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Research Article

FORMULATION AND EVALUATION OF DICLOFENAC TOPICAL GEL WITH ANALGESIC ACTIVITY

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ABSTRACT

The present investigation is concerned with formulation and Evaluation of Diclofenac topical gel an anti-inflammatory, analgesic drug to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. The diclofenac gel were prepared by using different concentration of different polymers. Six formulations were developed with varying concentrations of polymers like Carbopol, HPMC. The gels were tested for clarity, homogeneity, washability, spreadabiliy, PH, percentage drug content, skin irritation, permeability studies. From the study it was concluded that HPMC gel containing diclofenac sodium showed good consistency, homogeneity, spreadability, washability and permeability and has wider prospect for topical preparations as compared to Carbopol gel containing diclofenac sodium.

Keywords: Diclofenac sodium, Topical drug delivery, HPMC, Carbopol, Analgesic.

INTRODUCTION

Topical drug administration is a localized drug delivery system in the body through ophthalmic, rectal, vaginal and skin as topical routes. Skin is one of the readily exposed organs on human body for topical administration and is main route of topical drug delivery system. For topical treatment of dermatological disease as well as skin care, a wide variety of vehicles ranging from solid to semisolid and liquid preparations is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels as expanded both in cosmetics and pharmaceutical preparations. A gel is having two unique sorts of segment, cross connected three-dimensional organisation comprised of underlying materials. The materials that structure the gel organisation can be comprised of inorganic particles or natural macromolecules, primarily polymers. A gelling agent also called polymer and water are the primary ingredients used to form gels. The main property of a gel is swelling. The mechanism of swelling of gel is explained by exerting osmotic pressure on the polymer in the gel. This acts as driving force for water to enter the gel and cause swelling. Most of the polymers have the ability to absorb water or other liquid. Hydroxy propyl methyl cellulose (HPMC), Carbopol has been used as hydrophilic polymers topically in gel drug delivery system which has high molecular weight and do not penetrate the skin and are non-toxic. Osteoarthritis and rheumatoid arthritis are major inflammatory diseases occurring across the globe, mostly in developing countries. NSAIDs are common drugs and have widespread use for chronic and acute musculoskeletal conditions. They are convenient for local action without developing central adverse effects and comprehensive impairments. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) designated for use in painful and inflammatory rheumatic and particular non-rheumatic conditions. This review estimates the safety and efficacy of topical diclofenac in a range of painful and inflammatory disorders [1-5]

MATERIALS AND METHODS

Formulation of diclofenac topical gel is prepared by using different ingredients like diclofenac as active ingredient; HPMC and Carbopol as polymers; propylene glycol as humectant; NaOH as neutralizer and distilled water as solvent. Diclofenac sodium was gifted by Dr Reddy's laboratory, Hyderabad. Other excipients were purchased from S.D. Fine chemicals, Mumbai.

Preparation of diclofenac gel

For formulation F1, F2, F3, 0.2g of diclofenac sodium was weighed and dissolved in a 3ml of propylene glycol with the help of mild heat (SOLUTION A). Weighed quantity of HPMC was added to the 16ml of distilled water and stirred until dissolved (SOLUTION B). Solution A and B were mixed thoroughly and the final weight was made up to 20g. For formulation F4, F5, F6, 0.2g of diclofenac sodium was weighed and dissolved in a 3ml of propylene glycol with the help of mild heat (SOLUTION A). Weighed quantity of carbapol 934P was added to the 16ml of distilled water and stirred and dissolved. Then neutralized by 10% NaOH (SOLUTION B). Solution A and B were mixed thoroughly and the final weight was made up to 20g [Table 1][1].

Precipitation occurs in some of the batches (F1, F3, F4, F6) of polymer based gel containing Diclofenac sodium which could be due to the incompatibility in the system. Hence these batches were discarded and remaining batches (F2, F5) were considered for further studies.

F2

F5

Evaluation of polymer based gel containing diclofenac sodium

Preformulation studies

Identification test
Drug is mixed with 1ml of 0.4% w/v solution of methanol and 1ml of nitric acid to produce red colour.
Solubility of drug in methanol, ethanol, water and GAA were carried out [Table 2].

Physical examination:(Colour, Odour, Smoothness)
Formulated gel was evaluated for its colour, visually colour was checked. Odour was found smelling the product. The smoothness was tested by rubbing the paste formulation between the fingers [Table 3].

About 6 formulations i.e, F1 to F6 were conducted. Gels were evaluated for their clarity, PH, viscosity, spreadability, extrudability, skin irritation test, percentage drug content, homogeneity, consistency by using standard procedure. All the studies were carried out and average values were reported.

The above formulated polymer-based gel containing diclofenac sodium was subjected to evaluation for the following:

pH: The pH of various gel formulations was determined by using digital PH meter [Table 4][6].

Clarity: Clarity of various formulation was determined by visual inspection under black and white background and it was graded as follows: Turbid+; clear++; very clear(glassy)+++ [Table 4][7].

Homogeneity: All formulated gels were tested for homogeneity by visual examination. They were checked for the presence of any aggregates [Table 4][6].

Washability: The formulated gels were applied on the skin and then checked for ease of washing with water[9].

Consistency: The consistency of developed gels was examined by dropping the cone attached to a holding rod from a fixed distance of 10cm in other way that it should fall down on the centre of the glass cup with the gel. The penetration by the cone was accurately measured from the surface of the gel to the tip of the cone of inside of the gel. The distance travelled by cone in a period was noted down after 10 seconds [Table 4][6].

Spreadability: For the determination of spreadability, excess of sample was applied in between two glass slides and was compressed to uniform thickness by placing 100g weight for 5 min. Weight was added to the pan. In which the upper glass slide moves over to the lower slide was taken as measure of spreadability [Table 4].

$$S=ML/T$$

Where; M-Weight tied to the upper slide, T-Time taken, L-Length moved on the glass.

Drug content: A specified quantity of developed gel and marketed gel were taken and dissolved in 100ml of phosphate buffer of PH 6.8. The volumetric flask containing gel solution was shaken for the period of 2 hour on mechanical shaker in order to get absolute solubility of drug. This solution was filtered and estimated spectrophotometrically at 285.0 nm using phosphate buffer (PH 6.8) as blank [Table 4][6].

Skin irritation test: The hair on the dorsal side of mice was removed by clipping one day before the experiment. The mice were divided into 2 groups. Group 1 served as control; group 2 received optimized formulation. Then, the application sites were graded according to visual scoring scale. (KCP/IAEC/P.CEUTICS/UG/210/2021-22)

Grittiness: All the gel preparations are examined microscopically for the presence of any particulate matter.

Viscosity: Viscosity was evaluated by using Ostwald viscometer. The viscometer was attached vertical position on a suitable stand. Viscometer was filled with water upto mark A. The time was counted for water to flow form mark A to mark B. The same procedure was repeated for the gel. [Table 4].

Permeability studies: The diffusion studies of the prepared gel can be carried out by using cellophane membrane. Gel sample was taken in cellophane membrane and the diffusion studies were carried out at 37+/- 1 ^{0}C using phosphate buffer as the dissolution media. Few milli litre of each sample is withdrawn periodically at 30, 60, 90, 120 min. and all the samples were restored with equal volume of fresh dissolution medium. Then the samples were analyzed for the drug content by using phosphate buffer as blank [Table 5][8].

RESULTS AND DISCUSSION

In the pre formulation studies, the drug is identified by treating with methanol and nitric acid which produced red colour. The melting point of drug was formed to be 280 ^{0}C.The drug was very soluble in methanol, soluble in ethanol, slightly soluble in water. The partition coefficient was found to be 3.5. The PH values of all formulated gels (F2 And F5) were found to be 7.3 and 6.9 respectively. All gels were found free from presence of particles. HPMC gels were found to be sparkling and transparent, Carbopol gels were found to be translucent. All formulated gels showed good homogeneity with absence of lumps. The clarity of developed gels (F2, F5) was found to be very clear(glassy) and easily washable. The consistency of F2 formulation was better when compared to F5 formulation. The consistency reflects the ability of gel to get ejected in uniform and desired quantity when the tube is squeezed. Spreadability of formulated gels (F2, F5) were 5.7 and 3.6 therefore, the spreadability of F2 formulation was good as compared to F5 formulation. The percentage drug content of formulated gels was (F2, F5) found to be 99.80% and 99.7% respectively. The viscosity of formulated gels (F2, F5) was calculated as $0.93X10^{-3}$ and $1.5X10^{-3}$ respectively. In vitro permeability studies showed that permeation of formulations was comparable with each other.

Table 1: Composition and concentration of Diclofenac sodium gel

Batch No.	Drug (g)	Polymer HPMC (g)	Polymer Carbopol (g)	10% NaOH	Propylene glycol	Distilled Water (ml)
F1	0.2	0.6	---	---	3	Up to 20
F2	0.2	0.7	---	---	3	Up to 20
F3	0.2	0.8	---	---	3	Up to 20
F4	0.2	---	0.05	q.s	3	Up to 20
F5	0.2	---	0.1	q.s	3	Up to 20
F6	0.2	---	0.15	q.s	3	Up to 20

Table 2: Preformulation study of the drug

Solubility in Methanol	Solubility in Ethanol	Solubility in water & GAA	Partition coefficient	Melting point (^{0}C)
++++	+++	++	3.4	280

++++Very soluble, +++Moderately soluble, ++Slightly soluble, +Practically soluble

Table 3: Physical examination of Diclofenac sodium gel

Parameters	Observation
Colour	White transparent
Odour	Characteristic
Smoothness	Good consistency and smooth texture

Table 4: Values of evaluation parameters of developed Diclofenac sodium gel

Batch no	pH	Clarity	Spreadability(g.cm/sec)	Viscosity(dyn. s/cm^2)	Consistency(60 sec)	Homogeneity	Drug content(%)
F2	7.3	+++	5.7	$0.93X10^{-3}$	7mm	Excellent	99.80
F5	6.9	++	3.6	$1.5X10^{-3}$	6mm	Good	99.75

Table 5: Permeability studies of developed gel

Time interval (min.)	Medium pH	% Drug release Batch F2	% Drug release Batch F5
30	6.8	38.53	44.62
60	6.8	64.77	71.34
90	6.8	81.21	84.37
120	6.8	96.86	97.73

This study shows that permeation of formulation (F2, F5) was comparable with each other.

CONCLUSION

The polymer being macromolecules of very high molecular weight remain unabsorbed on the skin and from our studies it was observed that Hydroxy propyl methyl cellulose (HPMC) gel containing diclofenac sodium (F2) produced better consistency and spreadability as compared to carbapol gel (F5) formulation. The formulated gel showed good homogeneity, no skin irritation, good stability and invitro permeability. As the HPMC is water soluble, it forms water washable gel and has vast hope to be used as used as topical drug delivery system.

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