AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Optimization of Diclofenac Sodium Gel by Using Calendula Oil as Sorption Promotor

Vishalkumar Kavade*[1], Mitali Bodhankar[1], Arun Patil[2]

1. Gurunanak College of Pharmacy,Nagpur, India, 440026.

2. Department of Pharmaceutical Sciences,Nagpur, India, 440066

ABSTRACT

Diclofenac sodium (DFS) is a Non-Steroidal Anti-Inflammatory drug, used in the treatment of inflammation and degenerative disorder of the musculoskeletal system. The present study is based on the preparation of DFS topical gel for the purpose of obtaining optimized gel which will give better results considering the formulation and patient compliance. For the preparation of topical gel carbopol polymer and different excipients are used for final preparation. The calendula oil is used as penetration enhancer in this final formulation in different concentration. These formulations with and without calendula oil were compared with marketed preparation with respect to its permeation, pH, viscosity, spreadability, extrudability. Permeation experiments were performed on excised rat skin (675/02/C/CPCSEA or GNCP/IAEC/2011-2012/Pharmaceutics-2). On the basis of *in–vitro* drug diffusion study and other properties of gel, we have concluded that calendula oil is best penetration enhancer for DFS gel. The solubility of DFS in the solvent system containing 1%calendula oil also checked and it was similar to that without enhancer. These results suggest that the enhancing effect of calendula oil is independent on the solubility of drug in the solvent system and were dependent on the concentration of calendula oil.

Keywords: Diclofenac sodium, Calendula oil, Terpenes, Penetration enhancer, Gel evaluation

*Corresponding Author Email: vishalkumar.kavade@gmail.com

Received 14 April 2012, Accepted 28 April 2012

Please cite this article in press as: Kavade V *et al.*, Optimization of Diclofenac Sodium Gel by Using Calendula Oil as Sorption Promotor. American Journal of PharmTech Research 2012.

INTRODUCTION

Diclofenac sodium is a popular, potent Non-Steroidal Anti-Inflammatory drug, used in the treatment of inflammation and degenerative disorder of the musculoskeletal system. Upon oral administration it undergoes first pass metabolism and because of its short biological half- live, the drug has to be given frequently. The oral use of DFS is associated with various side effects mainly gastrointestinal disturbances, epigastric pain etc. Topical application of the drug prevents these side effects and offers potential advantage of delivering the drug at the site of action. Topical formulations are available in various forms like ointments, creams, gels. Out of that gels are very widely used. For this purpose topical DFS gel is prepared but DFS is not easily absorbed on topical application because of its low permeability through stratum corneum[1, 2].

To overcome the low permeability of drugs through the skin, many strategies have been used. Most of them use of penetration enhancer which is a popular technique. These agents partition into, and interact with, the stratum corneum constituents to induce a temporary, reversible increase in skin permeability [3-6].Therefore for the preparation DFS gel calendula oil has been used as penetration enhancer because the calendula oil contains terpenes and they are widely used as penetration enhancer [7].

In this study the DFS gel was prepared by using carbopol gelling agent and different excipients such as methyl salicylate, menthol, calendula oil, surfactant, solubilizing agent, antiseptic and preservatives.These formulations with and without calendula oil were compared with marketed preparation with respect to its permeation, pH, viscosity, spreadability, extrudability.

MATERIALS AND METHOD:

Materials:

Diclofenac sodium (a gift sample of zim laboratory Pvt. Ltd. India), carbopol-934 was purchased from Loba chemicals, propylene glycol and triethanolamine was purchased from Research Lab Fine chemical, menthol was purchased from Burgoyne lab, methyl salicylate was purchased from Research Lab Fine chemicals ,calendula oil (extracted from calendula flowers by using Clevenger apparatus).

Methods:

Drug formulations:

The Various gels were prepared by adding 1% drugs in the formulations named as F1 (without calendula oil), F2 (1% calendula oil), F3 (2% calendula oil) shown in **Table 1.**

Solubility measurement:

The solubility of DFS in different pH value solvent systems was determined by addition of excess amount of the drug to the appropriate solvent (Ph 6.8, 7.4) at 37º C [8]. These suspensions were shaken for 1 to 2 hrs and filtered then concentration of DFS in above solvents measured by using UV spectrophotometer at 276 nm.

Table 1: Different formulations of DFS gel

Ingredients (gm)	F1	F2	F3
Diclofenac sodium	1	1	1
Methyle salicylate	10	10	10
Carbopol-934	1	1	1
Triethanolamine	1.8	1.8	1.8
Propylene glycol	5	5	5
Calendula oil	--	1	2
Menthol	5	5	5
Solubilising agent	7.5	7.5	7.5
Chlorocresol	5	5	5
Surfactant	5	5	5
Preservatives	0.1	0.1	0.1
Water	(ad 100gm)		

EVALUATION OF GEL [9, 10]:

Measurement of pH:

The pH of various gel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml distilled water and stored for 30 minutes. The measurement of pH of each formulation was done in triplicate and average values are calculated.

Drug content:

1gm of the prepared gel was mixed with 100ml phosphate buffer. Aliquots of different concentration were prepared by suitable dilutions after filtering the stock solution and absorbance was recorded using UV spectrophotometer at 276 nm measured. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve.

Viscosity:

The measurement of viscosity of the prepared gel was done with a Brookfield Viscometer. The gels were rotated at 100 rotations per minute and the corresponding dial reading was noted. The viscosity of the gel was obtained by multiplication of the dial reading with factor given in the Brookefield Viscometer catalogues.

Spreadability:

One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on

application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value.

Spreadability (S) is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula:

$S = M \times L / T$

Where M = wt. tied to upper slide

L= length of glass slides

T= time taken to separate the slides

Extrudability study:

The formulations were filled into collapsible metal tubes after the gels were set in the container. The extrudability of formulation was determined. It is a usual empirical test to measure the force required to extrude the material from tube. In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity of gel and gel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of gel in 10 seconds. More quantity extruded better was extrudability.

***In- vitro* permeation study:**

The artificial skin membrane was equilibrated in isotonic phosphate buffer (pH 7.4) for 2 h before being mounted on a Franz-type diffusion cell with an available diffusion area of 1.76 cm^2.The receptor phase consisted of a phosphate buffer solution (pH 7.4, 25 ml), stirred at 600 rpm and maintained at 37°C. 1 g of the test gel was placed on the donor side. The composition of the gels used in this study is shown in Table 1. At predetermined time intervals, 1ml samples were taken from the receiver compartment and replaced by the same volume of fresh buffer. The concentration of DFS present in the samples was determined by using UV spectrophotometer apparatus. Detection was at 276nm.

Different permeation parameters:

Based upon permeation study flux and lag time are calculated. The flux, J, was determined from the slopes at steady-state and the lag time was calculated from the x-intercept. All these above parameters are shown in Table 3.Flux values of different DFS gel also shown graphically in Figure 2.

RESULTS AND DISCUSSION:

Solubility of drug:

Table 2 shows the solubility of DFS. The solubility of DFS was not much affected by the addition of 1% calendula oil and dependent on the pH value of the solvents. It was suggested that 1% calendula oil would not affect the lipophilicity of the solvent system.

Other evaluation of gel:pH, viscosity, spreadability, extrudability of optimized Diclofenac gel are better or same when compared with marketed products.

Table 2: Solubility of DFS in pH 6.8 and 7.4 buffer / alcohol system

Drug	pH	Solubility (mg/ml)[a]	
		No enhancer	1% Calendula oil
Diclofenac sodium	6.8	31.86	32
	7.4	63.35	63.74

[a] Phosphate buffer/ alcohol solvent system

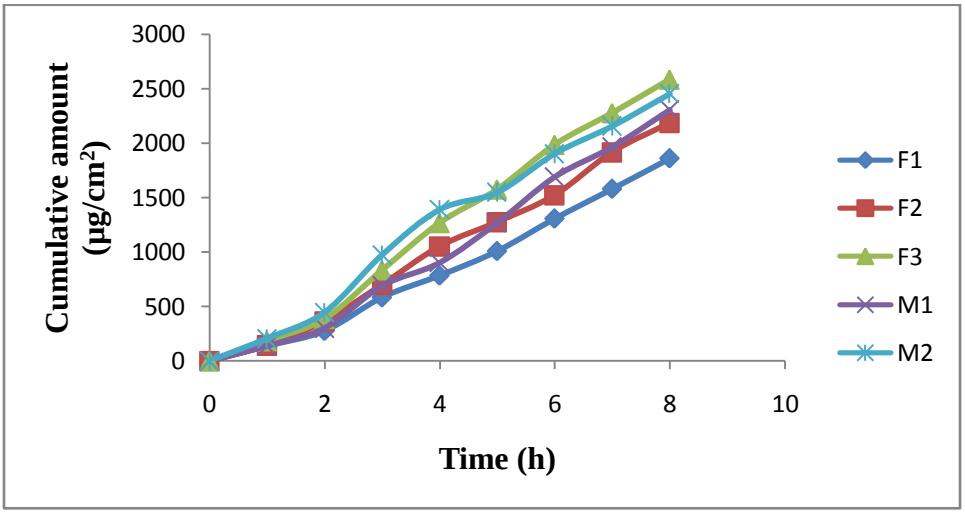

Figure 1: Permeation profile of DFS through rat skin membrane from carbopol gel (F1,F2,F3) and marketed products (M1 (parnac gel),M2 (voveron gel). Each points represents the ± S.E. of three experiments.

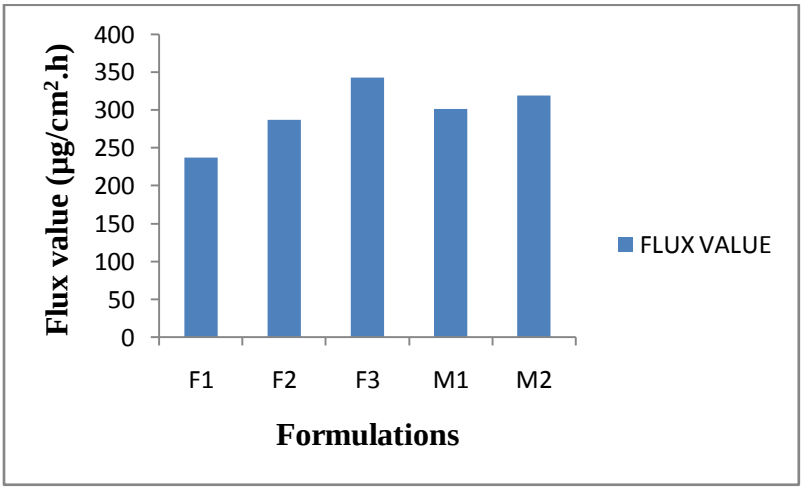

Figure 2: Flux values of different DFS gel

Table 3: Evaluation of Diclofenac sodium gels

Test	F1	F2	F3	M1	M2
pH	6.5±0.2	6.8±0.4	7.0±0.5	6.8±0.3	6.7±0.4
Drug content (%)	98.67±1.2	98.55±0.9	98.75±0.5	99.15±1.5	99.25±0.5
Viscosity(cps)	5800±50	5800±70	5700±55	5600±65	5500±40
Spreadiability(g.cm/sec)	8.15±0.15	8.45±0.10	9.15±0.35	9.20±0.3	9.35±0.2
Extrudiability	Excellent	Excellent	Excellent	Excellent	Excellent
Flux (ug/cm2.hrs)	237.5±26	286.6±30	342.8±35	300.9±21	318.9±25
Lag time (hrs)	0.47±0.03	0.39±0.02	0.4±0.02	0.58±0.05	0.14±0.03

***In vitro* permeation study:**

Figure 1 shows permeation profile and **Table 3** shows flux and lag time of different gels. These results suggest that highest increase in the DFS permeation was observed using calendula oil (2%) i.e.F3 then M2 followed by M1, F2 and then F1. Also the higher flux value is observed in F3 then M2 followed by M1, F2 and then F1 shown in **Figure 2** indicates higher permeability in F3 formulation.

CONCLUSION:

In conclusion, calendula oil was an effective penetration enhancer for DFS and it was suggested that the enhancing effect of calendula oil was not due to changing the solubility of drug in solvent system and was dependent on the pH value of solvent system and concentration of calendula oil.

ACKNOWLEDGEMENT:

The authors are thankful to Gurunanak College of Pharmacy, Nagpur, India for providing the necessary facilities.

REFERENCES:

1. Beale JM, Block JH. Wilson and Griswold's Textbook of Organic Medicinal and Pharmaceutical Chemistry. 12th ed., New Delhi: Lippincott-Raven Publishers; 1998: 716 - 718.
2. Chien YW, Robinson JR, Lee VHL. Transdermal Therapeutic Systems in Controlled Drug Delivery: Fundamentals and Applications. 2nd ed., New York: Marcel Dekker Inc; 1987: 523 - 552.
3. Nishihata T, Kamada A, Sakai K, Takahashi K, Matsumoto K, Shinozaki K, Tabata Y, Keigami M, Miyagi T, Tatsumi N. Percutaneous absorption of diclofenac in rats and humans: aqueous gel formulation. Int J Phar.1988; 46: 1-7.
4. Santoyo SA, Martin C. Enhancing effect of terpenes on the in vitro percutaneous absorption of diclofenac sodium. Int J Pharm 1996; 130: 141-145.

5. Naito S, Tominaga H. Percutaneous absorption of diclofenac sodium ointment. Int J Pharm1985; 24: 115-124.
6. Takahashi K, Tamagawa S, Katagi T, Yoshitomi H, Kamada A, Rytting J, Nishihata T, Mizuno N. In vitro transport of sodium diclofenac across rat abdominal skin: Effect of selection of oleaginous component and the addition of alcohols to the vehicle. Chem Pharm Bull 1991; 39: 154-158.
7. Muley BP, Khadabadi SS, Banarase NB. Phytochemical Constituents and Pharmacological Activities of Calendula officinalis Linn (Asteraceae). Tropical Journal of Pharmaceutical Research, 2009; 8 (5): 455-465.
8. Huang YB, Wu PC. Cardamom oil as a skin permeation enhancer for indomethacin, piroxicam and diclofenac. International Journal of Pharmaceutics 1995; 126: 111- 117.
9. Jain H, Shah B. Effect of penetration enhancer on *in-vitro* release of diclofenac sodium gel formulation. IJPRD, 2011; vol 2: 18-25.
10. Shivhare UD, Jain KB, Mathur UB. Formulation development and evaluation of Diclofenac sodium gel using water soluble polyacrylamide polymer. Digest journal of nanomaterial and biostructers, 2009; vol 4: 285-290.