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Formulation, evaluation and comparison of Ketorolac tromethamine transdermal gel containing natural and synthetic permeation enhancers

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ABSTRACT

The present research has been undertaken with the aim to develop a transdermal gel formulation of Ketorolac tromethamine, which would avoid the gastrointestinal related toxicities associated with oral administration. The various gastrointestinal disorders associated with oral administration of KT (NSAID's) can be limited by delivering the drug by transdermal route to the inflammation site. Transdermal gels are becoming more popular because of ease of application, patient compliance and comparatively more percutaneous absorption than other semisolid formulations. Therefore, KT gel formulations were made with carbopol 940 having different concentration of tulsi oil and DMSO as penetration enhancers. KT gels containing various concentrations of tulsi oil and DMSO (2.5 %, 5.5 %, 7.5 %, 10.5 % and 12.5%) were prepared. The fixed oil of tulsi (ocimum sanctum) is reported to possess significant anti inflammatory activity. Formulations were evaluated for drug content, pH, viscosity, spreadability and drug release. In vitro release studies were performed using Franz diffusion cell. Release kinetic analysis was done to find the kinetics of drug release.

Key words: Transdermal, ketorolac tromethamine permeation enhancers, *in vitro* release

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INRODUCTION

Ketorolac Tromethamine (KT) is potent non-steroidal anti-inflammatory drug, used for various inflammatory conditions like rheumatoid arthritis, osteoarthritis and musculoskeletal problems like strains & sprains. Like other NSAIDS oral administration is associated with severe side effects on oral administration (such as gastrointestinal injury, renal injury, hypertension, and platelet aggregation inhibition, the most common and severe are gastrointestinal complications, like mucosal erosion, ulcers, bleeding due to localization of high concentration of drugs in gastrointestinal lumen and cell membranes [1]. Transdermal delivery system can be formulated for alternate route for oral delivery of KT. Transdermal gels are becoming more popular because of ease of application, patient compliance and comparatively more percutaneous absorption than other semisolid formulations.

Stratum corneum, the outermost layer of the skin is the greatest resistance to penetration in topical formulations & this is the rate limiting step in percutaneous absorption [2].SC is multilayered wall like structure in which keratin rich epidermal cells (corneocyted) are embedded in lipid rich matrix. To overcome this barrier various approaches has been used. Chemical penetration enhancers modify SC & increase drug permeability of gel to make it comparable commercial formulation [3]. As synthetic permeation enhancers have side effects like irritation and toxicity to the skin. Hence the inclusion of permeation enhancers from natural source has been increased. In present

study Tulsi oil in concentration ranging from 2.5-12.5% were incorporated in the carbopol gel & evaluated for optimized concentration of permeation enhancer for a successful novel transdermal delivery system.

MATERIALS AND METHODS

Ketorolac tromethamine was received as a gift sample from Ranbaxy laboratory ltd. Gurgaon, India. Carbopol, liquid paraffin, triethanolamine and other chemicals were of analytical grade and used without further purification.

METHOD OF PREPARATION OF GEL [4]

Carbopol gel was prepared by mixing carbopol 940 with distilled water, ethanol and drug (mixture I). Mixture II was prepared by mixing triethanolamine, ethanol distilled water and enhancer. Then add mixture II drop by drop to mixture I and the gel was prepared.

Compositions were provided in table 1.

PHYSICO-CHEMICAL EVALUATION OF GEL: [5-9]

pH

The pH of formulations was determined by using digital pH meter. One gm of gel was dissolved in 100 mL of distilled water and stored for two hours. The measurement of pH of each formulation was done in triplicate and standard deviations were calculated.

Viscosity study

The measurement of viscosity of the prepared gel was done with Brookfield Viscometer.

Spreadability

The spreadability of the gel was determined using the following technique: 0.5g gel was placed within a circle of 1 cm diameter premarked on a glass plate over which a second glass plate was placed. A weight of 500 g was allowed to rest on the upper glass plate for 5min. The increase in the diameter due to spreading of the gels was noted.

Extrudability

The extrusion of the gel from the tube is an important during its application and in patient acceptance. This study is useful in explaining whether the gel is removing from the collapsible tube during application in proper manner or not. Gels with high consistency may not extrude from the tube whereas, low viscous gels may flow quickly, and hence suitable consistency is required in order to extrude the gel from the tube. The formulations were filled into collapsible aluminium tubes. The tubes were pressed to extrude the 0.5 cm ribbon of the gel in 10 second and the extrudability of formulation

Homogeneity

All prepared gels were tested for homogeneity by visual inspection after the gels have been set in the container for their appearance and presence of any aggregate was checked.

Drug content

A specific quantity (100mg) of gel was taken and dissolved in 100ml of phosphate buffer of pH 7.4. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 322 nm using phosphate buffer (pH 7.4) as blank.

***In vitro* permeability studies**

Franz diffusion cell is one of the most widely used systems for *in vitro* skin permeation studies. The cell consists of a small donor and receptor compartment which is stirred by a teflon coated magnetic bead (figure 5.2). The drug delivery is by the vertical movement of drug from donor phase through the skin into the receptor phase. The skin was mounted with the stratum corneum side facing the donor compartment. In the donor compartment, the formulation of gel (500 mg) was placed in intimate contact with the skin. The receptor compartment was filled with phosphate buffer pH 7.4 and stirred with a magnetic stirrer. The top of the donor compartment was covered with aluminium foil. At appropriate intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24 hr), 5 ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh receptor solution. Samples were analyzed spectrophotometrically at 322 nm.

Release kinetics study

Various in vitro release data various kinetic models were used to establish the order and mechanism of drug release. Release data of all the formulations were fitted to different kinetic models as zero order, first order, higuchi and korsmeyer-peppas model and. Regression Co-efficient (r^2) values obtained from various Plots were studied to find the plot showing best linearity of data. The value which was closer to 1 was selected as the best fit model for the drug release.

RESULTS AND DISCUSSION

The compositions of the gel formulations were shown in **table 1**. From the result, it is clearly evident that all the formulations showed good extrudability, spreadability, drug content and, viscosity.IR studies indicated that no chemical interaction between drug and excipients took place during preparation gel of KT. Drug content of the formulations for ketorolac tromethamine were well within the range between 97 % to 99 %. Viscosity of formulation ranged from 8675 to 13098 Cps. The diffusion data of G5 were treated with different kinetic equations as zero, first, higuchi, and korsmeyer-peppas to determine the order of release of ketorolac tromethamine and the coefficients of correlation (R^2). The developed gel formulations were subjected to the stability study as per ICH guidelines for the period of one month. The stability evaluation data were mentioned in **table 6**. The studied formulations was found to be stable and do not show any loss of drug content, change in % drug release, viscosity and pH.

Table1: Composition formula of carbopol 940 formulations

S. No.	Composition	G_1	G_2	G_3	G_4	G_5	G_6	F_1	F_2	F_3	F_4	F_5
1	KT	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2	Carbopol 940	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
3	Propylene glycol	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
4	Polyethylene glycol 400	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
5	Glycerin	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
6	Peppermint oil	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
7	Ethanol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
8	Triethanolamine	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
9	Distil. Water	50.4	50.4	50.4	50.4	50.4	50.4	50.4	50.4	50.4	50.4	50.4
10	Tulsi oil	-	**2.5**	**5.5**	**7.5**	**10.5**	**12.5**	-	-	-	-	-
11	DMSO	-	-	-	-	-	-	**2.5**	**5.5**	**7.5**	**10.5**	**12.5**

Table 2: Value of ph, percent drug content, viscosity, spreadability and extrudability of formulations

Formulation Code	pH	Spreadability (cm)	Drug Content analysis	Extrudability	Viscosity Measurement (Cps)
G_1	6.4±0.1	3.9	98.391±0.02	+	8,675±21.54
G_2	6.5±0.13	2.5	97.374±0.06	+	12,889±30.01
G_3	6.3±0.15	3.4	99.010±0.14	+	8,953±15.17
G_4	6.4±0.1	2.8	99.209±0.15	+	13,817±20.19
G_5	6.8±0.1	3.5	97.733±0.116	+	8,851±15.45
G_6	6.6±0.12	2.9	97.354±0.176	+	13,098±23.76
F_1	6.7±0.1	2.5	99.000±0.134	+	9,832±32.16
F_2	6.5±0.15	3.4	97.344±0.145	++	10,928±30.00
F_3	6.7±0.13	2.7	98.162±0.167	++	10,219±14.98
F_4	6.6±0.12	2.8	98.501±0.156	+	10,676±21.05
F_5	6.3±0.15	2.6	98.571±0.123	++	10,704±20.01

IN VITRO RELEASE

EFFECT OF PENETRATION ENHANCER

Two penetration enhancer's tulsi oil and DMSO were used with optimized polymer concentration to enhance the release. Release studies were performed to find the best penetration enhancer form the formulations G1-G6 and F1-F5. The maximum release was obtained 29.02% (G1), 70.84% (G5), and 63.63 % (F4) respectively. The study showed that for the both studies Tulsi oil was found to be best penetration enhancer.

Table 3: Drug release of formulationsG1-G6, F1-F5

S. No.	Formulation Code	% CDR (in 8hr)
1	G_1	29.02
2	G_2	50.63
3	G_3	66.23
4	G_4	64.03
5	G_5	70.84
6	G_6	70.00
7	F_1	43.13
8	F_2	50.18
9	F_3	57.79
10	F_4	63.63
11	F_5	63.45

Table 4: Release kinetics of optimized batch G5

Time (Hrs)	Cumulative % Drug release	log Cumulative %drug release	%drug remained	Log % drug remained	√Time	Log time
0.5	33.56	1.5258	66.44	1.822	0.707	-
1	36.43	1.5614	63.57	1.803	1.000	0.000
2	39.57	1.5973	60.43	1.781	1.414	0.301
3	45.17	1.6548	54.29	1.734	1.732	0.477
4	52.67	1.7215	47.33	1.675	2.000	0.602
5	55.48	1.7441	44.52	1.648	2.236	0.699
6	59.63	1.7754	40.37	1.606	2.449	0.778
7	64.61	1.8103	35.39	1.548	2.646	0.845
8	70.84	1.8502	29.16	1.464	2.828	0.903

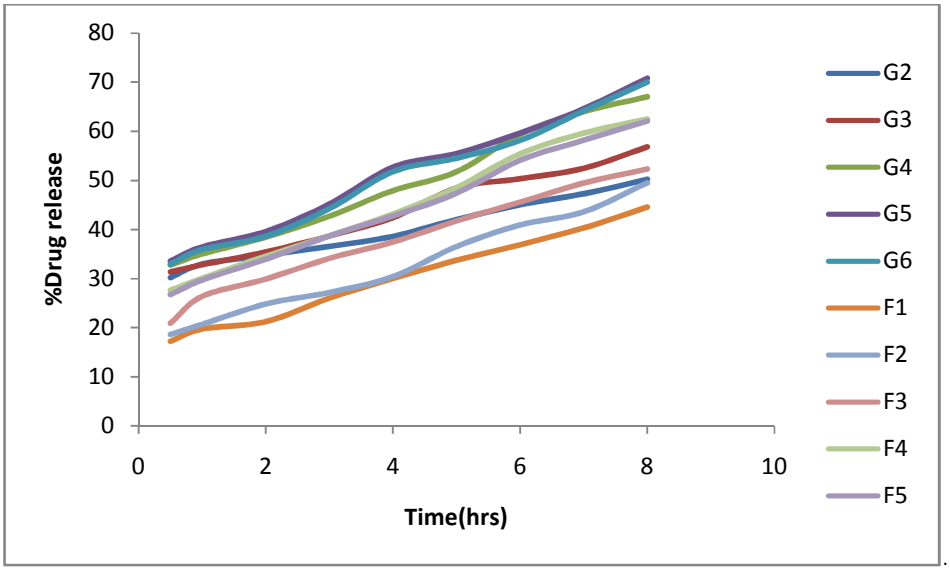

FIGURE 1: DRUG RELEASE PROFILE OF FORMULATION G_1-G_6, F_1-F_5

Table 5: Regression Co-efficient (r2) values of optimized formulation G_5.

Formulation Code	R^2			
	Zero order	First order	Higuchi model	Korsmeyer Peppas model
G_5	0.994	0.980	0.966	0.925

TABLE 6: Stability studies of formulation G_5

Parameters	Storage conditions G_5	
	25° C/60 % RH	40°C/75%RH
Drug content (%)	99.35	98.93
Viscosity (KcP)	8851	8788
pH	6.8	6.5

EFFECT OF CONCENTRATION OF PENETRATION ENHANCER

Four different concentration of oleic acid as penetration enhancer were evaluated 2.5, 5.5, 7.5, 10.5 and 12.5 % w/w. It was interesting to note that the release first increased with increase in concentration of Tulsi oil from 2.5 % to 10.5% w/w and then almost same on further increase to12.5%. The study showed that the maximum release was obtained 10.5%w/w concentration of Tulsi oil. From the results of data fitting to various models, it was found that the optimized batch G5 showed Zero order kinetic model of drug release.

CONCLUSION

From the above study we have concluded that the transdermal gel prepared along with Carbopol 940 by using natural penetration enhancer in concentration 10% can be used to prepare an ideal transdermal gel preparation. All developed gels showed good homogeneity with absence of lumps. *In vitro* drug release study showed that the formulations containing tulsi oil releases the drug faster as compared to DMSO. It may be concluded from the results that as the concentration of tulsi oil increases from 2.5-10.5 w/w in the formulations the rate of drug release also increases and decreases on further increase of concentration to12.5%.

Formulations viscosity shows inverse relationship with the amount of drug released and this observation is according with a vast previous literature study showed that the topical gel formulation G_5 formulated using Carbopol 940 with polymer concentration of 1%, and tulsi oil 10% is having the maximum release of 70.84 % and observed as optimized batch. The best kinetic model which described the release of drug is zero order model which states the release rate from insoluble matrix is independent of drug concentration. The stability studies carried out on optimized KT gel formulations G_5 showed no alteration in drug content, pH, viscosity, etc., hence were stable for the studied period of 6 month.

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