Applied Medical Research

Original Research

DOI: doi.org/10.47363/AMR/2015(2)118

Development and characterization naproxen gel bearing eucalyptus oil for topical delivery

Vikas Jain, Monika Thakur

Department of Pharmaceutics, Mahakal Institute of PharmaceuticalStudies, Ujjain, Madhya Pradesh, India

Address for correspondence:
Vikas Jain, Department of Pharmaceutics, Mahakal Institute of Pharmaceutical Studies, Ujjain - 456 664, Madhya Pradesh, India.
E-mail: vikasjain11118059@rediffmail.com

Received: February 07, 2015
Accepted: March 05, 2015
Published: ***

ABSTRACT

Aim: Eucalyptus oil-based naproxen loaded gel system was developed for topical application on to the scalp in order to avoid the disadvantages associated with the oral administration of naproxen. **Materials and Methods:** Eucalyptus oil, propylene glycol, and Carbopol P-934 were used with different ratios in an attempt to develop topical gel formulations of naproxen. Eucalyptus oil also has the property to reduce inflammation and arthritis pain. The tropical gel containing naproxen was evaluated for appearance, homogeneity, gelling, pH, viscosity, spreadability and drug content. *In-vitro* diffusion studies of prepared gel formulations were carried out in phosphate buffer pH 6.8 using Francz diffusion cell. **Results:** The results of *in-vitro* drug release showed that the highest release (99.37% of drug released after 3 h) was from in formulation F3 containing Carbopol P-934 (1%) and eucalyptus oil (0.6 ml). **Conclusion:** The overall results of this study suggest that the F3 formula could be used in the preparation of naproxen gel containing eucalyptus oil as a topical dosage form to be used in the treatment of inflammation.

KEY WORDS: Carbopol P-934, eucalyptus oil, Naproxen, topical gel

INTRODUCTION

Topical drug delivery is a very attractive route for local and systemic treatment. It can easily penetrate deeper into the skin and hence give better absorption. In the topical gel, effectiveness of the drug is achieved easily and successfully whereas the systemic side effects can be minimized or avoided.

They are more effective and lesser toxic as compared to conventional oral dosage forms. They avoid gastrointestinal (GI) - irritation and prevent the metabolism of the drug in the liver. Topical preparations of many drugs are available in the market that includes GI-irritating, non-steroidal anti-inflammatory drugs, local anesthetic and antihistaminic agents, antibacterial, antifungal [1].

Topical gel containing naproxen is already present in the market. Product name is naprosyn and xenobid gel, but both have certain disadvantages, i.e., burns, skin redness and rashes. Eucalyptus oil, due to its soothing and calming effects may overcome these disadvantages associated with marketed formulations [2]. Eucalyptus oil is also used to reduce inflammation and arthritis pain.

The objective of this study was to formulate naproxen gel bearing eucalyptus oil to enhance efficacy and safety of naproxen drug and overcome disadvantages associated with marketed formulations.

MATERIALS AND METHODS

Naproxen was taken as gift sample by Elder Pharmaceutical Ltd., Mumbai. Eucalyptus oil was received from Svas International, Mumbai. Carbopol 934 was obtained from Central Drug House Pvt. Ltd. New Delhi. All other ingredients used in this study were of analytical grade.

Formulation and Characterization

Preformulation study

Organoleptic properties
Hundred milligram of naproxen was taken to study the organoleptic properties, i.e. color and odor.

Identification of drug sample
Infrared spectroscopy (IR), ultra violet (UV) and melting point are used for identification and purity of drug sample.

IR
IR spectrum of any substance gives information about the group present in a specific substance. An IR spectrum of drug was taken using (KBr potassium bromide) pellets. Small quantities of drug sample were mixed with oil, and a drop was placed between KBr pellets and spread uniformly. The pellets were placed in the holder, and an infrared spectrum was taken.

The range of scanning was 400-4000 cm^{-1}, Different peaks in the infrared spectrum were interpreted for presence of various group in the structure of the drug. The observed IR spectra of the drug are shown in Figure 1.

UV spectroscopic studies
One mg of the drug was weighed accurately and dissolved in ethanol and volume was made up to 10 ml in a volumetric flask (stock Solution I). One ml of this stock solution was further diluted up to 10 ml in ethanol to get a stock Solution II of 10 μg/ml. The spectrum of this solution was observed in a range from 200 nm to 400 nm in UV spectrophotometer (Shimadzu-1800).

Melting Point

Ten mg of the drug sample was weighed accurately and placed into a capillary tube. Tube was placed in the melting point apparatus and was heated to a temperature below 5-10°C of the temperature at which powder started to melt, and temperature at which the sample started to melt was observed. Melting point of naproxen is observed in between 150°C and 152°C.

Quantitative Estimation of Naproxen Drug Sample

Ten mg of the drug was weighed and transferred into 10 ml of volumetric flask. Volume was made up to 10 ml with phosphate buffer pH 6.8. 1 ml of this solution was and transferred to 10 ml of volumetric flask and further diluted to 10 ml with phosphate buffer pH 6.8 (stock Solution I). From stock Solution I, aliquots of 0.3 ml, 0.6 ml, 0.9 ml, 1.2 ml, 1.5 ml, 1.8 ml, 2.1 ml, 2.4 ml, 2.7 ml, 3.0 ml were transferred to a series of 10 ml volumetric flasks. The volume was made up 10 ml with phosphate buffer pH 6.8 to give 3 μg/ml, 6 μg/ml, 9 μg/ml, 12 μg/ml, 15 μg/ml, 18 μg/ml, 21 μg/ml, 24 μg/ml, 27 μg/ml, 30 μg/ml of naproxen. The absorbance of these solutions was measured at 263 nm against blank. Standard calibration curve of naproxen in phosphate buffer pH 6.8 are presented in Figure 2.

Partition Coefficient

Hundred μg/ml solution of pure drug in distilled water was prepared. The mixture of water and octanol was prepared in the ratio of 1:1 and transferred to separating the funnel. The mixture was mixed for ½ h in separating the funnel. The mixture was then allowed to stand for 1 h and then centrifuged at 2000 rpm at 25°C for 10 min. Now the mixture was allowed to stand for 24 h at room temperature. Aqueous layer from the mixture was separated, and absorbance was measured by UV spectroscopy. The partition coefficient was calculated from the following formula.

$$P_{o/w} = C_{n\text{-octanol}}/C_{water}$$

Where, $P_{o/w}$ is partition coefficient, $C_{n\text{-octanol}}$ is concentration of drug in n-octanol, C_{water} is concentration of drug in water. The partition coefficient of naproxen was observed at 3.

Drug Excipients Compatibility Study

Naproxen and carbopol P-934 were mixed in the ratio similarly to that to be taken in the formulation. The mixtures were transferred to transparent vials, sealed properly and kept at different storage conditions, i.e., at 25°C ± 40% RH and 40°C ± 75% RH for 1 month. Any incompatibility between drug and polymers was observed visually as change in the physical appearance of the mixture.

Preparation of Gel

Naproxen (2%) was dispersed in propylene glycol and then carbopol P-934 was dispersed in propylene glycol drug mixture, and water was added and stirred continuously at 300 rpm for 3 h. Then, eucalyptus oil was added drop wise with continuous stirring for 1 h[2]. The formulations of different gel preparation are listed in Table 1.

Evaluation of Gel

Determination of homogeneity

It was tested visually and also by elegance effect. The + sign indicated the confirmation of good homogeneity that is free from any lumps and also have good elegance effect [3].

The formulations were evaluated with the help of the microscope for the presence of particles if any. No appreciable

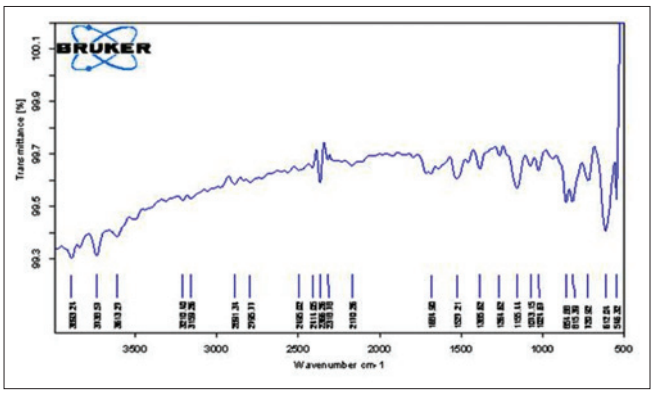

Figure 1: Observed infrared spectra of drug

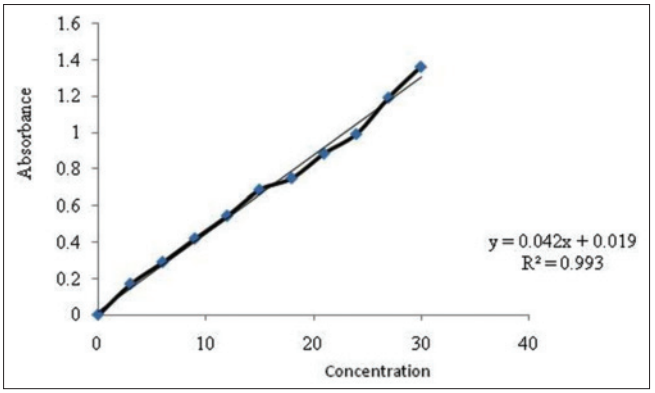

Figure 2: Standard calibration curve of naproxen in phosphate buffer pH 6.8

Table 1: Formulation design of naproxen gel preparation (10 ml)

Ingredients	Formulations (quantity%)					
	F1	F2	F3	F4	F5	F6
Naproxen (mg)	200 (2)	200 (2)	200 (2)	200 (2)	200 (2)	200 (2)
Carbopol P- 934 (mg)	50 (0.50)	75 (0.75)	100 (1)	125 (1.25)	150 (1.50)	175 (1.75)
Eucalyptus oil (ml)	0.2	0.4	0.6	0.8	0.10	0.12
Propylene glycol (ml)	5.0	4.8	4.6	4.4	4.2	4.0
Water (ml)	qs	qs	qs	qs	qs	qs

particulate matter was seen under light microscope [4]. The topical preparation as the grittiness is required.

Determination of pH

The pH of the gels was measured using a digital pH meter (III E/101 E, INDIA) [5].

Viscosity, appearance, gelling, determination

Viscosity of all the formulation was measured using the brook field viscometer (DV-E [RV], USA), using spindle number - 06 at 10 RPM. Appearance, gelling was measured by visually.

Drug Content

One g gel was weighed accurately and transferred to 100 ml volumetric flasks. The drug was dissolved phosphate buffer pH 6.8 and volume was made up to 100 ml with phosphate buffer pH 6.8. This solution was suitably diluted, and absorbance was measured at 263 nm [6].

In-vitro Drug Release by Diffusion Cell

The drug diffusion studies of prepared gel were carried out in Francz diffusion cell using semi-permeable membrane, attached to the diffusion cell such that the cell's drug releasing surface toward the receptor compartment, which was filled with phosphate buffer solution of pH 6.8 at 37°C ± 2°C. The solution was continuously stirred. The sampling was done in 15 min of the time interval, i.e. 5 ml of the aliquots were withdrawn and the same volume was replaced with phosphate buffer of pH 6.8. The samples were analyzed for drug content using UV spectrophotometer at 263 nm [7].

Analysis of Drug Release Kinetics

The drug release mechanism of minoxidil nanosponges loaded the hydrogel was analyzed using the data obtained from *in-vitro* diffusion study. The data were fitted to zero order, first order, Higuchi and Korsmeyer–Peppas model.

RESULTS

Organoleptic Properties (Color and Odor)

The drug naproxen was taken to study its organoleptic properties, i.e., color and odor. It was found to be white and odorless.

Identification of Drug Sample

UV and melting point are used for the identification of drug sample and functional group analysis, for the determination of λ_{max} and purity of the drug. The λ_{max} of the drug was found to be 262.60 which same, as per specified in Florey, 21st vol., 1979.

Melting Point

The melting point of the drug was determined using 10 mg of the drug sample was weighed capillary tube method. Melting point of naproxen was found in-between 146°C and 148°C.

Partition Coefficient

The partition coefficient of the drug was determined using UV spectroscopy. The partition coefficient of the drug was found to be 3.0.

Solubility Analysis

Quantitative solubility study

The solubility of the drug was found in ethanol, phosphate buffer pH 7.4, phosphate buffer pH 6.8 and water. The drug was freely soluble in ethanol, soluble in phosphate buffer pH 7.4 and phosphate buffer pH 6.8 and practically insoluble in water.

Determination of pH

The pH of the gels was measured using a digital pH meter (III E/101 E, INDIA) [5]. The pH value of gel formulations were found in between 6.6 and 6.79.

Viscosity, appearance, gelling, determination

Viscosity of all the formulation was measured using Brookfield Viscometer (DV-E [RV], USA), using spindle number-06 at 10 RPM. Appearance, gelling was measured by visually. The viscosity, appearance and gelling properties of gel formulations are reported in Table 2.

Drug Content

Drug content of the drug was measured in phosphate buffer pH 6.8. The % drug content of deferent formulations was found in-between 90.68% ± 1.3 and 93.04 ± 1.5.

In-vitro Drug Release by Diffusion Cell

The drug diffusion studies of prepared gel were carried out in Francz diffusion cell using semi-permeable membrane. The observations are shown in Tables 3 and 4. There corresponding graph are shown in Figures 3 and 4.

Analysis of Drug Release Kinetics

The drug release mechanism of minoxidil nanosponges loaded the hydrogel was analyzed using the data obtained from *in-vitro* diffusion study. The data were fitted to zero order, first order, Higuchi and Korsmeyer–Peppas model.

DISCUSSION

The preformulation study is the first step in the development of dosage forms of drug molecules. On the basis of organoleptic properties, drug was found to white colored, odorless, crystalline powder. These observations are comparable with the standard observations. Melting point was determined by melting point apparatus. The melting point was found in the range between 150°C and 152°C. That was within the standard melting range. The melting point showed that the drug sampled was pure. UV spectra of the drug were scanned with the help of UV spectrophotometer. The λ_{max} of the drug was found to be 263 nm.

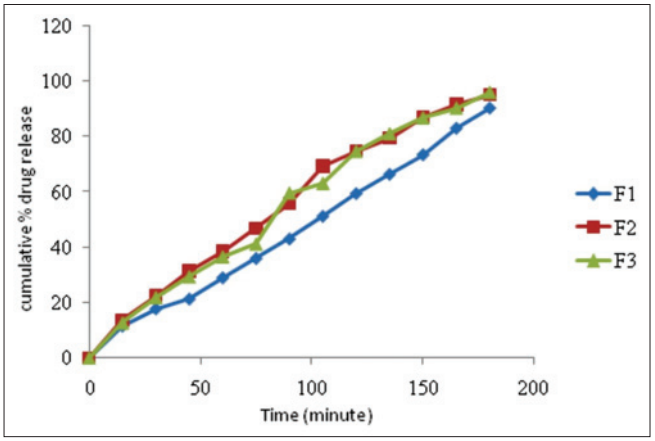

Figure 3: C%DR of formulation from F1, F2, and F3

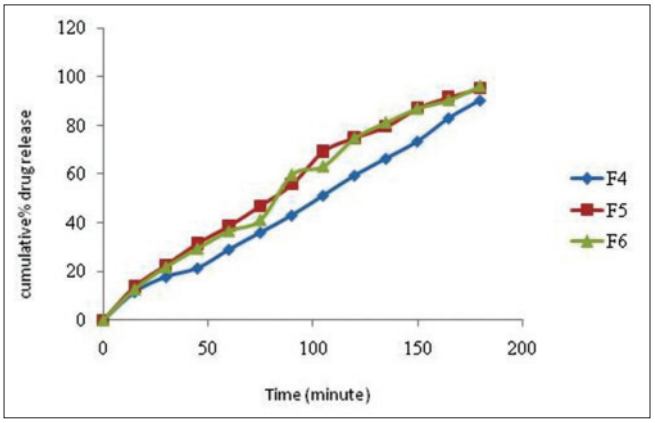

Figure 4: C%DR of formulation from F4, F5, and F6

The partition coefficient (log P) was determined in octanol and water by shake flask method. Partition coefficient was found to be 3.0 that showed the drug was partitioned maximum in the hydrophobic phase, so the drug nature was found being lipophilic. The quantitative estimation of drug was done by preparing a calibration curve. Calibration curve was prepared in phosphate buffer; value of R^2 was found to be 0.993, which also show linearity in the graph.

The drug excipients compatibility study was performed by physical observation test, and the result of the study indicated that drug and excipients are compatible with each other.

Table 2: Determination of viscosity, appearance, gelling

Formulation	Viscosity (CPS)	Appearance	Gelling
F1	14420±75.68	Translucent	+
F2	15330±86.34	Translucent	+
F3	16261±87.65	Translucent	+++
F4	16427±54.76	Translucent	++
F5	16734±67.45	Translucent	++
F6	16856±43.35	Translucent	++

Naproxen gel; (±) SD for n=3; +: Poor, ++: Good, +++: Excellent, SD: Standard deviation

Table 3: C%DR of formulations F1, F2 and F3

Time (min)	Formulation		
	F1	F2	F3
0	0.0±0.00	0.0±0.00	0.0±0.00
15	10.55±0.15	9.03±0.36	14.05±0.17
30	17.75±0.17	14.25±0.24	27.80±0.30
45	23.82±0.28	20.05±0.42	32.33±0.24
60	30.85±0.25	27.33±0.40	39.41±0.40
75	41.11±0.36	34.32±0.15	46.71±0.23
90	50.33±0.30	46.18±0.45	52.23±0.12
105	62.80±0.24	52.43±0.43	68.03±0.37
120	72.40±0.38	58.17±0.20	75.39±0.35
135	80.62±0.41	67.82±0.35	86.33±0.56
150	87.33±0.45	72.45±0.51	91.66±0.40
165	91.01±0.40	81.29±0.30	95.62±0.63
180	93.50±0.75	86.92±0.87	99.37±0.45

Table 4: C%DR of formulations F4, F5 and F6

Time (min)	Formulation code		
	F4	F5	F6
0	0.0±0.00	0.0±0.00	0.0±0.00
15	11.54±0.14	13.75±0.26	12.68±0.18
30	17.75±0.19	22.57±0.25	21.86±0.39
45	21.32±0.28	31.43±0.40	29.39±0.29
60	28.99±0.22	38.57±0.40	36.57±0.44
75	35.98±0.39	46.93±0.15	41.19±0.25
90	43.03±0.37	55.73±0.47	59.73±0.18
105	51.19±0.28	69.24±0.45	63.23±0.31
120	59.43±0.33	74.82±0.20	74.82±0.34
135	66.39±0.42	79.39±0.35	81.22±0.56
150	73.45±0.47	86.95±0.50	86.95±0.49
165	83.04±0.39	91.51±0.30	90.45±0.62
180	90.33±0.67	95.06±0.88	96.17±0.49

The optimization of naproxen gel containing eucalyptus oil was done on the basis of experimental design. The gel base was analyzed on the physical basis such as appearance color, clarity, homogeneity, and gelling (rigidity). The gel base was found to be clear, transparent and homogeneous.

The gel was formulated by changing the polymer concentration in the range of 0.50%, 0.75%, 1%, 1.25%, 1.50%, 1.75%. All these formulation were subjected to evaluation on the basis of appearance, gelling, viscosity and drug release. The gelling of the gel formulations F1, F2 was found to be poor, in case of F4, F5, F6 formulations the gelling produced was only good but not to be acceptable and all the formulations were translucent visually while formulation F3, were excellent in its gelling nature and was clear.

The viscosity range of all the gel formulations shows a gradual increase in the viscosity as the concentration of polymer was increased. Viscosity of formulation was found to be 14420, 15330, 16261, 16427, 16734, 16856 cps unit.

The drug release study of the gel formulations was compared which showed variations in drug release with the change of carbopol P - 934 concentration. The drug release was found to be 93.50% with 0.50% carbopol, 86.92% with 0.75% carbopol, 99.37% with 1% carbopol, 90.33% with 1.25% carbopol, 95.06% with 1.50 % carbopol, 96.17% with 1.75 % carbopol.

On the basis of combined data of appearance, gelling, elegancy, viscosity and % drug content F3 formulation was selected as the optimized formulation and final formulation was prepared with respective concentration for further evaluations.

Optimized formulation F3 was further evaluate on different evaluation parameters such as viscosity, pH, homogeneity, grittiness and feel on application, drug content, and drug diffusion.

Homogeneity was observed on the visual basis which showed good homogeneity in F3 and free from any lumps and aggregation. No appreciable particulate matter was seen under the light microscope. No foreign particulate particles observed and the gel was smoothly applicable. The topical preparation was found to possess the grittiness as required for the topical gel [5].

The pH of gel formulation was determined by the digital pH meter. The pH was found to be 6.7, which are within the acceptable limit for topical formulations. The viscosity range of the F3 gel formulation was 16427 cps, which is within an acceptable range for topical formulations.

The drug content in the formulation F3 was determined 93.04%.

Drug diffusion studies were carried out using a cellophane membrane. The cumulative present drug release was found to be 99.37% in 3 h. At the end the release kinetics of the optimized gel was studies on the basis of different models suggested for release kinetics such as zero-order model, first order model, Higuchi model and Krosmeyer–Peppas model [6]. The values of regression coefficient was found to be $R^2 = 0.986$ for zero-order model, $R^2 = 0.985$ for first order model, $R^2 = 0.983$ for Krosmeyer–pepps model, $R^2 = 0.945$ for Higuchi model. On the basis of data obtained, the optimized formulation was found to possess the release pattern of zero order model that shows the drug release pattern is sustained release.

CONCLUSION

The present study involved preparation of topical gel system of naproxen. On the basis of evaluation parameters, it can be concluded that naproxen gel containing eucalyptus oil can be an effective drug delivery system in the treatment of rheumatoid arthritis since it relives the side effects of naproxen. Therefore, the present topical drug delivery system can be a useful alternative to the currently available marketed preparation, i.e. Xenobiod gel.

REFERENCES

1. Kaur LP, Kumar TG. Topical gel: A recent approach for novel drug delivery. Asian J Biomed Pharm Sci 2013;3:1-5.
2. Gupta V, Dwivedi A, Trivedi N, Jain NK, Garud N, Jain DK. Formulation and evaluation of naproxen gel containing tulsi oil as penetration enhancer. Indian J Pharm Sci 2009;71:153-5.
3. Prakash PR, Raghavendra NG, Rao CS. Formulation, evaluation and anti-inflammatory activity of topical etoricoxib gel. Asian J Pharm Clin Res 2010;3:126-9.
4. Kumar TG, Kaur LP. Formulation and evaluation of topical gel of aceclofenac. J Drug Deliv Ther 2013;3:51-3.
5. Das MK, Ahmed AB. Formulation and *ex vivo* evaluation of rofecoxib gel for topical application. Acta Pol Pharm 2007;64:461-7.
6. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Int J Drug Deliv 2009;1:41-51.
7. Kikwai L, Babu RJ, Prado R, Kolot A, Armstrong CA, Ansel JC, *et al. In vitro* and *in vivo* evaluation of topical formulations of spantide II. AAPS PharmSciTech 2005;6:E565-72.

Source of Support: Nil, Conflict of Interest: None declared.