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Effects of Vehicles and Penetration Enhancers in Transdermal Delivery of Ketorolac Tromethamine

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Abstract

The aim of the present work was to evaluate the transdermal permeability of ketorolac tromethamine hydro-alcoholic gel in vitro and ex-vivo. The prepared hydro-alcoholic gel significantly improved drug permeation and reduced the lag time. Hydro-alcoholic gel prepared with various concentrations of permeability enhancers (DMSO, menthol and propylene glycol) and Isopropanol used as vehicles that provided a higher KT flux across the coat skin. Gel was prepared with Carbopol 940 as the base; the effects of percutaneous enhancers on the transdermal permeability of hydro-alcoholic gel were investigated by in vitro permeation experiments. Cumulative permeation at different times was determined by UV Spectroscopy. In vitro drug release was analyzed from hydro-alcoholic gel, using Franz diffusion cells. Ex vivo permeation of KT across coat skin was studied using a Franz diffusion cell, with phosphate buffer (pH 7.4) at 32 ℃ as receptor solution. The aim of this study is to investigate the capability of permeability enhancers and vehicles used in hydro-alcoholic gel formations, which may increase the diffusion coefficient of the drug into the stratum corneum or improve partitioning between the formulation and the stratum corneum. Hydro-alcoholic gel prepared were characterized by pH, Viscosity, *In-Vitro* and *Ex-vivo* drug release and stability testing under experimental conditions. Formulation F6 showed the highest permeation flux, which was 3.331 µg/cm^2.hr and permeability coefficient was 3.180 cm.h^{-1}.10^{-3}. Even though DMSO alone did not show high permeation rate, the skin permeability of KT was markedly increased by the addition of isopropanol as vehicle respectively. Results revealed that the hydro-alcoholic gel formulations exhibited high drug release especially at permeability enhancer and vehicle concentration increases and the release follows diffusion controlled mechanism. All enhancers showed enhancement in ketorolac penetration specially (DMSO< Propylene glycol<Menthol) the optimized formula F6 contain Ketorolac tromethamine 15mg, DMSO 15mg and Isopropanol 4ml. The transdermal process of ketorolac tromethamine fits to a zero-order kinetic equation, and its release profile remains of the zero-order despite the addition of enhancers.

Key-Words: Hydro-alcoholic gel, Ketorolac tromethamine, Skin permeation and Carbopol 940

Introduction

Inflammation is as local response of living mammalian tissue to injury due to any agent or injury. Inflammation recognizable usually in form of painful swelling connected with some changes in skin covering the site.1 Inflammation can be categorized as either acute or chronic. Acute inflammation is the preliminary response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood into the injured tissues. Extended inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells which are present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory course of action.2

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Ketorolac tromethamine (KT) is a non-steroidal anti-inflammatory drug. The potency of KT is 800 times greater than commonly used aspirin .3 Non-steroidal anti-inflammatory drugs (NSAIDs) like KT, use their effect due to inhibition of the cycloxygenase (COX) enzymes.4 KT are given orally, but in last year's; several clinical data exposed that occurrences of several gastrointestinal side effects from oral administration of this KT. the major negative aspect for its use include its short biological half-life (4–6 h), thereby demanded frequent administrations to achieve the desired therapeutic response. Frequent administrations of KT lead to severe gastrointestinal side effects combined with cyclooxygenase inhibition; these side effects can lead to high patient incompliance.5,6

Novel strategy attempt to eliminate or decrease this GIT adverse effects have been the development of transdermal preparation .7

One of the best topical dosage forms is the gel. Gels are semisolid systems consisting of dispersion of small or large molecules in an aqueous or non- aqueous liquid vehicle provided jelly-like formation through the addition of a gelling agent.8 Gels are classified according to vehicle into hydrogels or organogels. A hydrogel is defined as an aqueous phase with an interconnected polymeric component. An organogel is defined as an organic phase with an interconnected polymeric component.9

The transdermal route of administration is recognized as one of the most promising route for the local and systemic administration of the drugs. Transdermal route has advantages over conventional form of drug administration as it avoids hepatic first pass metabolism as well as improves patient compliance.10 However, the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be ad- ministered.

Ketorolac is a non-steroidal anti-inflammatory drug with potent analgesic and moderate anti-inflammatory activities by inhibiting prostaglandin synthesis. 11, 12 KT's low molecular weight makes it a good candidate for transdermal administration, showing high anti-inflammatory activity and thus increasing the potential for a useful transdermal preparation. Likewise, transdermal delivery of KT would reduce the dose required to achieve a therapeutic effect and would reduce the possibility of adverse actions in the gastrointestinal tract.13

Ketorolac tromethamine salt is presently administered intramuscularly, intravenously, or orally. whereas oral bioavailability of ketorolac was reported to be 90% with a very low first-pass metabolism, its short biological half-life (4–6 h) and many adverse effects, such as upper abdominal pain and gastrointestinal ulceration, restrict its oral use.14

This requirement implies that the transdermal dosage form must allow the drug to penetrate deeply into the skin, which is important considering that KT is hydrophilic in nature and its absorption through the skin is poor. Therefore, a number of different methods have been investigated in order to enhance the transdermal delivery of KT. 15, 16

Consequently, the aim of this work was to formulate hydro-alcoholic gel containing KT and to evaluate their in vitro drug release properties as well as effects of vehicles and penetration enhancers in transdermal delivery of Ketorolac Tromethamine.

Material and Methods

Materials

Propylene Glycol, Menthol and Triethanolamine were purchased from Himedia Chemicals. Carbopol 940,Disodium Hydrogen Phosphate, Potassium Di Hydrogen Phosphate, Sodium Chloride and isopropyl alcohol were purchased from Loba Chemie (Mumbai, India), Dimethyl Sulfoxide (DMSO) were purchased from Sisco Research Lab, Mumbai, and A gift sample of ketorolac tromethamine (KT) was procured from Piramal Health care Pvt Ltd. (Mumbai, India)

Method of Preparation and Optimization of Formula

Preparation of hydro-alcoholic gel of Ketorolac tromethamine: As a base, carbopol 940 was slowly dispersed into distilled water (3ml) and allowed to swell for 12 h under normal temperature; base of the gel and enhancer dissolved in Isopropanol: water ratio and with continuous mixing using a magnetic stirrer until a homogenous gel was formed. The gel was set aside for few minutes until the bubbles disappeared. The gels were kept in plastic well-closed containers and stored at room temperature until the time of analysis. 17, 18, 19

Table 1: Formulation of Hydro-Alcoholic gel

Formulations	Drug (mg)	Propylene glycol (ml)	DMSO (ml)	Menthol (mg)	Isopropanol and water ratio (ml)	Carbopol 940 (mg)	Triethanolamine (ml)
F1 Control Batch	15	-	-	-	6 ml water	12	QS
F2	15	10	-	-	3:1	12	QS
F3	15	15	-	-	4:2	12	QS
F4	15	20	-	-	5:3	12	QS
F5	15	-	10	-	3:1	12	QS
F6	15	-	15	-	4:2	12	QS
F7	15	-	20	-	5:3	12	QS
F8	15	-	-	10	3:1	12	QS

F9	15	-	-	15	4:2	12	QS
F10	15	-	-	20	5:3	12	QS

DMSO: Dimethyl Sulfoxide

Evaluation Parameters of Hydro-Alcoholic Gel of KT

Determination of pH: - 1gm of the gel was taken and dissolved in 10 ml of distilled water with sonication and filtered, pH of the filtrate was checked with digital pH meter.

Viscosity: - The measurement of viscosity of the prepared hydro-alcoholic gel was done with Brookfield Viscometer (DV-E). 10g of gel was taken into a beaker and the spindle was dipped into the gel formulation, viscosity of the gel formulation was measured by rotating the spindle 96 at 10rpm.

***In-vitro* Drug Diffusion Study**

In-vitro drug release studies were performed by using a modified Franz diffusion cell which is consists of a receptor and donor compartment with capacity of 20 ml. Diffusion cell was separate by synthetic cellophane membrane, which is mounted between the donor and receptor compartment of the cell.

The formulated gels were weight up to 1 g and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was set on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred at 60 RPM using magnetic stirrer; the temperature was maintained at 37 ± 0.50 °C.

The samples of 1 mL were withdrawn at time interval of 0, 1, 2, 3, 4, 5, 6, 7 and 8 hrs analyzed for drug content spectrophotometrically at 322 nm against blank. The receptor phase was replenished with an equal volume of fresh phosphate buffer at each time of sample withdrawal. The cumulative amounts of drug diffused from gels were plotted against time.

Table 2: % Cumulative Drug release of Hydro-Alcoholic gel
Ex vivo Permeation Studies

Time	Drug Solution F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	5.223 ± 0.120	7.586 ± 0.073	6.022 ± 0.071	8.943 ± 0.027	14.117 ± 0.048	15.098 ± 0.071	10.570 ± 0.048	10.411 ± 0.048	8.117 ± 0.048	9.272 ± 0.027
2	11.346 ± 0.120	14.779 ± 0.102	15.866 ± 0.029	16.559 ± 0.048	27.962 ± 0.074	28.481 ± 0.640	19.608 ± 0.049	21.695 ± 0.049	15.195 ± 0.049	17.026 ± 0.320
3	18.213± 0.230	26.228 ± 0.0401	23.895 ± 0.028	26.252 ± 0.027	44.044 ± 0.049	38.768± 0.051	34.707 ± 0.047	32.722 ± 0.074	23.482 ± 0.049	28.540 ± 0.218
4	21.333± 0.174	33.797 ± 0.056	37.931 ± 0.100	38.816 ± 0.048	59.526 ± 0.049	49.813 ± 0.049	41.835 ± 0.047	42.896 ± 0.050	30.880 ± 0.049	36.611 ± 0.280
5	30.385± 0.110	45.931 ± 0.300	43.957 ± 0.129	50.095 ± 0.027	64.520 ± 0.481	61.996 ± 0.049	53.373 ± 0.293	47.409 ± 0.481	41.250 ± 0.049	50.462 ± 0.407
6	38.182± 0.300	58.094 ± 0.312	58.161 ± 0.406	59.139 ± 0.278	70.552 ± 0.494	68.329 ± 0.498	62.984 ± 0.488	53.663 ± 0.494	53.650 ± 0.049	58.975 ± 0.284
7	41.472± 0.109	62.733 ± 0.721	68.614 ± 0.744	71.214 ± 0.480	77.204 ± 0.495	77.138 ± 0.494	70.331 ± 0.494	65.586 ± 0.495	68.465 ± 0.481	63.505 ± 0.487
8	53.221± 0.250	70.696 ± 0.755	77.249 ± 0.756	78.928 ± 0.494	83.874 ± 0.495	89.350 ± 0.577	77.022 ± 0.495	68.969 ± 0.495	70.288 ± 0.494	73.112 ± 0.494

Mean value ± SD; N=3

Preparation of Goat Dorsal Skin: The experiment was carried out using freshly killed goat dorsal skin obtained from the local slaughterhouse and stored at - 20°C. The hair of test animals were carefully trimmed short (<1.8 mm) with a pair of scissors and to remove any skin content skin was shaved using a hand razor to removed subcutaneous tissue. The epidermis was prepared surgically by heat separation technique 20. The epidermis

was washed with water and used for ex vivo permeability studies

Franz diffusion cell with a surface area of 3.56 cm2 was used for ex vivo permeation studies. The goat dorsal skin was mounted between the compartments of the diffusion cell with stratum corneum facing the donor compartment. The stratum corneum side of the skin was kept in intimate contact with the release surface of the TDDS under test. The receiver phase is 12 ml of phosphate buffer saline (PBS) pH 7.4 stirred at 500 rpm on a magnetic stirrer; the whole assembly was kept at 37 ± 0.5ºC. The amount of drug permeated was determined by removing 1 ml of sample at appropriate time intervals up to 8 hr, the volume was replenished with an equal volume of PBS pH 7.4. The absorbance was measured at 322 nm spectrophotometrically. Cumulative amounts of drug permeated in µg/cm2 were calculated and plotted against time.

Calculation of permeation parameters

The permeation data were analyzed by the method developed for the flow-through diffusion cell system.21 The steady-state flux (Js), and diffusion coefficient (D), are defined by Eqs. (1–2). 22

The permeation profile of hydro-alcoholic gel through goat skin were constructed by plotting the total cumulative amount of drug permeated per unit surface area (dM/A mg/cm2) versus time t (h). Hydro-alcoholic gel steady state flux, Jss (mg/cm^2/h) is calculated as the slope of the linear regression line.23

The **steady-state flux (Js**), calculated by following equation

$J_{SS} = (dq/dt)_{ss}. 1/A$ …… (1)

A = the effective diffusion area,

$(dq/dt)_{ss}$ = the steady-state slope.

The **permeability coefficient (Kp**) is calculated using the relation derived from Fick's first law of diffusion as follow:

$Kp = J_{SS}/C_0$ ..... (2)

where C_0 is the initial drug concentration in the donor compartment.24

Mechanism of Drug Release

Various models were investigated for explaining the kinetics of drug release.

To test the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order and Higuchi release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = H_O.t$

Where 'F' is the drug release, 'H_O' is the release rate constant and't' is the release time.

The plot of percentage drug release versus time is linear.

First order release rate kinetics

The release rate date are fitted to the following equation

$Log (100 – F) = H_O t$

A plot of log % drug release versus time is linear.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$F = K t^{1/2}$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of percentage drug release versus square root of time is linear. 25, 26, 27

Results and Discussion

The method of preparation of hydro-alcoholic gel is based on the simple idea that the mixture of gelling agent: alcohol: aqueous phase can be used to form the hydro-alcoholic gel. **Carbopol 940** was chosen as gelling agents, Isopropanol was used as vehicle and propylene glycol, menthol, DMSO were used as penetrations enhancing agents in this study.

Evaluation of hydro-alcoholic gel of ketorolac Tromethamine:

4pH measurement

The pH of all the hydro-alcoholic gel formulations was in the range of 6.0 to 7.3, which lies in the normal pH range of the skin and would not generate any skin irritation. Comparison of pH in hydro-alcoholic gel has been showed in the table No.03.

Table 3: pH of Hydro-Alcoholic Gel

S. No	pH
F1Drug solution	6.2 ± 0.096
F2	6.8 ± 0.241
F3	6.3 ± 0.165
F4	6.8 ± 0.287
F5	7.1 ± 0.081
F6	6.8 ± 0.081
F7	6.7 ± 0.161
F8	6.8 ± 0.243
F9	6.9 ± 0.083
F10	6.0 ± 0.081

Viscosity

The viscosity of the hydro-alcoholic gel formulations generally reflects its consistency. The results of viscosity measurement of KT hydro-alcoholic gels containing fixed concentration of carbopol 940 polymer (12mg) and different concentration of permeation enhancers (10, 15, 20 mL or mg) Results showed that as the concentration of permeation enhancer increases, viscosity of gel formulations slightly decreases or no change in viscosity and permeability of drug increases.

Viscosity was found in the range of 8629 cps to 10511 cps, for hydro-alcoholic gel formulations has been showed in the table no. 04.

Table 4: Viscosity of Hydro-Alcoholic Gel

S. No.	Viscosity (cps)
F1 Drug Solution	10511± 0.713
F2	10417 ± 0.806
F3	10227 ± 1.246
F4	9740 ± 1.631
F5	10350 ± 1.45
F6*	8629 ± 1.246
F7	8630 ± 2.051
F8	10514± 0.813
F9	10291 ± 0.811
F10	9330 ± 3.16

***In-vitro* Drug Diffusion Study**

Formulation F6 showed highest drug release of 89.350 % and formulation F1 showed lesser drug release of 53.221 % in 8 hrs. After incorporation of permeability enhancers (Menthol) and Isopropanol as vehicle in hydro-alcoholic gel formulation F6, they show significant enhancement in *In-vitro* drug release. Formulation F6 showed highest drug release of 89.350 % and formulation F1 showed lesser drug release of 53.221 % in 8 hrs in fig no 01.

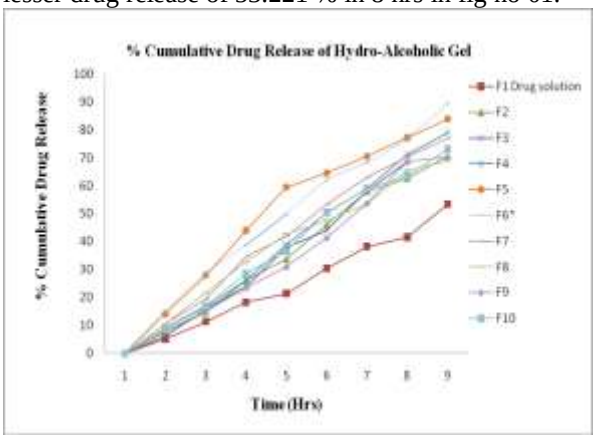

Fig. 1: % Cumulative Drug Release of Hydro-Alcoholic Gel Formulations

***Ex vivo* Permeation Studies**

Ex vivo permeation studies were performed on gel formulations (F4, F5 and F6) because these formulations show higher drug release as compared to other gel formulations (F1, F2, F3, F7, F8 and F9). Gel formulations F6 showed highest drug release of 88.340 % and formulation F4 showed lesser drug release of 72.028% in 8 hrs. The results of ex vitro permeation are shown in Fig 02.

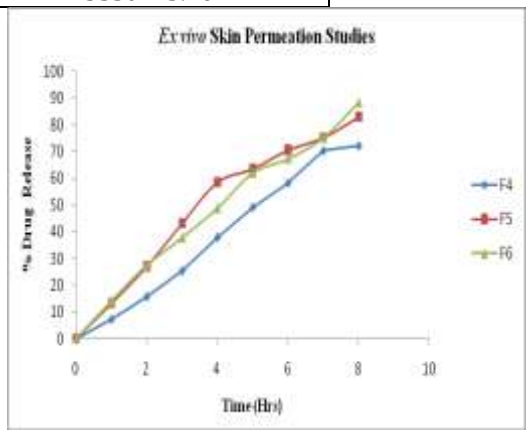

Fig. 2: % Ex vivo Skin Permeation Studies of Hydro-Alcoholic Gel Formulations

Calculation of permeation parameters

The flux values of F4, F5 and F6 were found to be 2.987, 3.331 and 2.758 µg/cm^2. hr respectively. The higher flux value of gel F6 indicates its higher drug permeability behavior as compared to formulations F4 and F5. The Permeability coefficient of F4, F5 and F6 gel were found to be 2.01, 2.48 and 3.18 cm.h^{-1}.10^{-3}. (Table 5)

Table 5: Permeation Parameters of KT Hydro-alcoholic gel formulations

Formulation	Flux (J) µg/cm^2.hr	Permeability coefficient (Kp) (cm.h^{-1}.10^{-3})
F4	2.987 ±0.034	2.01±0.00001
F5	2.758 ±0.071	2.48±0.00038
F6	3.331 ±0.052	3.18±0.00005

Mechanism of Drug Release

Drug release kinetics: - The results obtained for F6 were showed in Table 06. The all kinetics models were described in its respective graphs and shown in Fig 03, 04 and 05. The best fit with higher correlation was found with the Zero order with the R^2 value of 0.991 (Table 07).

Table 6: Kinetic Release study of Hydro-alcoholic gel of Ketorolac Tromethamine (F6)

Time (hrs)	% CRD	log CRD	% Drug remaining	log % Drug remaining	√ time	log time
0	**0**	0	100	2	0	0
1	15.098	1.176	84.90	1.928	1	0
2	28.481	1.454	71.51	1.854	1.414	0.150
3	38.768	1.588	61.23	1.786	1.732	0.238
4	49.813	1.697	50.18	1.700	2	0.301
5	61.996	1.792	38.00	1.579	2.236	0.349
6	68.329	1.834	31.67	1.500	2.449	0.388
7	77.138	1.887	22.86	1.359	2.645	0.422
8	89.350	1.951	10.65	1.027	2.828	0.451

Table 7: Kinetic Release model Regression Coefficient (F6)

S. No.	Kinetics Model	Regression Coefficient
1.	Zero Order	0.991
2.	First Order Kinetics	0.929
3.	Higuchi Equation	0.8678

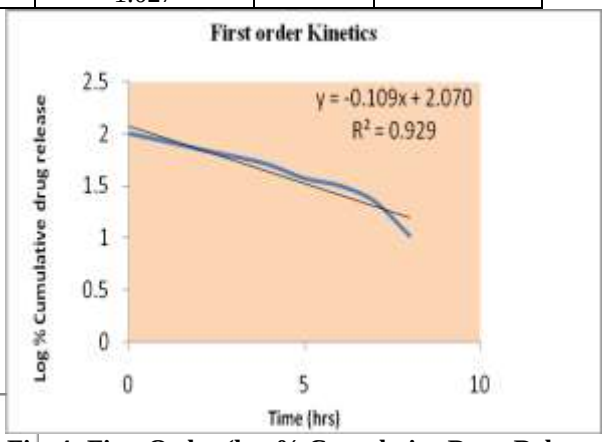

Fig. 4: First Order (log % Cumulative Drug Release vs. time)

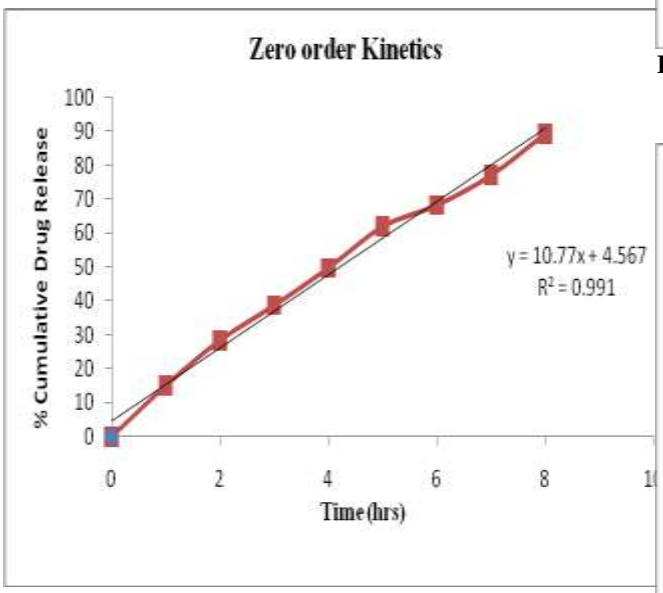

Fig. 3: Zero Order (% Cumulative Drug Release vs. time)

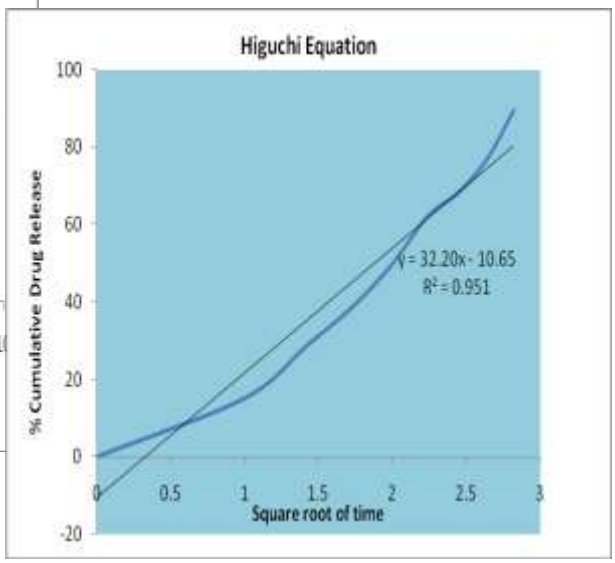

Fig. 5: Higuchi Equation (% Cumulative Drug Release vs. √ time)

Conclusion

Ketorolac tromethamine is the drug of choice in the treatment of local inflammation. Transdermal gel of Ketorolac tromethamine was prepared with aim to deliver the drug throughout transdermal route as it provide quick onset of action in contrast of oral route. In preliminary study permeability enhancers (DMSO, Propylene glycol and menthol) and vehicle were evaluated for their efficiency to form a transdermal gel. Different parameters studied were carried out for hydro-alcoholic gel formulations. In formulation F6, DMSO as permeability enhancer and Isopropanol as vehicle were found to be suitable ingredients which gives better consistency and produce in-vitro drug diffusion across goat skin and synthetic cellophane membrane. Carbopol was used as gelling agent.

Results showed that in-vitro drug diffusion increase after addition of permeation enhancer in transdermal gel formulation. So it was concluded that topical hydro-alcoholic gel enhanced permeation of ketorolac and gives an effective anti- inflammatory activity, with avoidance of GIT adverse effect.

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