, in case of KTRA-CD solution, the amount of KTRA permeated through the skin was as high as 68% which indicates that there was significant transdermal transport of the KTRA from the skin. The flux values were around 2.5 and 4 times higher than that of KTRA solution and KTRM solution respectively. The permeation enhancing ability of the HPBCD has been well established in the literature (12). However, there are contrary reports on the mechanism of the permeation enhancement. Some studies have demonstrated that the HPBCD interacts with the corneocytes resulting in increased permeation whereas in certain cases, increased drug solubility and the higher concentration gradient appeared to be responsible for the permeation enhancement (12, 15). The complexation of KTRA with HPBCD resulted in almost 50- to 60-fold increase in the solubility. This results in a very high concentration gradient across the skin. It is also possible that the complexation with cyclodextrin may have altered the permeability characteristic which is reflected in the permeability coefficient (Table I). It is evident from the Fig. 1 that for the first 6 h, the permeation curve of KTRA-CD is nearly linear ($R^2=0.99$). After this period, there is a decrease in the flux value due to decrease in the KTRA concentration in the donor compartment. The other systems show zero order release or pseudo-zero order release of the drug. It is evident that both the liposomal dispersions (KTRM-L and KTRA-CD-L) showed significantly lower transport of the KTRM or KTRA through the skin ($P<0.05$ when compared to the other systems). The flux values were significantly lower as compared to all other systems. Between the liposomal systems, KTRA-CD containing liposomal dispersion showed slightly higher flux than that of the KTRM containing liposomes though the differences were not significant. These results are similar to that observed by Maestrelli *et al.*, in the case of ketoprofen (16). As transdermal delivery is desired in the case of ketorolac, KTRA-CD system was chosen for the *in vivo* anti-inflammatory studies.

Evaluation of Anti-inflammatory Activity

The performance of the topically applied KTRA-CD gel was compared with the orally administered KTRM. It was hypothesized that if the KTRA-CD system results in significant transdermal transport, then the topically applied KTRA-CD gel would give performance similar to that of the orally delivered KTRM. The results of the anti-inflammatory study are shown in Fig. 2. The topical application of KTRA-CD gel demonstrated anti-inflammatory activity similar to that of the oral treatment with KTRM ($P>0.05$) during the 6 h of the study. Furthermore, the mean percentage inhibition showed by KTRA-CD gel was higher than KTRM oral solution at the end of fourth, fifth, and sixth hours though the differences were not significant. The results of this study corroborate the observations of the *in vitro* skin permeation study. The developed KTRA-CD topical gel can be a viable alternative to the oral ketorolac therapy.

CONCLUSION

Topical application of the KTRA–HPBCD complex successfully resulted in transdermal delivery of ketorolac whereas liposomal KTRA and KTRM dispersions promoted dermal localization of the drug. The therapeutic performance of KTRA-CD topical gel was comparable to the orally delivered KTRM. Thus, topical KTRA-CD gel would be an interesting approach for ketorolac delivery which would circumvent the adverse effects associated with oral ketorolac therapy without compromising the efficacy.

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