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Comparison of topical 1% diclofenac sodium gel and its performance with Marketed gel (Rofenac)

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ABSTRACT

Diclofenac sodium is an effective NSAID used in the long treatment of acute and chronic arthritic conditions and ankylosing spondylitis. Diclofenac sodium when administered orally produces severe gastrointestinal bleeding, ulceration and perforation of the stomach or the intestines which could be fatal especially on long-term use. Diclofenac sodium gel was prepared using Carbopol P934, and Hydroxypropyl methylcellulose (K4M) as gelling agents and physicochemical characterization such as homogeneity, pH evaluation, spreadability, drug content and *in vitro* drug diffusion were evaluated. The prepared gel was compared with marketed gel, i.e. Rofenac gel, and similarity factor (F2) was determined. The diclofenac sodium gel 1% using Carbopol P 934 was found to be optimum with appearance, pH, consistency and spreadability. Thus, this was chosen for the comparative evaluation with Rofenac gel. The drug content of the gel was found to be 97.54% ± 0.41% when compared to 96.83% ± 0.73% of Rofenac gel. Skin irritation studies revealed that there was no sign of erythema or edema for both prepared gel containing drug and placebo gel. *In vitro* drug diffusion was found to be 99.25% ± 0.12% in an hour when compared to 98.09 % ± 0.12% of marketed gel. The similarity factor (F2) was found to be 93.50 proving prepared gel is pharmaceutically equivalent with marketed gel. The flux (J) of the optimum gel was found to be 52.55 µg/cm^2/min with the permeability coefficient of 5.255 (cm/min) 10^{-3}.

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INTRODUCTION

It is a promising tactic delivering drugs through skin since a long time because therapy on the skin (topical) is a target for treating pain, inflammation and dermatological symptoms of allergic reactions as well as treating systemically. Topical drug delivery is of importance for the drugs that proved to be irritants and persist systemic side effects. Topical delivery has also earned fame because it circumvents hepatic first pass breakdown and metabolic degradation allied with oral administration. Further, topical gel systems offer a suitable dais for delivery of drugs owing to their non-greasy nature, and they can provide vanish able film on the skin when compared to ointments and cream. Topical gels have several beneficiaries such as good thixotropy, greaseless, easy spreading, easy removing, and palliative, non-staining, well-matched with numerous excipients (Jaganadhan *et al.,* 2016).

Diclofenac sodium is an NSAID universally castoff in the treatment of arthritis for its excellent anti-inflammatory and analgesic effects, and it is a derivative of phenylacetic acid (Jadhav RT *et al.,* 2009). It is commonly used as tablets or suppositories exhibiting excellent anti-inflammatory and analgesic effects. However, the ulcerogenic potential of diclofenac sodium is high

in both stomach and intestine, and also it is prone to produce hepatic and renal toxicities when it is used for long-term, especially upon oral administration (Pawar J *et al.,* 2017). So diclofenac sodium in the form of gel when administered through the skin the side effects are expected to be reduced (Shingade GM *et al.,* 2012). Thus, diclofenac sodium gel could be an effective alternative for oral therapy.

The present study was with the objectives to develop diclofenac sodium gel using various gelling agents like Carbopol P 934 and Hydroxypropyl methylcellulose (K4M) and to study the physicochemical characterization such as homogeneity, pH evaluation, spreadability, drug content and *in vitro* drug diffusion. Further, it is to perform a comparative study between the prepared gel and marketed gel, i.e. Rofenac gel in Aseer region of Saudi Arabia and to find out similarity factor (F2).

MATERIALS AND METHODS

Diclofenac sodium was obtained from Aurobindo Pharma Pvt Ltd, India. Carbopol P934 and Hydroxy Propyl Methyl Cellulose (K4M) were obtained from Sigma Aldrich. All the other chemicals are of analytical grade and are generally regarded as safe (GRAS).

Solubility studies: Solubility of the drug was determined in different solvents, e.g. distilled water, diethyl ether, ethanol, chloroform and methanol by shake flask method. It was done by dissolving excess of drug in the above-mentioned solvents in thermostat (37 ± 2°C) for 48 hours. Samples from each solvent system were taken, filtered, and analysed for drug concentration after suitable dilution using UV at 277.2 nm.

Preparation of Diclofenac sodium gel: In the first step solution A was prepared by dissolving 1g of diclofenac sodium in 10g of ethanol. A stated measure of propylene glycol and glycerin were added to solution A and dissolved. The contemplated quantity of carbopol 934 or HPMC was added to water containing PEG 400 and dissolved. The solution was neutralized and made glutinous by adding triethanolamine (solution B). Solution B was added dropwise to Solution A with constant stirring, and the final weight was made up to 100g to get the final gel preparation (Mundada MS *et al.,* 2013; Saroha K *et al.,* 2013).

Characterization of Diclofenac sodium gel

Homogeneity: The gel systems were categorised for checking homogeneity by visual assessment of gel after the settlement of gel inapposite containers. Gels were analysed for their look and presence of any clog up (Yen WF *et al.,* 2015).

pH evaluation: The pH of the gel was documented using a digital pH meter. It was done by getting the gel in interaction with the electrode of pH meter. pH was recorded after letting the pH meter to equilibrate. All the experiments were performed in triplicate (Dey S *et al.,* 2011).

Skin irritation test: The test was executed on Wistar rats (n=3). Rats were maintained with day and dark cycle with a good diet for 24h before starting the test. The test was accomplished by smearing gel on an area of 1 square inch to the dorsal surface of the rat after a mechanical depilatory process. Then it was examined for the presence of erythema or edema after application for 24h (Hiren P *et al.,* 2012).

Spreadability: Spreadability (g ·cm/sec) was articulated as time taken in seconds by two glass slides to slip off from each other and the gel placed between them under the consistent weight that tied on the upper plate which was 20g and length of the glass slide was 7.5cm (Mohd Q *et al.,* 2017; Zhenwei Yu *et al.,* 2016; Muhammad U *et al.,* 2016). The value of Spreadability was calculated by consuming the following formula:

Spreadability = (Weight × Length) /Time

The smaller the time occupied for the parting of the two slides the enhanced was its spreadability (Muhammad U *et al.,* 2016).

Drug content: A specified extent of the gel was taken and dissolved in 100 ml of phosphate buffer of pH 7.4. Similarly, a solution of marketed diclofenac sodium gel was also prepared. The gel solution was shaken continuously for 2 hours. This solution was filtered and analysed spectrophotometrically at 277.2 nm using a buffer (pH 7.4) as blank (Azza SZ *et al.,* 2016; Rajasekaran A *et al.,* 2016; Abdul WK *et al.,* 2013; Sanju N *et al.,* 2014).

Preparation of Standard Curve: A stock solution containing 1 mg/ml of pure drug Diclofenac sodium was prepared by dissolving 100mg of Diclofenac sodium in sufficient amount of ethanol, and the volume was made up to 100ml with phosphate buffer pH 7.4 in a volumetric flask. 1ml of the stock solution was further diluted to 100ml with phosphate buffer pH 7.4 to obtain a working standard solution containing 10mcg/ml. The aliquots of working standard solution were diluted serially with sufficient phosphate buffer pH 7.4 to obtain 2, 4, 6, 8, 10 mcg/ml concentrations as the linearity range of diclofenac sodium is found to be 0 – 10mcg/ml. The above solutions were subjected to scanning between 200 – 400 nm and absorption maximum are determined. A calibration curve of diclofenac sodium was obtained by measuring the absorbance at the λmax of 277.2 nm[2].

Table 1: Formulae of the diclofenac sodium gel

S.No	Ingredients	Quantity in	
		Gel A	Gel B
1.	Diclofenac sodium	1%	1%
2.	Carbopol 934	1%	--
3.	Hydroxy Propyl Methyl Cellulose (K4M)	--	2%
7.	Propylene Glycol	20	20
8.	Polyethylene Glycol 400	5	5
9.	Glycerin	10	10
10.	Ethanol	10	10
11.	Triethanolamine	1.5	1.5
12.	Water	51.5	50.5
	Total	100	100

***In vitro* diffusion studies:** Modified USP XXI diffusion assembly (an alternate to Franz diffusion cell) was used to carry out the *in vitro* diffusion studies (Japan P *et al.,* 2011; Sreenivasa RM *et al.,* 2006).The model consisted of beaker 250 ml (receptor compartment), and a plastic or glass tube of diameter 17.5mm opened from both the ends (donor compartment). In receptor compartment, phosphate buffer pH 7.4 was packed while in the donor compartment, the gel equivalent to the 10mg drug was applied on the treated cellophane sheet (soaked for 1hour in glycerine 10%). The temperature of the assembly was maintained at 37 ± 0.5˚C. The receptor compartment was stirred magnetically to ensure thinning of the diffusion layer and uniform distribution. Drug diffusion studies were conducted for 6 hours. The samples were introverted from the receptor compartment at steady time intervals and were examined spectrophotometrically at 277.2nm[2]. The experiments were performed in triplicate.

Determination of similarity factor (F2)

Comparative *in vitro* diffusion study was conducted between the optimized diclofenac sodium gel and marketed Rofenac gel, and similarity factor (F2) was determined using the following formula,

$$F2 = 50*\log[1+1/n*\Sigma(Rt-Tt)^2]^{-0.5}*100$$

Where, Rt is the percentage drug release for the reference or marketed gel formulation at time t, Tt is the percentage drug release for the test or prepared gel formulation at time t, The F2 value range from 50 to 100 is used to indicate both test and reference products are similar.

Diffusion Kinetic Analysis

Fick's law of diffusion was used to know the permeation rate of the drug by believing that diffusion was involved in drug permeation through rat skin. J= A. dm/dt. As we know that flux is proportional to concentration gradient so, J = -D. dc/dx, Where J denotes permeation rate of drug through the membrane, dc/dx is concentration gradient while D is the diffusion coefficient of the permeant. Flux was calculated from the given equation. J ss= Kp Co, Where Kp is permeability coefficient, and Co is drug concentration leftovers constant in the vehicle. And the permeability coefficient that was derived from the steady-state flux was K p = J/Co.

RESULTS AND DISCUSSION

Solubility studies

Diclofenac sodium was found to be soluble in water, ethanol and methanol.

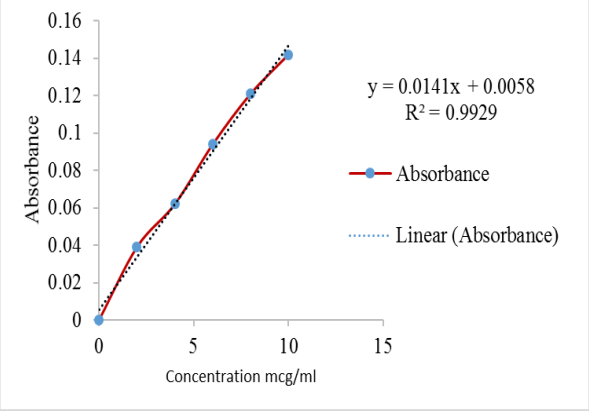

Figure 1: Calibration curve of Diclofenac Sodium

Construction of Standard Curve of Diclofenac Sodium

A stock solution containing 1 mg/ml of pure drug Diclofenac sodium was primed by dissolving 100mg of Diclofenac sodium in 5ml of ethanol, and the volume was made up to 100ml with phosphate buffer pH 7.4. 1ml of the stock solution was further watered down to 100ml with phosphate buffer pH 7.4 to obtain 10µg/ml solution. The aliquots of working standard solution were diluted serially with sufficient phosphate buffer pH 7.4 to obtain 2, 4, 6, 8, 10µg/ ml concentrations. A calibration curve of diclofenac sodium was obtained by measuring the absorbance at the λmax of 277.2 nm. It was constructed with the R^2 value of 0.9929.

Characterization of Diclofenac sodium gel

Homogeneity: Homogeneity was tested by visual assessment of gel after the settlement of gel inapposite containers. Gels were analysed for their look and the presence of any clog-up. Both the gels were found to be transparent and were free from the presence of particles. Both the gel formulations showed good homogeneousness with non-appearance of tumours/clogs/ aggregates. The gel prepared using HPMC as the gel base was found to be thin when compared to gel prepared using Carbopol P934 as the gel base.

pH evaluation: The pH of the gel was documented using a digital pH meter. It was done by getting the gel in interaction with the electrode of pH meter (Table 2). There were no much differences between pH values of Gel A and Gel B. Additionally; there was no noteworthy variation in pH values as a function of time for both the formulations.

Spreadability: Decent spreadability is the prime benchmarks for the gel to meet ideal qualities. It is the term uttered to signify the magnitude of the area to which gel readily spreads on the application. Therapeutic effectiveness of a gel also is contingent on its spreading value. In addition, spreadability is very imperative as it displays the behaviour of the gel when it originates out from the tube. Spreadability was found to be better for Gel A when compared to Gel B. This might be due to the very good spreading characteristics of Carbopol P934 as gel base in Gel A when compared to HPMC K4M as gel base in Gel B (Table 2).

Table 2: Results of pH evaluation and spreadability

S.No	Gel A	Gel B
pH	6.995	7.053
Spreadability (g.cm/Sec)	23	20

Drug Product Optimization: Based upon the appearance, pH, consistency and spreadability result Gel A was found to be with optimum characteristics and chosen for further studies.

Drug content: Drug content was determined for the optimum gel, i.e. Gel A and for the marketed gel Rofenac. The drug content of the gel A was found to be 97.54% ± 0.41% when compared to 96.83% ± 0.73% of Rofenac gel. Drug content of both the gel formulations was found to be within the official limits (100 ± 5%).

Table 3: Results of Drug Content

S.No	Gel A	Rofenac gel
% Drug Content	97.54 ± 0.41	96.83 ± 0.73

Skin irritation test: Skin irritation studies revealed that there was no sign of erythema or edema for both prepared gel containing drug (Gel A) and placebo gel.

Figure 2: After immediate application of gel A on the dorsal surface of rat skin

Figure 3: After 6 hours of application of gel A on the dorsal surface of rat skin

Figure 4: Modified USP XXI diffusion assembly

***In vitro* diffusion studies:** Modified USP XXI diffusion assembly (an alternate to Franz diffusion cell) was used to carry out the *in vitro* diffusion studies. The test was repeated for 3times, and average cumulative % drug release with standard deviation was determined. *In vitro* % cumulative drug diffusion was found to be 99.25% ± 0.12% in an hour when compared to 98.09 % ± 0.12% of marketed gel. Thus, both the gel formulations released almost similar amounts of the drug.

Table 4: % Cumulative drug release of Gel A and Rofenac gel

S.No	Time in Minutes	Gel A	Rofenac gel
1	5	11.69 ± 0.32	10.7 ± 0.28
2	10	19.35 ± 0.55	18.78 ± 0.36
3	15	29.42 ± 0.27	27.29 ± 0.7
4	30	55.66 ± 0.17	54.1 ± 0.26
5	45	78.07 ± 0.15	76.94 ± 0.58
6	60	99.25 ± 0.61	98.09 ± 0.33

Table 5: Results indicating Determination of F2

n	t	Rt	Tt	Rt-Tt	$(Rt-Tt)^2$	$F2 = 50*\log\{1+1/n*[\Sigma(Rt-Tt)^2]^{-0.5}\}*100$
1	5	10.7	11.69	0.99	0.98	
2	10	18.78	19.35	0.57	0.32	
3	15	27.29	29.42	2.13	4.53	
4	30	54.1	55.66	1.56	2.43	
5	45	76.94	78.07	1.13	1.28	
6	60	98.21	99.2	0.99	0.98	
					$\Sigma(Rt-Tt)^2 = 10.52$	F2=93.50

The drug release was owing to the fact that dissolution of an aqueous soluble segment of the polymer matrix leads to the establishment of gelaneous stomas. The formation of such stomas leads to cut down the mean diffusional path length of the drug to release into the diffusion medium and hence, to effect sophisticated release rate. Thus, both the formulations displayed extreme drug permeation in 1 hour.

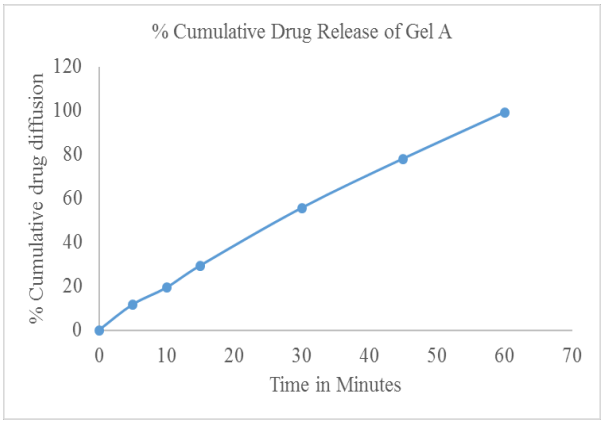

Figure 5: % Cumulative drug release of Gel A

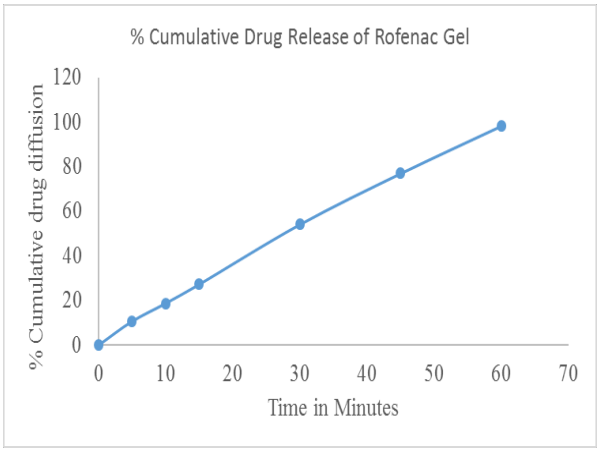

Figure 6: % Cumulative drug release of Rofenac gel

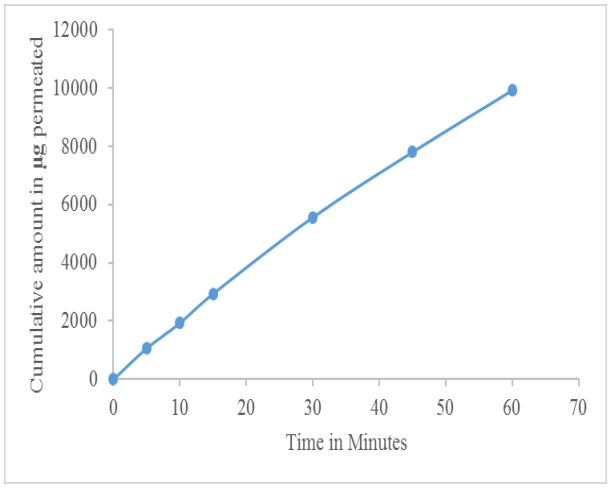

Figure 7: Cumulative amount of Diclofenac Sodium permeated

Determination of similarity factor (F2)

The similarity factor (F2) was found to be 93.50 proving prepared gel is pharmaceutically equivalent with marketed gel. It was calculated as follows using the formula,

$$F2 = 50*\log[1+1/n*\Sigma(Rt-Tt)^2]^{-0.5}*100$$

Where, Rt is the percentage drug release for the reference or marketed gel formulation at time t, Tt is the percentage drug release for the test or prepared gel formulation at time t, The F2 value range from 50 to 100 is used to indicate both test and reference products are similar.

Diffusion Kinetic Analysis

Determination of Flux: The flux (J) of the optimum gel was found to be 52.55 µg/cm^2/min with the permeability coefficient of 5.255 (cm/min) 10^{-3}. The results showed the efficiency of gel in terms of permeability and also it further confirmed the results of *in vitro* drug release studies.

Table 6: Cumulative amount of Diclofenac Sodium permeated from Gel A

Time (Minutes)	Amount of drug (µg/cm^2)
5	1069.6
10	1934.75
15	2941.84
30	5565.96
45	7807.09
60	9920.57
Flux(µg/cm^2/hr)	52.55
Permeation Coefficient (Cm/hr)10^{-3}	5.255

CONCLUSION

From the above results, it was concluded that diclofenac sodium gel formulations prepared with gelling agent carbopol P934 showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value when compared to the gel prepared with HPMC K4M. *In vitro* % cumulative drug diffusion was found to be very much comparable with marketed gel Rofenac. The similarity factor (F2) was found to be 93.50 proving prepared gel is pharmaceutically equivalent with marketed gel Rofenac. The flux of gel A was 52.55 µg/cm^2/min which is appreciable to be transported across the skin. Permeation Coefficient was found to be 5.255 cm/min10^{-3}. Ex vivo skin irritancy studies showed no signs of erythema or edema. Thus, the effective diclofenac sodium local therapy can be prepared using simple gel base carbopol P 934 to improve skin absorption and to prevent side effects.

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