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FORMULATION DEVELOPMENT AND EVALUATION OF DICLOFENAC SODIUM GEL USING WATER SOLUBLE POLYACRYLAMIDE POLYMER

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High molecular weights water soluble homopolymer of acrylamide are reported to possess very high viscosity in low concentration, transparency, film forming properties and are useful in formation of gel. The diclofenac sodium gels were prepared by using different concentration of polyacrylamide for topical drug delivery with an objective to increase transparency and spreadability. These preparations were further compared with marketed diclofenac sodium gel. Spreadability and consistency of polyacrylamide gel containing diclofenac sodium (F9) were 6.5g.cm/sec and 5mm as compared to 5.5g.cm/sec and 10mm respectively of marketed gel, indicating good spreadability and consistency of the prepared gel (F9). The transparency of prepared batch F9 was good as compared to the marketed gel. The percent drug release was 97.11 and 98.66 from F9 and marketed gel respectively. No irritation was observed by skin irritation test. Stability studies under accelerated condition showed satisfactory results. It can be concluded that polyacrylamide gel containing diclofenac sodium showed good consistency, homogeneity, spreadability and stability and has wider prospect for topical preparations.

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1. Introduction

Topical gel preparations are intended for skin application or to certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action.(1) Gels are typically formed from a liquid phase that has been thickened with other components. The continuous liquid phase allows free diffusion of molecules through the polymers scaffold and hence release should be equivalent to that from a simple solution.(2) NSAID's are nonsteroidal drugs having excellent anti-inflammatory and analgesic activity but NSAID produces GIT ulceration, liver and kidney trouble especially in case of oral administration. In view, of adverse drug reaction associated with oral formulations, diclofenac sodium is increasingly administered by topical route. (3)

Polyacrylamide is used as water soluble or hydrophilic polymers topically in gel drug delivery system. (4) A range of grades based on molecular fractions of these polymer are available, they are typically used at a concentration between 1 to 5% in topical gel formulation. Due to their non greasy properties, they can provide easily washable film on the skin.(5) Polyacrylamide polymer of high molecular weight do not penetrate the skin and are non toxic. (6)

Human cutaneous tolerance tests performed to evaluate the irritation of 1-5% w/w polyacrylamide indicated that the polymer was well tolerated. Polyacrylamide polymers have the

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potential to be naturally broken down and biodegradable and do not persist or accumulate in the environment. [7]

2. Material and methods

Diclofenac sodium was recived as gift sample from H-Jules Corporation (Nagpur, India). Polyacrylamide homopolymer were purchased by Suyog Chemicals Ltd (Nagpur, India). Sodium metabisulphite AR grade was procured by Sigma Pvt. Ltd. (Mumbai, India). All other ingredients were of analytical grade. Voveran Emulgel of Novarties Pvt Ltd. was purchased from market.

Procedure of gel preparation:

About 3g of diclofenac sodium was weighed and dissolved in 5g of isopropyl alcohol, to this solution, specified quantity of glycerin or propylene glycol or cocodiethanolamide was added and dissolved (solution A). Weighed quantity of polyacrylamide was added to the 75g of distilled water containing 0.1g of sodium metabisulfide as antioxidant and stirred to dissolve the same (solution B). Solution A and B were mixed thoroughly and the final weight was made upto 100g. (Table 1)

Table 1. Composition and concentration of diclofenac sodium gel.

Batch No	Polymer (g)	Drug (g)	Isopropyl alcohol (g)	Sodium metabisulphite (g)	Glycerin (g)	Propylene glycol (g)	Coco-diethanolamide (g)	Distilled water (g)
F1	5	3	5	0.1	1	-	-	Upto100
F2	5	3	5	0.1	5	-	-	Upto100
F3	5	3	5	0.1	10	-	-	Upto100
F4	5	3	5	0.1	-	1	-	Upto100
F5	5	3	5	0.1	-	5	-	Upto100
F6	5	3	5	0.1	-	10	-	Upto100
F7	5	3	5	0.1	-	-	0.1	Upto100
F8	5	3	5	0.1	-	-	0.5	Upto100
F9	5	3	5	0.1	-	-	1.0	Upto100

Precipitation or turbidity occurs in some of the batches (F1, F2, F3, F4, F5 and F6) of polyacrylamide gel containing diclofenac sodium which could be due to the incompatibility in the system due to presence of glycerin or propylene glycol. Hence, these batches were discarded and remaining batches (F7, F8 and F9) were considered for further study.

Evaluation of polyacrylamide gel containing diclofenac sodium and marketed gel:

The above formulated polyacrylamide gel containing diclofenac sodium and marketed gel were subjected to evaluation for the following parameters:

A. pH:

The pH of the various gel formulations was determined by using digital pH meter. (Table 2)

B. Spreadability:

It was determined by wooden block and glass slide apparatus. Weights about 20g were added to the pan and the time was noted for upper slide (movable) to separate completely from the fixed slides. [8] (Table 2)

Table 2. Values of evaluation parameters of developed gel and marketed gel

Batch No	pH	Spreadability (g.cm/sec)	Consistency (60 sec)	Homogeneity	Skin irritation test	Drug content (%)
F7	6.8	5.0	5mm	good	Nil	99.95
F8	6.8	6.0	5mm	good	Nil	99.94
F9	6.8	6.5	5mm	good	Nil	99.98
Marketed gel	6.8	5.5	10mm	good	Nil	99.90

Spreadability was then calculated by using the formula:

$$S = M.L / T$$

Where,
S = Spreadability
M = Weight tide to upper slide
L = Length of glass slide
T = Time taken to separate the slide completely from each other

C. Consistency:

The measurement of consistency of the prepared gels was done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The penetration by the cone was measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone was noted down after 10sec. [9] (Table 2)

D. 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 2)

E. Skin irritation test:

Test for irritation was performed on human volunteers. For each gel, five volunteers were selected and 1.0g of formulated gel was applied on an area of 2 square inch to the back of hand. The volunteers were observed for lesions or irritation. (Table 2)

F. Drug content :

A specific quantity (100mg) 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 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 276.0nm using phosphate buffer (pH 6.8) as blank. [10] (Table 2)

G. Accelerated stability studies:

All the selected formulations were subjected to a stability testing for three months as per ICH norms at a temperature of 40º ± 2º. All selected formulations were analyzed for the change in appearance, pH or drug content by procedure stated earlier. [11] (Table 3)

Table 3. Stability study of various developed gel and marketed gel.

Sr No	Batches	Months	Appearance	pH	Drug Content (%)
01	F7	0	Clear	6.8	99.95
		1	Clear	6.8	98.60
		2	Clear	6.7	97.00
		3	Clear	6.6	96.20
02	F8	0	Clear	6.8	99.94
		1	Clear	6.6	98.50
		2	Clear	6.6	97.40
		3	Clear	6.5	96.30
03	F9	0	Clear	6.8	99.98
		1	Clear	6.8	98.80
		2	Clear	6.8	97.30
		3	Clear	6.6	96.80
04	Marketed gel	0	Clear	6.8	99.90
		1	Clear	6.7	98.70
		2	Clear	6.6	97.20
		3	Clear	6.5	95.90

H. Permeability studies[12]:

Phosphate buffer of pH 6.8 was used for *in vitro* release as a receptor medium. The pretreated skin of albino mice was used in fraz diffusion cell. The gel sample was applied on the skin and then fixed in between donor and receptor compartment of diffusion cell. The receptor compartment contained phosphate buffer (100ml) of pH 6.8. The temperature of diffusion medium was thermostatically controlled at 37º ± 1º by surrounding water in jacket and the medium was stirred by magnetic stirrer at 500rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 276nm against their respective blank. (Table 4 and Figure 1)

Table 4. Permeability studies of F9 and marketed gel

Sr. No	Time Interval (min)	Medium pH	%Drug release	
			Batch F9	Marketed preparation
1	30	6.8	54.46	56.00
2	60	6.8	76.48	76.20
3	90	6.8	89.52	90.55
4	120	6.8	97.11	98.66

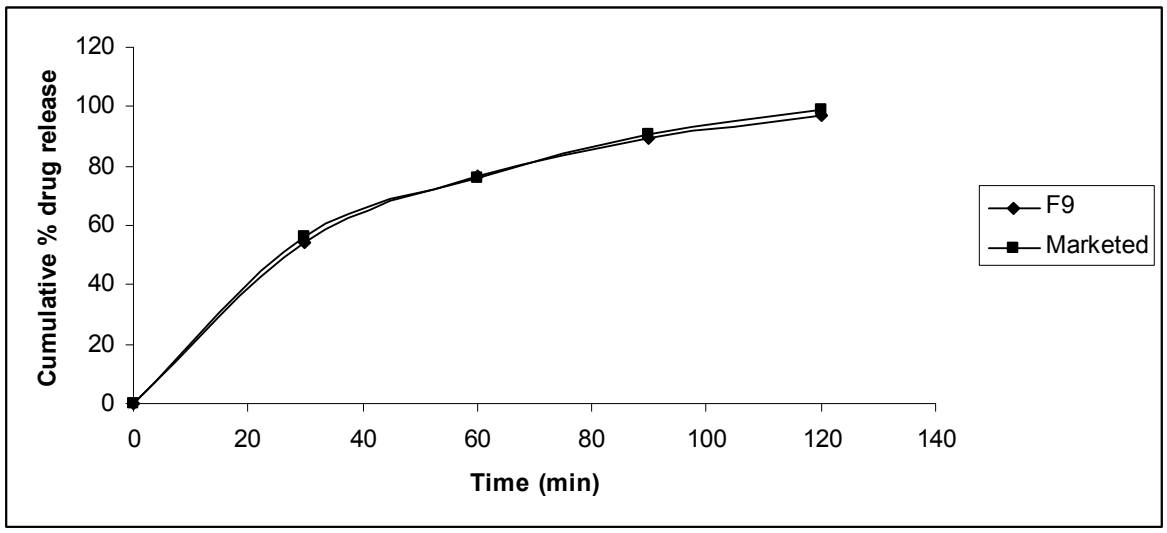

Fig 1. Drug permeability release profile of diclofenac sodium gel formulation.

3. Results and discussion

The pH values of all developed (F4, F7, F8 and F9) and marketed gel was 6.8.

The values of spreadability indicate that the gel is easily spreadable by small amount of shear. Spreadability of marketed gel was 5.5g.cm/sec while F9 was 6.5g.cm/sec, indicating spreadability of polyacrylamide containing diclofenac sodium gel was good as compared to the marketed gel.

The consistency reflects the capacity of the gel, to get ejected in uniform and desired quantity when the tube is squeezed. Consistency in terms of distance travel by cone was 5mm of all developed batches as compared to 10mm of marketed gel. Consistency is inversely proportional to the distance traveled by falling cone. Hence, the consistencies of polyacrylamide gel containing diclofenac sodium were better as compared with marketed gel.

All developed and marketed gel showed good homogeneity with absence of lumps. The developed preparations were much clear and transparent as compared to marketed gel.

The skin irritation studies of developed gel were carried out on human volunteers and that confirmed the absence of any irritation on the applied surface.

During the stability studies the appearance was clear and no significant variation in pH was observed. Considering the accelerated stability studies and physiochemical parameters, batch F9 was selected for *in vitro* permeability release studies as well as compared with the marketed gel.

In vitro Permeability study showed that permeation studies of F9 and marketed gel were comparable.

It was observed that polyacrylamide gel containing diclofenac sodium (batch F9) produced better spreadability and consistency as compared to marketed diclofenac sodium gel. The developed F9 gel showed good homogeneity, no skin irritation, good stability and *in vitro* permeability was comparable with marketed gel. The polyacrylamide forms water washable gel because of its water solubility and has wider prospects to be used as a topical drug delivery system.

4. Conclusion

The polymer being macromolecules of very high molecular weight remain unabsorbed on the skin and from our studies it can be concluded that polyacrylamide can be used for various topical dosage form for external application.

It has been observed that optimized batch produces the gel with good consistency, homogeneity, spreadabiltity and stability. Since, the polymer is water soluble; consequently, it forms water washable gel and has wider prospects to be used as a topical drug delivery dosage form.

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