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Formulation and Evaluation of Naproxen Gel Containing Tulsi Oil as Penetration Enhancer

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ABSTRACT
The present research has been undertaken with the aim to develop a transdermal gel formulation of naproxen, which would attenuate the gastrointestinal related toxicities associated with oral administration. The potential gastrointestinal disorders associated with oral administration of naproxen (NSAID's) can be avoided by delivering the drug to the inflammation site. Gel based formulations are better percutaneously absorbed than creams and ointment bases. It is reported that absorption profile of naproxen from carbopol gel base is better than other bases. Therefore, naproxen gel formulations were made with carbopol 940 having different concentration of tulsi oil as penetration enhancer containing 2 % of naproxen. Permeation experiments were performed on excised abdominal rat skin using Keshary Chien diffusion cell. The fixed oil of tulsi (ocimum sanctum) is reported to possess significant anti inflammatory activity. Naproxen gels containing various concentration of tulsi oil (1 %, 3 %, 5 %, and 7 %) were prepared. To assess the efficacy of formulations *in-vitro* release, rheological properties, drug content and skin irritation studies were performed. The results obtained were encouraging and formulation containing naproxen (2 %) and tulsi oil (5 %) found to be better than other formulations.

Keywords: Gel; Tulsi oil; Naproxen; Penetration enhancer.

INTRODUCTION

Naproxen [1] is **a** potent non-steroidal anti-inflammatory drug (NSAID) used for a variety of inflammatory conditions. However, its use has been associated with a number of gastrointestinal disorders. [2] Like other NSAIDs, the most common side effect of peroral naproxen is gastrointestinal irritation. These potential side effects may be overcome by the topical administration of the drug. Skin is one of the most readily accessible organs on human body for topical administration and is the main route for topical drug delivery system. For a topical formulation to be effective, it must first penetrate the skin, only when the drug has entered the lower layers of the skin it can be absorbed by blood and transported to the site of action, or penetrate deeper into areas where inflammation occurs. The stratum corneum provides the greatest resistance to penetration, and it is the rate-limiting step in percutaneous absorption. The permeation of drugs through skin can be enhanced by physical methods such as mechanical disruption, electrical disruption, and chemical modification or by the use of chemical penetration enhancers. The later compounds increase skin permeability by increasing the partition coefficient of the drug into the skin and by increasing the thermodynamic activity of the drug in the vehicle. [3] Chemical penetration enhancers modify barrier properties of the stratum corneum and hence increase drug permeability across skin. Ideally, the effects of the penetration enhancer on the skin should be reversible, non-toxic, non-allergenic, compatible with drugs and excipients and non-irritating. However the synthetic permeation enhancers are associated with adverse effect of producing irritation and toxicity to the skin. Hence natural products have increasingly been used as enhancers due to their better safety profile. [4]

Tulsi is a widely grown, sacred plant of India and it belongs to the *labiateae* family. Leaf contains eugenol (volatile oil), ursolic acid (triterpenoid) and rosmarinic acid (phenylpropanoid). Other active compounds include caryophyllene and oleanolic acid. Seeds contain fixed oils having linoleic acid and linolenic acid. It has long history of use in ayurvedic system of medicine to treat various ailments without any noticeable toxicity. [5] In the present study, attempts have been made to explore the penetration enhancing activity of tulsi oil.

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MATERIALS AND METHODS

Materials

Naproxen was received as a gift sample from Nicholas Piramal, Mumbai, India. Carbopol, propylene glycol,

triethanolamine and other chemicals were of analytical grade and used without further purification.

Method for preparation of gel

Carbopol 940 (1 %) was finely dispersed in 50:50 propylene glycol:water and stirred continuously at 300 rpm for 3 h. Then, the naproxen (2 %) passed through 100 mesh was finely dispersed in 15 ml of propylene glycol and then added to the carbopol mixture. Lastly tulsi oil was added and mixed for 1 h. The dispersion was then neutralized and made viscous by the addition of triethanolamine. [6] The compositions of different gel formulations are listed in Table 1.

Table 1: Composition of different gel formulations

Item	Material name	Quantity (%)				
		F1	F2	F3	F4	F5
1.	Naproxen	2	2	2	2	2
2.	Carbopol	1	1	1	1	1
3.	Tulsi oil	-	1	3	5	7
4.	Propylene glycol	48	46.5	46	45.4	45
5.	Water	48	46.5	46	45.4	45

Drug Content

For assay of the drug in gels, naproxen was extracted from 1 g of each gel formulations with 20 ml of methanol for 30 min. The resultant mixture was filtered through membrane filter (pore size 0.45 mm). The absorbance of the sample was determined spectrophotometrically at 272 nm (Shimadzu 1601 UV-VIS spectrophotometer) using methanol as a blank. The concentration of naproxen was estimated from the regression equation of the calibration curve.

Spreadability

Spreadability was determined by modified wooden block and glass slide apparatus. The apparatus consisted of a wooden block with fixed glass slide and a pulley. A pan was attached to another glass slide (movable) with the help of a string. For the determination of spreadability measured amount of gel was placed in the fixed glass slide, the movable glass slide with a pan attached to it, was placed over the fixed glass slide, such that the gel was sandwiched between the two slides for 5 min. Now about 50 g of weight was added to the pan. [7] Time taken for the slides to separate was noted. Spreadability was determined using the following formula:

$$S = M.L/T$$

Where S is the spreadability in g.cm/s,

M is the mass in grams and T is the time in seconds.

Extrudability

A closed collapsible tube containing gel was pressed firmly at the crimped end. When the cap was removed, gel extruded until pressure dissipated. Weight in grams required to extrude 0.5 cm ribbon of gel in 10 seconds was determined. [8]

Viscosity

Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to measure the viscosity (in cps) of the prepared gel formulations. The spindle T-D (spindle code S 94) was rotated at 2.5, 4, 5 and 10 rpm. The reading, near to 100% torque was noted. Samples were measured at 30 ± 1° C.

Skin irritation study

Three albino rabbits were selected for the study. 24 h prior to the test, the test sites were depilated on both sides of the spine and demarcated for the application of the formulation. The measured quantity of gel was applied over the respective test sites. The test sites were observed for the erythema and edema for 48 h after application.

***In vitro* diffusion studies**

Phosphate buffer of pH 6.8 was used for *in vitro* release as a receptor medium. The pretreated skin of albino mice was used in keshary - chien diffusion cell. The gel sample was applied on the skin and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer of pH 6.8. The temperature of diffusion medium was thermostatically controlled at 37±1ºC by surrounding water in jacket and the medium was stirred by magnetic stirrer at 100 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 262 nm using phosphate buffer pH 6.8 as a blank. [9]

RESULTS AND DISCUSSION

The present investigation aims to develop transdermal gel of naproxen containing tulsi oil as a natural penetration enhancer for improved penetration of naproxen. The mechanism of action of tulsi oil is not well established yet but it might be possible that it modifies the barrier properties of stratum corneum temporarily to enhance percutaneous absorption. Different gel formulations containing naproxen 2 % (alone) and naproxen 2 % with varying concentrations 1 %, 3 %, 5 % and 7 % of tulsi oil were prepared and evaluated for drug content, pH, spreadability, viscosity, extrudability, homogeneity, *in vitro* drug release, skin irritation and stability.

The drug content of all formulations ranges from 90.5 % - 92.9 % which shows content uniformity, the pH values of all developed gels ranges 6.83-6.89 which lies in the normal pH range and would not produce any skin irritation as shown in Table 3. The values of spreadability indicate that the gel is easily spreadable by small amount of shear. The result of spreadability varies from 6.08 to 6.82 g. cm / sec. where as the extrudability of gel formulations from the collapsible tube varies from 180 to 190 g and the viscosity of formulations ranges from 16241 cps to 16896 cps at 10 rpm as shown in Table 2.

Table 2: Rheological data of different formulations

Formulations	Spreadability (g.cm/sec)	Extrudability (g)	Viscosity (cps) at rpm			
			2.5	4	5	10
F-1	6.08	180	51432	38749	31765	16241
F-2	6.57	180	51643	38300	31856	16389
F-3	6.72	185	51954	38452	31521	16427
F-4	6.79	190	51208	38170	31405	16735
F-5	6.82	180	51485	38060	31218	16896

Table 3: Values of evaluation parameters of different formulations

Formulations	pH	Drug content (%)	Homogeneity
F-1	6.87	90.5	Good
F-2	6.89	91.7	Good
F-3	6.83	92.6	Good
F-4	6.86	91.8	Good
F-5	6.88	92.9	Good

Table 4: In vitro diffusion study of different formulations in PBS (6.8) using excised Rat abdominal skin

Time (hrs)	% Drug release				
	F-1	F-2	F-3	F-4	F-5
0.5	18.2	25.8	32.3	38.6	38.7
1	29.4	33.5	41.9	49.5	50.2
1.5	38.3	41.6	49.8	55.5	55.8
2	45.7	50.3	56.4	62.1	62.6
3	58.5	62.7	68.7	72.2	73.1
4	70.9	75.4	82.5	85.8	86.4
5	82.1	85.5	91.5	99.3	99.3
6	90.6	94.9	96.5	-	-

All developed gels showed good homogeneity with absence of lumps. No signs of erythema and edema were found after 48 h of application in albino rabbits. During the stability studies the appearance was clear and no significant variation in pH was observed. *In vitro* drug release study as shown in Table 4 that the formulations containing tulsi oil releases the drug faster as compared to formulation F- 1 which does not contain tulsi oil. It may be concluded from the results that as the concentration of tulsi oil increases in the formulations the rate of drug release also increases. Percent drug release data also shows that there is no any significant difference in the amount of drug released from formulation containing 5 % and 7 % of tulsi oil. Therefore, formulation containing 5 % of tulsi oil was selected as best among all the formulations. It is clear that tulsi oil can significantly enhance the penetration of naproxen from gel formulation across the skin.

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