RESEARCH PAPER

Accepted 27 June 2000
Revised 19 June 2000
Received 12 October 1999
Indian J. Pharm. Sci., 2000, 62 (5) 376-379

Formulation and Evaluation of Nimesulide Transdermal Drug Delivery Systems

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Different transdermal nimesulide gels were prepared using various gel bases, with an objective to formulate suitable transdermal formulation of nimesulide. The polymers selected were sodium alginate, HPMC, NA CMC and methyl cellulose. *In vitro* release studies of the prepared formulation were performed using dialysis membrane and results indicated that sodium alginate gel showed better release. *In vivo* antiinflammatory activity was studied in carrageenan-induced rat paw oedema and analgesic activity was studied in acetic acid-induced writhes in rats. Among the prepared formulations, sodium alginate gel showed better antiinflammatory and analgesic activity. Sodium alginate gel found to be more stable when stability study was performed. Sodium alginate gel containing nimesulide was found to be better in all aspects compared to other gel formulations and this was comparable to the marketed gel.

More recent approach to drug delivery is to deliver the drug in to systemic circulation at a predetermined rate which is known as controlled release drug delivery system. Such systems helped to overcome the side effects associated with conventional system of medication, which require multi-dose therapy. Transdermal therapeutic systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Thus, it is anticipated that, transdermal drug delivery system (TDDS) can be designed to input drugs at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy by using skin as the port of entry of drugs[1].

Nimesulide is a nonsteroidal antiinflammatory drug (NSAID), which acts by selectively inhibiting the cyclooxygenase-2 (COX-2)[2]. It showed better antiinflammatory and analgesic activity in clinical trials[2,3,8]. Nimesulide is generally well tolerated in short term treatments, but in case of long term treatments which require higher doses (200 mg or greater per day) as in the treatment of osteoarthritis, the incidence of adverse effects was greater[3]. Therefore, to minimize the adverse effects, to extend the drug action, to improve the delivery of the drug into systemic circulation, we attempted to formulate the suitable TDDS of nimesulide.

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MATERIALS AND METHODS

Nimesulide was a gift sample from BPRL-Recon Ltd. Bangalore. Sodium alginate (S.D. Fine Chemicals Ltd., Boisar); sodium carboxy methyl cellulose (Na CMC), methyl cellulose (MC), hydroxy propyl methyl cellulose (HPMC, 100 cps) were purchased from Genuine Chemical Co., Mumbai. Dialysis membrane (cut off 12000) was purchased from the Sigma Chemical Co., USA. All other ingredients were of analytical grade and were used as procured.

Preperation of transdermal gels:

The polymer (quantity of each polymer with the drug was specified in Table 1) was taken in a mortar and water was added. This was allowed to soak for about 24 h and then glycerin was added and triturated well. In case of sodium alginate gel, methyl paraben was dissolved in

TABLE 1 : FORMULATIONS OF VARIOUS NIMESULIDE GELS

Ingredients	Sodium alginate gel	HPMC gel	Na CMC gel	MC gel
Nimesulide	0.10 g	0.10 g	0.10 g	0.10 g
Sodium alginate	0.80 g	—	—	—
Methyl paraben	0.017 g	—	—	—
HPMC	—	0.20 g	—	—
Na CMC	—	—	0.65 g	—
MC	—	—	—	0.10 g
Glycerin	1.00 ml	1.00 ml	1.00 ml	1.00 ml
Water to make	10.0 ml	10.0 ml	10.0 ml	10.0 ml

Composition of various transdermal gels prepared are given in the table. HPMC is hydroxy propyl methyl cellulose, Na CMC is sodium carboxy methyl cellulose and MC is methyl cellulose.

the little warm water and incorporated in the above. The drug was then added slowly with trituration to get a homogeneous dispersion of the drug in the gel. The gel was then filled in the collapsible tubes and labelled.

***In vitro* release study:**

Specially designed cylindrical diffusion cell made up of glass (10 mm x 23 mm) was used in the study. Known quantity of gel was weighed (containing 1% w/w of drug) and was filled in such tube by placing it on a dialysis membrane, which was then tied to the diffusion cell. This diffusion cell was immersed in a beaker containing 100 ml of phosphate buffer saline (PBS) of pH 7.2 with methanol 20% v/v. The diffusion study was carried out for 6 h. The samples were withdrawn at predetermined time intervals and the same volume was replaced with fresh release medium. The absorbance of the withdrawn sample was measured after suitable dilution at 395 nm to estimate nimesulide. This experiment was carried out in triplicates and average values were reported.

Evaluation of antiinflammatory activity:

The procedure adopted was that of Winter *et al.*[4]. Male albino rats, each weighing 180-200 g were divided into different groups each containing six rats. Acute inflammation was produced by injecting 0.05 ml of 1% w/v carrageenan solution in the sub plantar region of the rat right hind paw. The animals received the formulation by topical smearing on the back (just below the neck area), one hour prior to the carrageenan injection. The paw oedema volume was measured at different time intervals after carrageenan challenge by the help of a water plethysmometer before and after 6 h of carrageenan injection.

Evaluation of analgesic activity:

For the analgesic activity, male albino rats, weighing about 180-200 g were divided in to six groups each group consisting of 6 rats. Writhings or stretchings were produced by intraperitoneal injection of the 1% v/v aqueous acetic acid solution[5]. The animals received the formulation by topical smearing on the back (just below the neck area), 1 h prior to the acetic acid injection. The number of writhes (abdominal stretchings) was observed for about 15 min. The graph of mean writhes was plotted for each group of rats to compare the analgesic activity of prepared gels with that of the marketed gel.

Measurement of Viscosity:

Viscosity was determined using a Brookfield viscometer. In the present study, we selected the rate of shear (G) of 6 rpm. All the formulated gels and the marketed gel were sheared at 6 rpm (constant rate of shear) for 5 min. The shear stress, (F) i.e., dial reading was recorded for each formulation. From this, viscosity was calculated for the purpose of comparison.

Stability study of transdermal gels:

The gels were formulated according to the formula (containing 1% w/w of the drug). The gels were then packed in the collapsible tubes. Each gel preparation was then kept at different temperature conditions like;

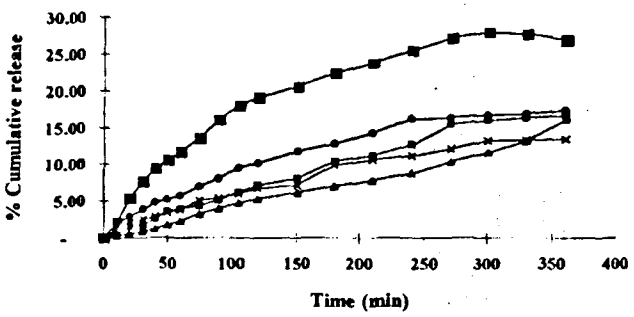

Fig. 1 : Comparative release of nimesulide from different gel bases

Release of nimesulide from sodium alginate gel (–●–) or HPMC gel (–■–) or Na CMC gel (–Δ–) or MC gel (-x-) or Marketed gel (–⊟–)

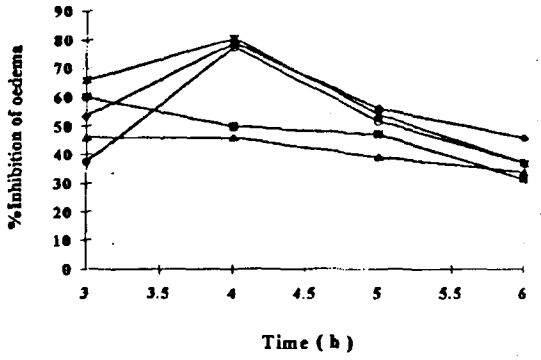

Fig. 2 : Antiinflammatory activity of nimesulide from different gel bases

Per cent inhibition of oedema from sodium alginate gel (–◆–) or HPMC gel (–□–) or Na CMC gel (–Δ–) MC gel (–○–) or Marketed gel (–*–)

ambient temperature (temperature in the working area) - 25° to 28°, 8±1° (refrigerator temperature), 37±2° temperature (in the incubator) for six weeks. The following parameters of the gel preparations were studied; colour, consistency, drug content and degradation rate constant (K).

RESULTS AND DISCUSSION

The results of the *in vitro* release study from different gels across the dialysis membrane are depicted in Fig. 1. The release pattern of drug from the marketed gel was found to be better than from other gels, the reason may be that the 66% alcohol content of the gel might have enhanced the solubility of the drug. In prepared gels, sodium alginate gel showed better release compared to other gels, because of its high hydrophilic nature compared to other polymers, which leads to the increased release of the hydrophobic drug. The tendecy of film formation is also high in case of cellulose polymers compared to sodium alginate, which ultimately results in poor release and absorption of drug from the gel. Methanol 20% v/v was used with the buffer system to increase the solubility of the drug in the diffusion medium and hence to maintain sink conditions.

In prepared formulations, the sodium alginate gel showed better antiinflammatory activity compared to other gels. The antiinflammatory activity showed by all four gels was comparable with that of the marketed gel, which is presented in Fig. 2. The order of antiinflammatory activity for different gels (in terms of % inhibition for rat paw oedema) is expressed in the decreasing order after 3 h, which is as follows:

Marketed gel (80.6) > Sodium alginate gel (78.7)>MC gel (77.3)> HPMC gel (49.85) > Na. CMC gel (46.2).

The reason for the greater antiinflammatory activity observed with sodium alginate gel may be attributed to high hydrophilicity and lower tendency to form the film when applied to the skin, compared to other gels.

The number of writhes was calculated for each group of rats for about 15 min. Mean writhes is then calculated by the statistical method (one way ANOVA) for each group of rats. The graph of mean writhes was then plotted as shown in the Fig. 3. The gels in their decreasing order of analgesic activity can thus be represented as follows;

Marketed gel>Sodium alginate gel>HPMC gel>MC gel>Na. CMC gel.

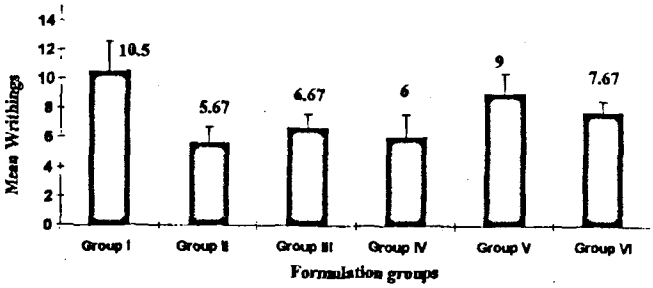

Fig. 3 : Analgesic activity of nimesulide from different gel bases

Mean writhes from Control (Group-I) or marketed gel (Group II) or HPMC gel (Group III) or Sodium alginate gel (Group IV) or MC gel(Group V) or Na CMC gel (Group VI).

TABLE 2 : VISCOSITY OF VARIOUS NIMESULIDE GELS

Gel	Viscosity in Centipoises (cps)
Sodium alginate	9222
HPMC	13780
Na CMC	4982
MC	5512
Marketed (Std)	7844

Viscosity of different gels was determined using a Brookfield viscometer. HPMC is hydroxy propyl methyl cellulose, Na CMC is sodium carboxy methyl cellulose and MC is methyl cellulose.

The viscosity of various formulated nimesulide gels and also the marketed gel was measured using a Brookfield viscometer. Viscosity of different formulations was presented in Table 2.

Except for the sodium alginate gel, the fading of the colour was observed for other gels. This was prominent in case of Na CMC gel. The consistency of sodium alginate and Na CMC gels was found to be same especially at ambient and 8° temperature, but at 37° there was slight decrease in the consistency of Na CMC gel after one month. The important observation in case of MC gel was pertaining to consistency. The consistency was changed dramatically at all three temperature conditions, especially there was dramatic increase in the consistency of the MC gel at 37° temperature.

Nimesulide was found to be more stable in the sodium alginate gel when compared to Na CMC and MC gel, as evidenced by the degradation rate constant (K) value at different temperatures. The K values for sodium alginate at ambient, refrigerator and incubator temperature were; 0.0229, 0.0142 and 0.041 per day respectively. Similarly K values for Na CMC gel were, 0.0285, 0.024 and 0.05 and for MC gel, 0.036, 0.033 and 0.065 per day respectively.

The stability of gel formulation made with the HPMC was found to be unsatisfactory. After two days, the gel consistency had decreased (visual examination), probably because of the oozing of the interpenetrant liquid. The reason may be that, the gel structure was not formed exactly or there may be some incompatibility of the HPMC with nimesulide, the reason for which was not exactly traced out.

In conclusion, sodium alginate gel containing nimesulide was found to be better in all aspects compared to other formulations and this was comparable to the marketed gel, which contains 66% alcohol. Moreover, the prepared transdermal gels were not containing any permeation enhancers, an important advantages as permeation enhancers resulted in many tissue irritation and skin sensitization reactions. These gel formulations are cost effective because no organic solvent and penetration enhancers were used in the preparation.

ACKNOWLEDGEMENTS

The authors thank the Recon Ltd., Bangalore for providing the drug sample and Mr. Sandeep Tiwari for technical assistance.

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