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Evaluation of Anti-Inflammatory Activity of Topical Gel by Carrageenan Induced Paw Oedema Method

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Abstract

The present study was aimed to prepare and characterize gel formulations of Diclofenac diethyl amine using different polymers as gelling agents, permeation enhancers like propylene glycol, dimethyl sulfoxide (DMSO) and also to evaluate anti-inflammatory activity of gel. For the study, polymers such as Hydroxy propyl methyl cellulose K4M, Hydroxy propyl methyl cellulose K100M, Lutrol F-127 were selected for preparation of different gel formulations. The prepared gels were evaluated for anti inflammatory activity. It was inferred from the results that gel formulation prepared by Lutrol F-127(10%w/w) and DMSO in the range of 15ml were found to be best formulations among the prepared batches.

Keywords: Diclofenac diethyl amine, DMSO, Anti-inflammatory, Lutrol F-127, Propylene glycol

Introduction

Topical drug delivery systems are gaining increase in popularity and several drugs have been successfully delivered by this route for both local and systemic action. Gels have better potential as a vehicle to administer drug topically in comparision to ointment, because they are non sticky, requires low energy during formulation.[1] Drug delivery through the skin has been a promising concept for a long time because skin is easy to access, has a large surface area with vast exposure to the circulatory and lymphatic networks and the route is noninvasive. Transdermal gel preparations are intended for superficial skin application or to some mucosal surfaces for local action or skin penetration of medicament or for their soothing or protective action. The nonsteroidal anti-inflammatory drugs (NSAID's) are having excellent anti-inflammatory and analgesic activity but NSAID's produces GIT ulceration, liver and kidney trouble in case of oral administration. To avoid the adverse effect, alternate routes of administration have been tried by investigators. The aim of this study was to develop suitable transdermal gel formulations of Diclofenac diethyl amine using various gelling agent with permeation enhancers in order to reduce adverse drug reaction associated with oral formulations.[2]

Diclofenac is a well-established NSAID agent used for a variety of painful and inflammatory conditions. It is available as topical dosage form like gel, emulgel, lotion, cream, and ointment and also available as of oral and parentral dosage form. It should be used in long term for musculoskeletal disorders like rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, but it produces GIT ulceration, liver and kidney trouble especially in case of oral administration.

In view, of adverse drug reaction associated with oral formulations, diclofenac is increasingly administered by topical route. Among various salts diclofenac diethyl amine is widely used for topical application due to its high lipophilic nature.[3]

Materials and methods

Diclofenac diethyl amine was received as gift sample from Aarti drugs limited, Mumbai. Hydroxy propyl methylcellulose K4M, Hydroxy propyl methylcellulose K15M gifted by Colorcon, Goa, Lutrol F-127 gifted by Signet chemicals, Bandra. Carrageenan was purchased from Yarrow chem. Products, Mumbai, and other chemicals used were of analytical grade.

Procedure of gel preparation

Gels were prepared by cold mechanical method described by Schmolka et al. (1972). Required quantity of polymer (Lutrol F-127and HPMC K4M, HPMC K100M) was weighed and it was sprinkled slowly on surface of purified water for 2 hrs. After which it was continuously stirred by mechanical stirrer, till the polymer soaked in the water. With continuous stirring, now the appropriate quantity of DMSO (Dimethyl sulfoxide) was added to the gel, which behaves as the penetration enhancer, followed by the required quantity of methyl paraben and propyl paraben as a preservative. Accurately weighed amount of Diclofenac diethyl amine was dissolved in a specified quantity of ethanol and propylene glycol. Finally Drug solution was added to gel with continuous stirring till drug get dispersed completely. The prepared gel was filled and sealed in aluminium collapsible tube.

Anti inflammatory activity

Experimental animals

Inbreed adult male/female Wistar rats, Weighing between 128-181gm, Maintained in standard laboratory conditions, at Temperature 25 ± 1°C and Relative humidity 55 ± 5% with a 12-hour light/dark cycle. These rats are randomly divided into 5 groups with 6 in each group.

Procedure

Wister rats were weighed and marks were made on right hind paw behind tibiatarsal junction. Each rat was placed in an observation chamber for 10 min to minimize stress-related behaviors. Pleurisy was induced by injecting 0.1 ml of 1% w/v carrageenan solution subcutaneously into the sub-plantar surface of the right paw of the rat. 0.5 g of the gel formulations or the reference was gently rubbed onto the plantar surface of the right hind paw 50 times with the index finger. All rats were subsequently returned to the observation chamber. The inflammatory response was assessed by measuring the volume of the paw at 1and2hr after carrageenan administration, using plethysmometer. The percentage of inhibition of edema was calculated using following formula.[4, 5]

Formula[6]

$$\frac{\text{Paw volume (ml) after carrageenan – paw volume after particular time (ml)} * 100}{\text{Paw volume after carrageenan (ml).}}$$

Measurement of Inflammatory Response

Group - I: control: inflamed, treated with gel base only.

Group - II: standard: inflamed, treated with the reference Voveran gel product.

Group - III: sample: inflamed, treated with the sample of Hpmc k4m gel.

Group –IV: sample: inflamed, treated with the sample of Hpmc k100m gel.

Group –V: sample: inflamed, treated with the sample of Lutrol F-127 gel.

Table 1: Formulation Design for the Preparation of Topical Gel

Sr. No	**Ingredients (%w/w)**	**Formulation**		
		F1	**F2**	**F3**
1.	Diclofenac diethyl amine	1.16	1.16	1.16
2.	Ethanol(ml)	10	10	10
3.	HPMC K4M(gm)	03	-	-
4.	HPMC K100M(gm)	-	02	-
5.	Lutrol F- 127(gm)	-	-	10
6.	Propylene glycol(ml)	20	20	20
7.	Dimethyl Sulfoxide(ml)	15	15	15
8.	Methyl paraben(mg)	15	15	15
9.	Propyl paraben(mg)	05	05	05
10.	Distilled water up to	100	100	100

Table2: Changes in paw volume of Rats

S. No	Group	Paw volume 0 Min. (ml.)	p-value at 0 min.	Paw volume after inflmmation (ml.)	Paw volume At 1Hr. (ml.)	p-value at 1 Hr.	Paw volume At 2Hr. (ml.)	p-value at 2 Hr.
1.	Control	2.63±0.35	0.014479 NS	3.44±0.35	3.44±0.35	0.465023 NS	3.42±0.37	0.151446 NS
2.	Voveran gel	2.75±0.29	0.000593 S	3.18±0.32	2.69±0.23	$8.61*10^{-05}$ S	2.44±0.95	0.003275 S
3.	HPMC K4m gel	3.20±0.20	0.004348 S	3.49±0.25	2.76±0.14	0.002129 S	2.59±0.19	0.000494 S
4.	HPMC K100m gel	2.67±0.25	0.001349 S	3.15±0.21	2.83±0.19	0.024829 S	2.81±0.35	0.004048 S
5.	Lutrol F-127 gel	3.24±0.60	0.007412 S	3.58±0.55	2.38±0.25	0.000936 S	2.39±0.30	0.001576 S

Statistical comparisons were made using Student's *t*-test at a significance level of $p < 0.05$.

S: significant

NS: Non significant

Table 3: Percent inhibition at various hours in rat paw volume after carrageenan treatment by different gel formulations

S. No.	Group	% Inhibition at 1Hr.	P-value at 1 Hr.	% Inhibition at 2 Hr.	P-value at 2 Hr.
1.	Control	0.04		0.62	
2.	Voveran gel	14.78		22.71	
3.	Hpmc K4M gel	20.44	0.089197 NS	25.87	0.500667 NS
4	Hpmc K100M gel	06.39	0.00594 S	11.10	0.018197 S
5	Lutrol F-127	32.77	0.000164 S	34.07	0.042572 S

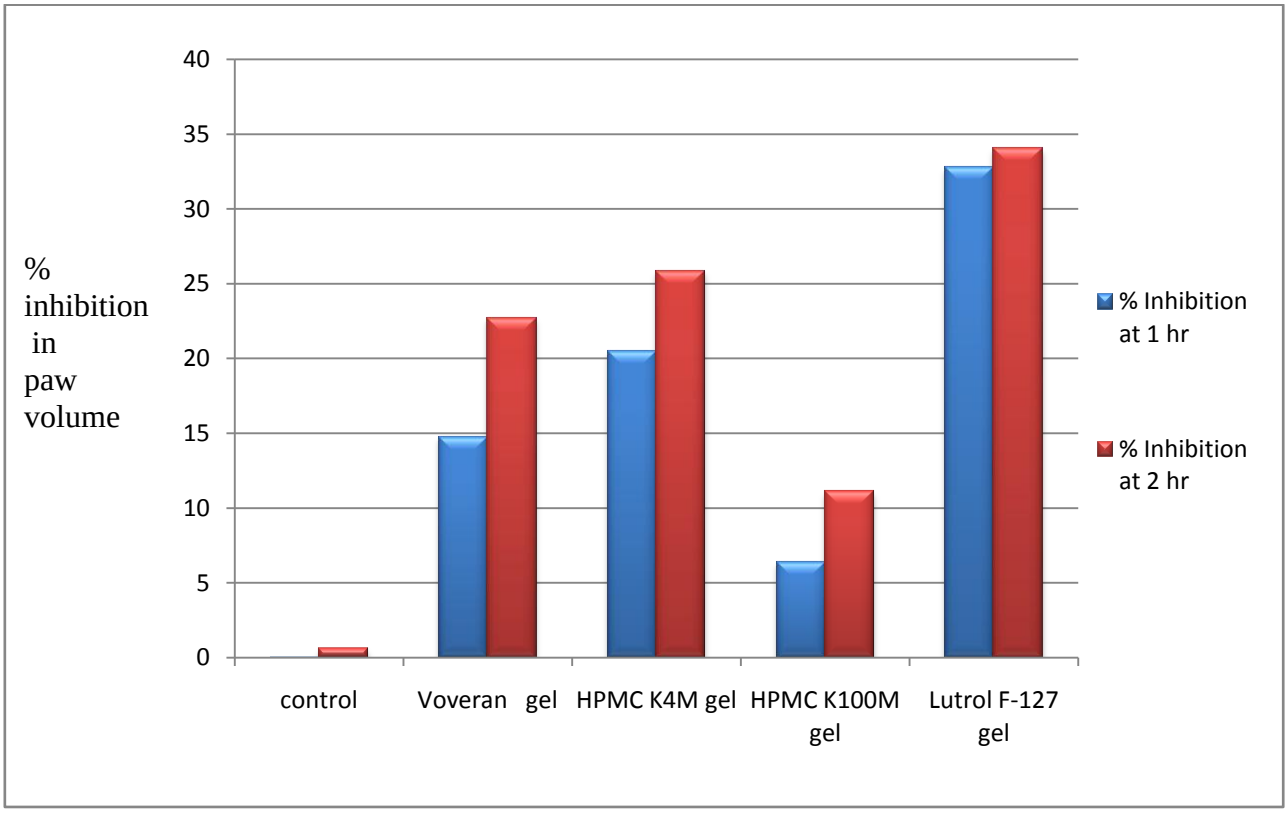

Figure 1: Bar diagram shows compairsion between various gel of different polymer of diclofenac diethylamine salt

Result and Discussion

The anti-inflammatory activity of Diclofenac diethyl amine gel in HPMC K4M, HPMC K100M and Lutrol F-127 was compared with that of NSAID topical gel preparation (marketed Voveran). Lutrol base gel (34.07%) and marketed formulation (22.71%) showed considerably inhibition of Oedema formation. Figure1. Represents the percent inhibition in paw volume after carrageenan treatment with control gel base, Voveran gel, and diclofenac diethyl amine gel of HPMC K4M, HPMC K100M, Lutrol F-127.As shown in Table 3. and Figure 1, the maximum 34.07% inhibition of edema was observed with diclofenac amine gel of lutrol at 2 hr after carrageenan treatment and maximum 11.10% inhibitions of edema was observed with Diclofenac amine gel of HPMC K100M, maximum 25.87% inhibitions of edema was observed with Diclofenac gel of HPMC K4M, maximum 22.71% inhibitions of edema was observed with voveran gel. According to student t-test significant p-values observed for HPMC K100M gel, Lutrol F-127 gel and Non-significant changes observed for HPMC K4M.In case paw volume changes p-value was significant for all gel formulations except control gel applied topically.

Conclusion

From the above study we have concluded that the topical gel prepared from the Lutrol F-127 having good anti-inflammatory activity. So the topical gel prepared from Lutrol F-127 will be better gelling agent for making an ideal topical preparation.

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