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Formulation Development and Characterization of Aceclofenac Gel Using Poloxamer 407

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ABSTRACT

Poloxamer 407 is used primarily as a thickening agent and gel former, but also as a co-emulsifier and consistency enhancer in creams and liquid emulsions. It is also used as a solubilizer for certain active substances Moreover, Poloxamer 407 is suitable for the formulation of active substances that show reduced solubility as a result of neutralization. Poloxamer 407 is reported to possess transparency, film forming properties and useful in formation of gel. The aceclofenac gels were prepared by using different concentration of Poloxamer 407 for topical drug delivery with an objective to increase transparency and spreadability. These preparations were further compared with marketed Hifenac® gel. Spreadability and consistency of Poloxamer 407 gel containing aceclofenac (A9) were 12.4g.cm/sec and 8mm as compared to 13.2g.cm/sec and 11mm respectively of marketed gel, indicating good spreadability and consistency of the prepared gel (A9). The transparency of prepared batch A9 was good as compared to the marketed gel. The percent drug release was 97.11 and 98.66 from A9 and marketed gel respectively in 120 min. No irritation was observed by skin irritation test. Stability studies under accelerated condition showed satisfactory results. It can be concluded that Poloxamer 407 gel containing aceclofenac showed good consistency, homogeneity, spreadability and stability and has wider prospect for topical preparations.

Keywords: Gel former, Aceclofenac, Poloxamer.

INTRODUCTION

The term "Gel" was introduced in the late 1800 to name some semisolid material according to pharmacological, rather then molecular criteria. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. [1] The inorganic particles form a three-dimensional "house of cards" structure. Gels consist of two-phase system in which inorganic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved in the continuous phase, randomly coiled in the flexible chains. [2]

Gels are typically formed from a liquid phase that has been thickened with other components. Aceclofenac is a NSAIDs 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, aceclofenac is increasingly administered by topical route. [3]

Poloxamer is used primarily as a gel former and thickening agent, but also as a co-emulsifier and consistency enhancer in creams and liquid emulsions. It is also used as a solubilizer for certain active substances. Moreover, Lutrol® F 127 is suitable for the formulation of active substances that show reduced solubility as a result of neutralization. Owing to its ability to affect viscosity, Lutrol® F 127 is suitable as a stabilizer for topical formulations. They are typically used at a concentration between 15 to 50% in gel formulation. Due to their non greasy properties, they can provide easily washable film on the skin. Poloxamer 407 a commercial grade has HLB value 18-23 and pH of 2.5% aqueous solution is 6-7.4. [4, 5]

EXPERIMENTAL SECTION

Aceclofenac was received as from Suyash Laboratories, India. Poloxamer 407 (Lutrol® F 127) was purchased by BASF Germany. All other ingredients were of analytical grade. Hifenac® gel of Intas Pharmaceuticals Pvt. Ltd. was purchased from market.

Table1. Composition and concentration of aceclofenac gel.

Batch No	Poloxamer 407 (g)	Drug (g)	Propylene glycol (g)	Methyl salicylate (g)	Linseed oil (g)	Polysorbate 80 (g)	Menthol (g)	Benzyl alcohol (g)	Distilled water (g)
A1	10	1.5	7.5	3.0	2	-	0.5	1.0	Upto100
A2	10	1.5	7.5	3.0	2	-	0.5	1.0	Upto100
A3	10	1.5	7.5	3.0	2	-	0.5	1.0	Upto100
A4	12	1.5	7.5	3.0	-	1	0.5	1.0	Upto100
A5	12	1.5	7.5	3.0	-	1	0.5	1.0	Upto100
A6	12	1.5	7.5	3.0	-	1	0.5	1.0	Upto100
A7	15	1.5	7.5	3.0	-	-	0.5	1.0	Upto100
A8	15	1.5	7.5	3.0	-	-	0.5	1.0	Upto100
A9	15	1.5	7.5	3.0	-	-	0.5	1.0	Upto100

Procedure of gel preparation:
About 1.5g of aceclofenac was weighed and dissolved in 7.5g of propylene glycol (Phase I). Specified quantity of methyl salicylate, linseed oil/polysorbate 80, menthol and benzyl alcohol were dissolved together (Phase II). Weighed quantity of Poloxamer 407 was added to the approx. 70 g of distilled water and stirred to dissolve the same (Phase III). Phase I, II and III were mixed thoroughly and the final weight was made up to 100g. (Table 1)

Precipitation or turbidity occurs in some of the batches (A1, A2, A3, A4, A5 and A6) of Poloxamer 407 gel containing aceclofenac 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 (A7, A8 and A9) were considered for further study.

Evaluation of Poloxamer 407 gel containing aceclofenac and marketed gel:
The above formulated Poloxamer 407 gel containing aceclofenac 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 (Cyberscan 521, Eutech Instruments). (Table 2)

B. Spreadability:
It was determined by wooden block and glass slide apparatus. Weights about 10g were added to the pan and the time were noted for upper slide (movable) to separate completely from the fixed slides. [6-8] (Table 2)
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

Table2. 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 (%)
A7	6.8	11.8	8mm	good	Nil	99.85
A8	6.8	11.6	8mm	good	Nil	99.88
A9	6.8	12.4	8mm	good	Nil	99.94
Hifenac® gel	6.8	13.2	11mm	good	Nil	99.81

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 Hifenac® gel were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 20 minutes. This solution was filtered and estimated spectrophotometrically at 275 nm 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 40ºC ± 2ºC / 75% ± 5% RH. All selected formulations were analyzed for the change in appearance, pH and drug content by procedure stated earlier. [11-14](Table 3)

Table3. Stability study of various developed Poloxamer 407 based aceclofenac gel and marketed Hifenac® gel

Sr. No.	Batches	Months	Appearance	pH	Drug Content (%)
01	A7	Initial	Clear, transparent gel	6.8	99.85
		1	Clear, transparent gel	6.8	98.60
		2	Clear, transparent gel	6.7	98.00
		3	Clear, transparent gel	6.6	97.20
02	A8	Initial	Clear, transparent gel	6.8	99.74
		1	Clear, transparent gel	6.6	98.50
		2	Clear, transparent gel	6.6	98.10
		3	Clear, transparent gel	6.5	97.60
03	A9	Initial	Clear, transparent gel	6.8	99.98
		1	Clear, transparent gel	6.8	98.80
		2	Clear, transparent gel	6.8	98.20
		3	Clear, transparent gel	6.6	97.80
04	Marketed Hifenac® gel	Initial	Clear, transparent gel	6.8	99.90
		1	Clear, transparent gel	6.7	98.70
		2	Clear, transparent gel	6.6	98.20
		3	Clear, transparent gel	6.5	97.70

H. Permeability studies [15, 16]

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 Franz 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 500 rpm. The sample at predetermined intervals were withdrawn and replaced by equal volume of fresh fluid. The samples withdrawn were spectrophotometrically estimated at 275 nm against their respective blank. (Table 4 and Figure 1)

Table4. Permeability studies of aceclofenac gel formulation and marketed Hifenac® gel.

Sr. No	Time Interval (min)	Medium pH	%Drug release	
			Batch A9	Marketed Hifenac® gel
1	30	6.8	56.46	58.00
2	60	6.8	74.48	78.20
3	90	6.8	87.52	88.65
4	120	6.8	97.11	98.66

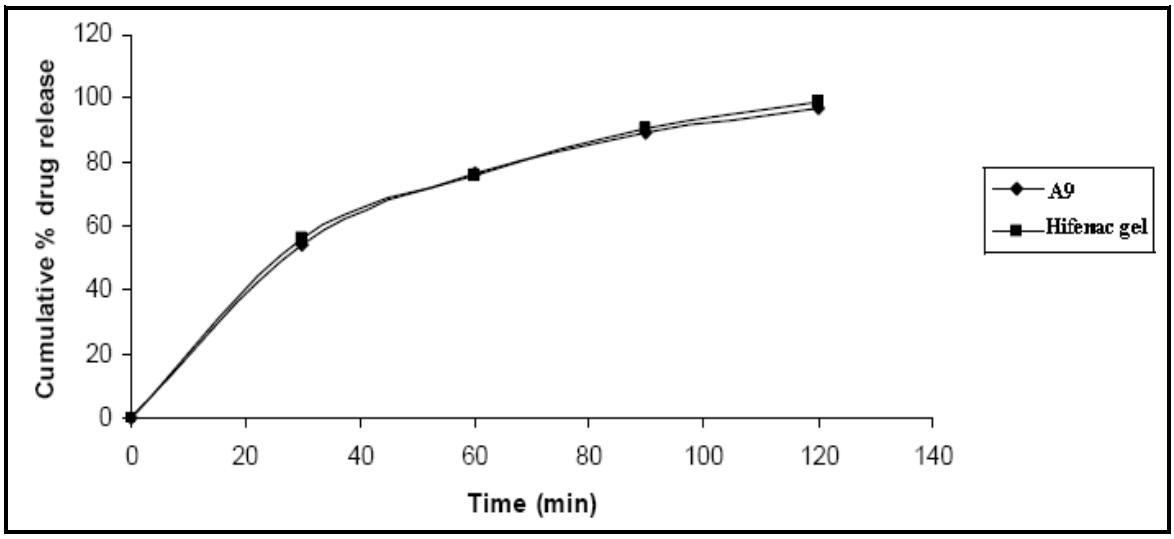

Figure1. Drug permeability release profile of aceclofenac gel formulation (A9) and marketed Hifenac® gel.

RESULTS AND DISCUSSION

The pH values of all developed (A7, A8 and A9) and marketed Hifenac® gel was 6.8. The values of spreadability indicate that the gel is easily spreadable by small amount of shear. Spreadability of marketed Hifenac® gel was 13.2 g.cm/sec while A9 was 12.4 g.cm/sec, indicating spreadability of Poloxamer 407 containing aceclofenac gel was good as compared to the marketed Hifenac® 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 8mm of all developed batches as compared to 11mm of marketed Hifenac® gel. Consistency is inversely proportional to the distance traveled by falling cone. Hence, the consistencies of Poloxamer 407 gel containing aceclofenac were better as compared with marketed Hifenac® 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 Hifenac® 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 A9 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 A9 and marketed Hifenac® gel were comparable. It was observed that Poloxamer 407 based gel containing aceclofenac (batch A9) produced better spreadability and consistency as compared to marketed Hifenac® gel. The developed A9 gel showed good homogeneity, no skin irritation, good stability and in vitro permeability was comparable with marketed Hifenac® gel. The Poloxamer 407 forms water washable gel because of its water solubility and has wider prospects to be used as a topical gel drug delivery system.

CONCLUSION

The polymer being macromolecules of very high molecular weight remain unabsorbed on the skin and from our studies it can be concluded that Poloxamer 407 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, spreadability 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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