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Original Article

FORMULATION AND *IN VITRO* EVALUATION OF DICLOFENAC SODIUM GEL

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ABSTRACT

Objective: The present research has been undertaken with the aim to develop a topical gel of diclofenac sodium (DS) 1%, evaluation of its physico-chemical characteristics and *in vitro* drug release through pig skin using vertical diffusion cell.

Methods: In the presented work was prepared a hydrophilic diclofenac sodium gel of hydroxyethylcellulose (HEC). Skin permeability of the preparation was evaluated *in vitro* using abdominal hairless pig skin, into water medium at 37°C and determined using spectrofotometer UV at 276 nm.

Results: From the study it was concluded that HEC gel containing diclofenac showed good homogeneity, spreadability, pH value and rheological properties within the limits allowed for dermatological preparations. HEC DS gel exhibited significantly better drug release when compared to commercial gel.

Conclusions: HEC can be used as gelling agent for the development of gel formulations, because of its good release profile, water-soluble nature and good spreadability.

Keywords: Hydrophilic gel, Hydroxyethylcellulose, Diclofenac sodium, *In vitro* drug release.

INTRODUCTION

Diclofenac sodium (DS) is a nonsteroidal anti – inflammatory drug (NSAIDs) widely used clinically to reduce inflammation and pain in conditions such as rheumatoid arthritis, menstrual pain, dysmenorrheal, fever, osteoarthritis or acute injury [1]. It has a short half-life in plazma (2 hrs) and only 50% of the drug reaches the circulation.

Oral dose of diclofenac potassium causes an increased risk of serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach or the intestines which could be fatal.

Transdermal delivery of the drug can improve its bioactivity with reduction of the side effects and enhance the therapeutic efficacy [1, 2].

DS has a potent anti-inflammatory effect, but it does not penetrate well through skin and cannot reach the effective concentration at the site of action after transdermal application. For this reason, we wanted to suggest new, alternative dosage forms for transdermal application of DS.

From the literature, the formulation with HEC gel base exhibited better properties for topical delivery of drugs when compared with the other formulations [3, 4].

HEC formulation was developed and *in vitro* transdermal penetration of this formulation was compared with that commercial Vurdon gel 1% - Help.

The objective of present study was conducted to develop a topical gel formulation of diclofenac sodium using HEC polymer. The gels were evaluated for physical appearance, rheological behaviour, drug release and stability. The drug release from the gels through abdominal hairless pig skin was evaluated using vertical diffusion cell.

MATERIALS AND METHODS

Materials

DS was provided by Blue Cross (India), HEC was purchased from Sigma Aldrich (Germany). All chemicals used were analytical grade.

Spectrophotometer Specord 40 – 232 E 129, Viscosimeter NDJ-1.

Preparation of gel

Hydrogels were formulated by first preparing a stock solution of the nipagin and nipazol in 50 g distilled water. Separately Diclofenac sodium (1% w/w) was dissolved in preweighted amounts of glycerol.

Solvent blend was transferred to conservation water and agitated by adding small amounts of HEC. The dispersion was then allowed to hydrate and swell for 60 min and then was stirred by the help of an electric mixing propeller [3, 5].

Characterization of Formulations

The prepared diclofenac sodium gels were inspected visually for their homogeneity, viscosity, spreadability, pH, drug content, *in vitro* drug release, stability studies.

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Table 1: It shows the gels formulation

Ingredients (%w/w)	Formulation		
	DC 1	DC2	DC3
Diclofenac sodium	1	1	1
HEC	2.5	2.5	2.5
Glycerol 85%	10	10	10
Nipagin	0.1	0.1	0.1
Nipazol	0.01	0.01	0.01
Water up to	100	100	100

Viscosity

The measurement of viscosity of the prepared gels was done with a NDJ-1 viscometer. The gels were rotated at 6 and 12 rpm using spindle no. 3. At each speed, the corresponding dial reading was noted [6].

Spreadability

Spreadability was performed with extensiometer apparatus. The apparatus consists of two square glass plates, 11 cm on each side. On the outside part of the inferior plate a coordinate paper is attached, on which five concentric circles with perpendicular diameter in millimeters are drawn. The spreadability was determined as follows: 1 g gel was placed between the plates and the upper plate was increasingly loaded with weights at equal time intervals [7, 8].

Based on the results of 3 measurements the mean calculated surfaces were plotted in the form of extensiometric curves. On Y-coordinate the ointment surfaces, in cm^2 were marked and on X-coordinate the loadings value, in grams (g) were marked.

pH

The pH was measured in water solutions of each gel, using a digital pH meter, which was calibrated before each use with standard buffer solutions at pH 4.6 and 8.6. The solutions are prepared by dissolving 2.5 g of each gel in 25 g water [9, 10].

Drug content

Drug content of the gels was determined by dissolving an accurately weighed quantity of gel (about 400 mg) in about 100 ml of water. The solutions were then filtered before estimated spectrophotometrically at 276 nm. Drug content was determined from the standard curve of diclofenac sodium.

***In- Vitro* Release**

The *in vitro* release experiments were carried out by using Vertical Diffusion Cell apparatus for DC gel formulations and the commercial gel. A glass cylinder with both ends open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. The pig skin (previously shaved and cleaned with water) was fixed to one end of the cylinder by adhesive tape in such a way that the epidermis was facing the gel formulations to be applied. One gram of the prepared gel was taken in the cell (donor compartment) and the cell was immersed in a beaker containing 100 ml of water (receptor compartment). The cell was immersed in to a depth of 1 cm below the surface of medium, which was agitated by a magnetic stirrer and the temperature was maintained at 37° ± 1°C throughout the experiment. Aliquots of 5 ml were withdrawn from the receptor compartment periodically (5, 10, 15, 20,..., 390 min). After each withdrawal, the volume of liquid in the receptor compartment was replaced by the same volume of water. The drug concentration was determined spectrophotometrically (Specord 40 – 232 E 129) at 276 nm [8, 11, 12].

Stability study

For the evaluation of stability study, the formulations were maintained at an ambient condition over a period of three months. The physical appearance, pH value, drug content, rheological properties were determined.

Statistical analysis

Datas were expressed as mean ±SD. Differences were considered statistically significant for $p < 0.05$. Statistical analyses were performed using GraphPad Prism 4.01 software.

Table 2: It shows the physicochemical characteristics of diclofenac sodium gels formulations and Vurdon gel

Formulation	Homogeneity	pH ± SD	Viscosity (mPas)		Drug content (%) ± SD
			6 rpm	12 rpm	
DC1	+++	7.33 ± 0.016	15000	10000	102.7 ± 7.40
DC2	++	8.06 ± 0.153	12000	9500	103.3 ± 4.10
DC3	+++	8.35 ± 0.136	18000	16000	109.4 ± 1.80
Vurdon	+++	7.63 ± 0.080	20000	18000	99± 1.10

+++ Excellent ++ Good + Satisfactory

RESULTS AND DISCUSSION

Characterization of Formulations

The prepared formulations shared a smooth and homogeneous appearance. The HEC diclofenac sodium gels were transparent while Vurdon gel was white viscous, opalescent. All preparations were easily spreadable, with acceptable bioadhesion and fair mechanical properties.

At table 2 are shown the values of pH, viscosity and drug content for each gel. The pH values ranged from 7.33 ± 0.016 to 8.35 ± 0.136, which are considered acceptable to avoid the risk of irritation after skin application.

Viscosity is an important physical property of topical formulations, which affects the rate of drug release; in general, an increase of the viscosity vehicles would cause a more rigid structure with a consequent decrease of the rate of drug release.

Spreadability

Mean results of three measurements expressed in the form of spreadability curve are shown at figure 1. The three DC formulations were found to express good spreadabilty compared with that of commercial gel.

Considering the stability studies and physiochemical parameters, batch DC1 and DC3 were selected for *in vitro* permeability release studies as well as compared with the marketed gel. The results are shown at the figures 2 and 3.

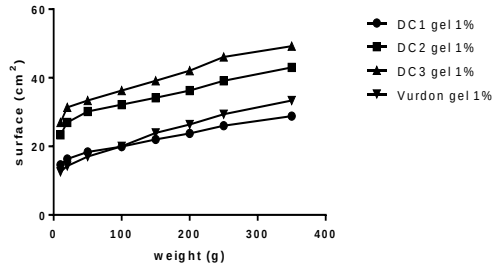

Fig. 1: It shows extensiometric curves of the four gels *In vitro* release

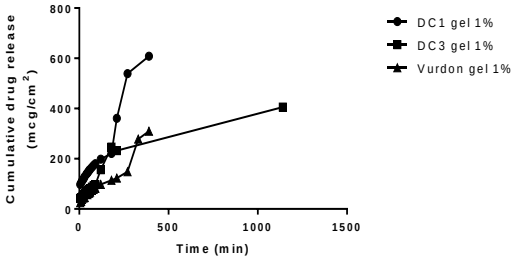

Fig. 2: It shows the release of DS from the two formulations and Vurdon gel

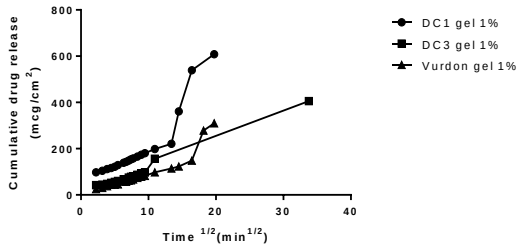

Fig. 3: It shows the release rate of DS from the two formulations and vurdon gel

When the amounts of drug released per unit area (µg/cm^2) were plotted against the square root of time, a linear relationship was obtained for each gel, showing that the release of drug from the gels could be well described by the Higuchi model, where the rate-controlling step is the process of diffusion through the gel matrix.

It is possible to calculate the steady state flux (J) from the slope of the linear portion (5-300 min) of the graph of the release rate of drug.

CONCLUSION

From the present studies, it could be concluded that HEC can be used as gelling agent for the development of gel formulations, because of its good release profile, water-soluble nature and good spreadability.

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