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Formulation and critical evaluation of piroxicam gel

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Abstract
The present study has been undertaken with the aim to formulate gel containing Piroxicam by using gelling agents like cabopol-940 and HPMC with different penetration enhancers. Five different formulae were prepared and characterized physically in term of color, spreadability, pH, drug content and rheological properties. The value of spredability indicated that these gels are easily spreadable by small amount of shear. Viscosity of gel was found in range of 36000-48900 cps. *In vitro* drug release was evaluated using Franz diffusion cell. The results of *in vitro* drug release and its permeation studies showed that the highest values was from F1 (86% of drug released after 8 hr.). Carrageenan induced rat paw oedema model was used for the evaluation of the anti-inflammatory activity of the gels. The rheological behaviour of the prepared formulae showed shear-thinning flow indicating structural breakdown of the existing intermolecular interactions between polymeric chains.

Keywords: Carbopol, *in-vitro*, diffusion, spreadability, rheology, skin irritation

Introduction
Piroxicam is COX inhibitor which has anti-inflammatory effect in addition to having antipyretic and analgesic effect. The cyclooxygenase enzyme exists in two forms. The constitutive (COX-1) and inducible (COX-2) Isoforms both isoforms are responsible for synthesis of cyclic endoperoxide intermediate from arachidonic from arachidonic acid which are substrate after prostaglandin and thromboxane syntheses.

Piroxicam main mechanism of action is inhibition of enzyme cyclooxygenase resulting in reduced prostaglandin synthesis. Piroxicam inhibits prostaglandin (thromboxane) synthesis in the platelet and thus inhibits secondary phase of platelet aggregation. Piroxicam stimulates immune function requiring lymph proliferation by suppressing the formation of PGE_2 which is natural inhibitor [1]. Piroxicam when given orally it produces the various side effects, so that drug is not used frequently so it is worthwhile to formulate the drug in other suitable i.e. topical drug delivery to eliminate the side effect [1-3].

The percutaneous absorption of drug involves two consecutive process; the release other drug from the topical formulation, and its absorption into the skin at the site of application, increasing the release rate of the drug from the dosage forms might therefore improve percutaneous absorption.4 The release rates of drugs from topical preparations depend directly on the physiochemical properties of the carrier and the drug employed. Topical application of anti-inflammatory agents at the site of inflammation can overcome their systemic side-effects and improve their therapeutic activity [5-6].

Material and Method
Material
Piroxicam was obtained as kind gift sample from Cipla, Vikroli (Mumbai), India. Carbomer 940 & HPMC was purchased from Oxford Laboratory, Mumbai, India. All other materials used of analytical grades.

Method
Preparation of piroxicam gel
Carbomer 940 gel
Carbomer 940 was soaked in 50 ml of water in different conc. of carbomer i.e. 0.5% and 1%. On the next day they stirred uniformly to form the mucilage. In each of the mucilage drug was added (previously dissolved in Dimethyl formamide/Dimethyl sulfoxide/Ethanol) with constant stirring. Preservative methyl paraben and propyl paraben were added.

It was neutralizing with Triethanolamine solution with constant stirring then glycerin was added to form a clear gel. The final gels were sparkling and light yellowish in colour [7].

Carbomer 940 and HPMC gel

Carbomer and HPMC were weighed in different conc. (0.5% and 0.5%) and to it distilled water was added with constant stirring. The stirring was done slowly to avoid the entrapment of air bubble. Preservative methyl paraben and propyl paraben were added to it. Drug (previously dissolved in Dimethyl formamide/Dimethyl sulfoxide/Ethanol) was added. The mixture was stirred to homogenize for about 10 min. It was neutralized with triethanolamine solution with constant stirring then glycerin was added to form a clear gel. The final gel were whitish yellow colour 8-9.

Table 1: Components of various gel formulations

Formulation					
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**
Piroxicam	0.5	0.5	0.5	0.5	0.5
Carbopol 940	1	1	1	0.5	0.5
HPMC	-	-	-	0.5	0.5
DMSO	5	-	-	5	-
DMF	-	5	-	-	-
Ethanol	-	-	5	-	5
Triethanolamine	5	5	5	5	5
Glycerin	10	10	10	10	10
Methyl paraben	0.18	0.18	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02	0.02	0.02
Water	q.s	q.s	q.s	q.s	q.s

Evaluation of physical properties of piroxicam gel

Homogeneity

All the developed gel was tested for homogeneity by visual inspection. They were tested for their appearance with no lumps [10].

Colour, odour, texture

The formulated gel were inspected visually for colour, presence of any clog and to evaluate the feel the formulated gel were applied on skin and feel was experienced psychorheologically [11].

pH

The pH of the gel was measured using pH meter. Gel was taken into a beaker and the pH was noted.

Viscosity

Viscosity of all the formulated gels was studied by using Brookfield Viscometer by using spindle no. 7 at 10 rpm.

Drug content

A specific quantity (1 gm) of developed gel were taken and dissolved in 100 ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 2 hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically at 287.0 nm using phosphate buffer (pH 6.8) as blank [12].

Spreadability

An excess of gel was placed between two glass slides and a 1000gm weight was placed on the slide for 5 minutes to compress the sample to a uniform thickness. The bottom slide was anchored to the apparatus and weights were placed in the pan. A time in second needed to separates to slide was taken as a measure of Spreadability, [13]

$$S = W \times L/t$$

Where, S = Spreadability
W = Weight tied to upper slides
t = Time taken in second to separates two slides
L = Length of slide

Extrudability

The gel formulations were filled in standard capped collapsible aluminum tubes and sealed by Crimping to the end. The weights of the tubes were recorded. The tubes were placed between two glass slides and were clamped. 500 gm was placed over the slides and then the cap was removed. The amount of the extruded gel was collected and weighed. The percent of the extruded gel was calculated (>90% extrudability: excellent, >80% extrudability: good, >70% extrudability: fair) [14].

Rheological properties

Rheological measurement are utilized to characterize the ease of pouring from a bottle, squeezing from a tube or other deformable container, maintaining product shape in a jar or after extrusion, rubbing the product on to and into the skin. It reflects effect of temperature and storage time on the products. The rheology of a particular product affects its patient acceptability, physical stability and even biological availability.

The Rheology of the formulations were studied using Brookfield Viscometer For Carbomer 940 and Carbomer & HPMC using spindle no 7 were found to be appropriate respectively and speeds of 10, 20, 30, 40, 50 and 70 rpm were selected.

Different viscosities at respective spindle speeds were obtained for an ascending and descending curve. Rate of shear and shearing stress were calculated by using following formula.

$$Shear\ rate\ (\gamma) = \frac{2\ \omega\ R_c^2\ R_b^2}{X\ (R_c^2\ R_b^2)} \quad (\sec^{-1})$$

Where,
ω = Angular velocity of spindle (rad^{-1})
$[\frac{2\pi}{60} * \text{spindle speed (rpm)}]$
R_c = Radius of container (cm)
R_b = Radius of spindle (cm)
X = Radius at which shear rate is being calculated (cm)

$$\text{Shear stress}(\sigma) = \frac{M}{2\ \pi\ R_b^2\ L} \quad \text{dyne/cm}^2$$

Where,
M = Measured torque

$$Torque\ input = \frac{Torque\ *Full\ scale\ torqu\ (7187.0)\ dynes/cm}{100}$$

L = Effective length of spindle (cm)
Rheogram were obtained by plotting rate of shear, (G) on Y-axis versus calculated value of shear stress, (F) on X-axis.

Pharmacological Evaluation

Animals

Male albino wistar rats, weighing 150-200 gm were used. They were housed in the standard environmental condition and fed with diet and water. All procedure was followed in accordance with the approved protocol by Institutional Animal Ethical Committee.

Carrageenan-induced rat paw edema

Animals are divided into three groups (n = 6) starved overnight with water ad libitum prior to the day of experiment. The control group receives vehicle orally, while other group receives test drug and standard drug respectively. Left paw is marked with ink at the level of lateral malleolus; basal paw volume is measured plethysmographically by volume displacement method using Plethysmometer (UGO Basile 7140) by immersing the paw till the level of lateral malleolus. The animals are given drug treatment. One hour after dosing, the rats are challenged by a subcutaneous injection of 0.1ml of 1% solution of Carrageenan into the sub-plantar side of the left hind paw. The paw volume is measured again at 0, 1, 2, 3, 4 & 6 hours after challenge. The increase in paw volume is calculated as percentage compared with the basal volume.

The difference of average values between treated animals and control group is calculated for each time interval and evaluated statistically [15-16].

The percent Inhibition is calculated using the formula as follows [17].

% Edema inhibition = (1-Vt/Vc) 100

Where,

Vt - Mean edema volume of test

Vc - Mean edema volume of control

Skin irritation study [18]

In the present study 10 albino Wister rats (approved by Institutional Animal Ethical Committee, Faizpur) of either sex weighing between (200-300 g) were used. Animals were divided in to 2 groups of 5 animals each. Hairs were depleted from the back of Wister rats with the help of depilatories and area 4 cm^2 was marked on both the sides. One side served as control while the other as test and animals were used after 24 hrs., after hair depletion. Gel was applied (1g /rat) once a day for 7 days and sight was covered with cotton bandage and observed for any sensitivity and the reaction if any was graded as

0 - No reaction

0.5 - Slight, patchy erythema

1 - Slight but confluent or moderate but patchy erythema

2 - Moderate erythema

3 - Severe erythema with or without edema.

***In-Vitro* diffusion study**

The freshly excised full-thickness rat skin was mounted mounted on the Franz diffusion cell with the stratum corneum side facing the donor compartment and dermal the dermal side facing the receptor compartment. Two gram of piroxicam gel formulation were applied on the skin and the top cell was clamped and covered with Parafilm. The sampling port was also sealed with Para film to prevent the evaporation of the receptor medium. The receptor medium was pH 6.8 phosphate buffers, which was maintained at constant temperature by circulating water bath. The temperature was maintained at 37 ºC in all diffusion studies except for the temperature effect study. The sample were withdrawn from receptor compartment at predetermined time intervals and replaced by equal volume of fresh buffer solution. The sample were analysed by a UV specrophotometer at 287 nm [19].

Stability studies

The selected formulations were subjected to following condition of temperature and relative humidity during stability studies. 40 ˚C ± 2 ˚C at 75 ± 5% RH Samples of the formulation were evaluated for various parameters after every month for 3 months. The parameters studied were Drug content, pH, Spreadability [20-21].

Result and Discussion

The pH of all formulation lies in between 6.5 to 6.8 in normal range of skin and did not produce any skin irritation.

The viscosity of all formulation were measured using spindle no. 7 to 10 rpm the viscosity of F1 formulation lies in between 45200-82250, F2 formulation lies in between 34200-88900, F3 formulation lies in between 48900-88600, F4 formulation lies in between 47600-89000 and F5 formulation lies in between 36000-102250cps respectively.

All the gel formulation was also evaluated for Spreadability test it was found in the range180.5 to 12.26. This is for F1-172.16, F2-28.65, F3 16.42, F4-12.266 and F5-180.5% drug content was found in range of 97 ± 0.018 to 98 ± 0.027. Extrudability was found to be 91.73 ± 0.005%.

Table 2: Result for pH, viscosity, spreadability

Batch	pH	Viscosity (cps)	Spreadability* (gcm/sec)	% Drug content
F1	6.2	45200	172.16 ± 0.9410	97 ± 0.027
F2	5.46	34200	28.65 ± 0.5074	98 ± 0.027
F3	5.23	48900	16.42 ± 0.5456	97.5 ± 0.017
F4	4.8	47600	12.266 ± 0.2028	98 ± 0.012
F5	5.7	36000	180.5 ± 0.8544	97 ± 0.018

***In-vivo* evaluation**

In Carrageenan induced rat paw edema test F1 shows 58.33% inhibition after 3 hr. as compared to std. 70.83 at 3 hr. which show it is potent anti-inflammatory activity and its effectiveness while F2 shows % inhibition 50 at 3 hr. F3 shows % inhibition 41.66. F4 shows 33.33% inhibition at 3 hr. and F5 shows less 12.5% inhibition which shows that F1and F2 formulation shows maximum % inhibition as that of other formulation.

Table 3: Effect of topical administration of piroxicam gel on carrageenan induced paw edema in rats

Group	Dose (mg/kg)	Carrageenan induced rat paw edema (Percent inhibition of paw volume)					
		30	1	2	3	4	6
Control	50	0.13 ± 0.017	0.18 ± 0.017	0.24 ± 0.039	0.24 ± 0.038	0.30 ± 0.055	0.36 ± 0.060
Std.	50	0.10 ± 0.038 (23.07)	0.10 ± 0.038 (44.44)	0.08 ± 0.038[b] (66.66)	0.07 ± 0.022[b] (70.83)	0.10 ± 0.024[b] (66.66)	0.10 ± 0.008[b] (72.22)

F1	50	0.12 ± 0.039 (7.69)	0.13 ± 0.047 (27.77)	0.12 ± 0.035[a] (50)	0.09 ± 0.033[b] (58.33)	0.13 ± 0.039[b] (60.60)	0.12 ± 0.038[b] (66.66)
F2	50	0.10 ± 0.036 (23.07)	0.15 ± 0.026 (16.66)	0.13 ± 0.038[a] (45.83)	0.12 ± 0.028[a] (50)	0.15 ± 0.040[b] (50)	0.24 ± 0.039[b] (61.11)
F3	50	0.12 ± 0.021 (7.69)	0.17 ± 0.027 (5.55)	0.15 ± 0.028 (37.5)	0.14 ± 0.020[a] (41.66)	0.17 ± 0.043[a] (43.33)	0.17 ± 0.043[a] (52.77)
F4	50	0.11 ± 0.028 (15.38)	0.16 ± 0.032 (11.11)	0.17 ± 0.031 (29.16)	0.16 ± 0.024 (33.33)	0.18 ± 0.036[a] (40)	0.18 ± 0.022[a] (50)
F5	50	0.09 ± 0.016 (30.76)	0.16 ± 0.032 (12)	0.21 ± 0.025 (12.5)	0.21 ± 0.025 (12.5)	0.20 ± 0.037 (33.33)	0.21 ± 0.034 (41.06)

[*] 0.5 g of preparation was applied to the planter surface of the right hind paw by gently rubbing with the index finger.
[**] Values are mean ± S.D. *n = 6*
[***]Dunnett test showed that all the test group were drastically different from control group (*P*<0.001).

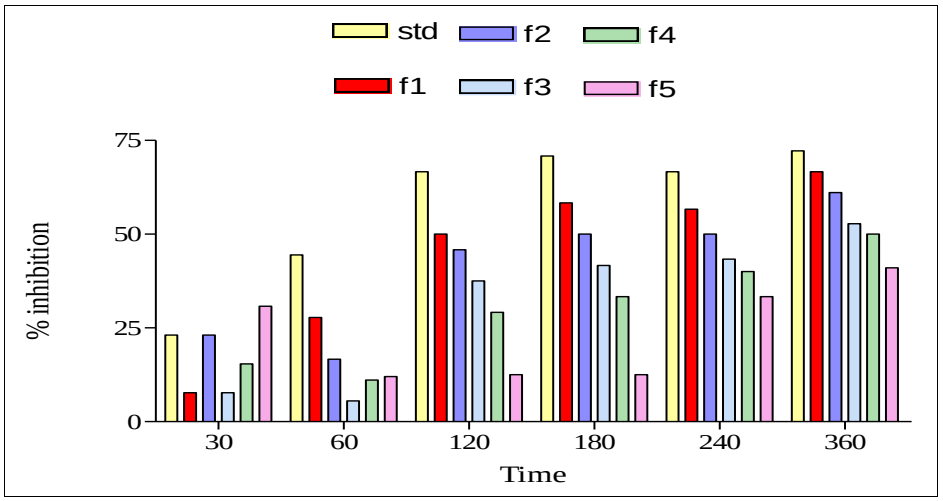

Fig 1:% Inhibition of edema

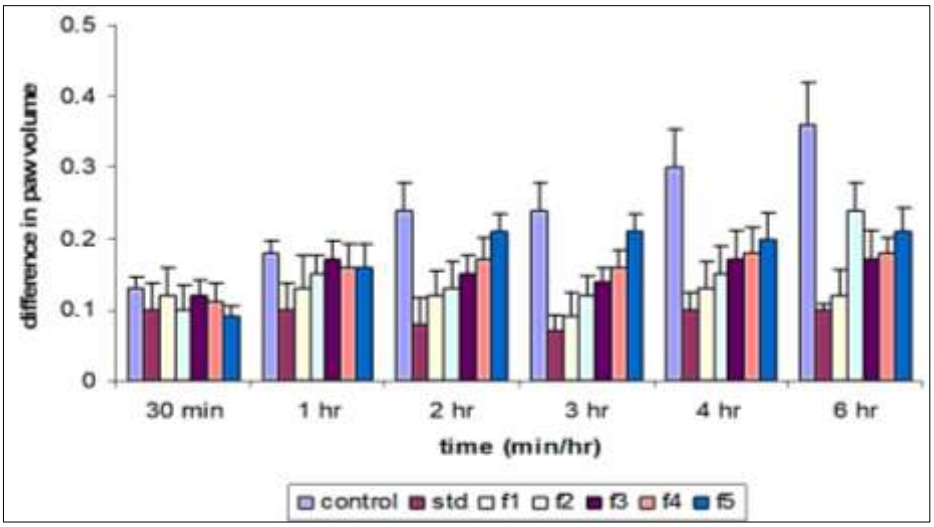

Fig 2: Difference in paw volume

Skin irritation study

The skin irritation study done on Wister rat's skin showed no irritation to the skin and hence supposed to be safe for human use too.

Table 4: Skin irritation study of selected gels

Sr. No.	Scores on respective days							
	Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1.	Control C	0	0	0	0	0	0	0
2.	F1	0	0	0	0	0	0	0
3.	F2	0	0	0	0	0	0	0
4.	F3	0	0	0	0	0	0	0
5.	F4	0	0	0	0	0	0	0
6.	F5	0	0	0	0	0	0	0

In-vitro diffusion study

The *In-vitro* diffusion study were taken by using Franz diffusion cell which shows Cumulative% release of Piroxicam from the gel formulation was 85% from F1(C_1), 80% from F2(C_2), 68% from F3(C_3), 66% from F4 (C_1H_1) and 63% from F5 (C_2H_2). The formulation C_1 and C_2 showed good released pattern.

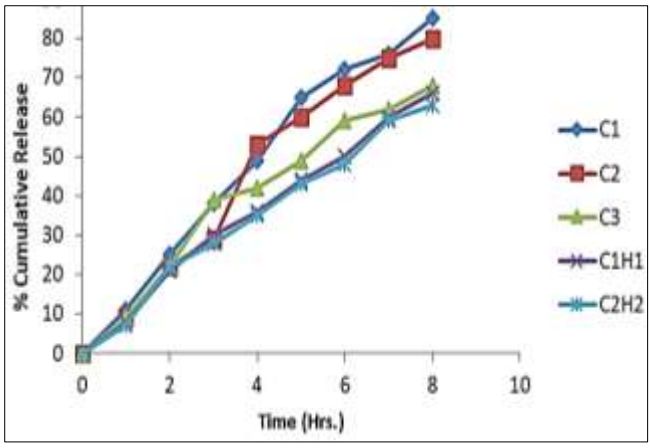

Fig 3: % Cumulative release of gel

When the rate of shear is increased as shown in graph viscosity decrease that proves that the Formulation is shear thinning pseudo-plastic in nature. Results are given in fig. no. 4-8.

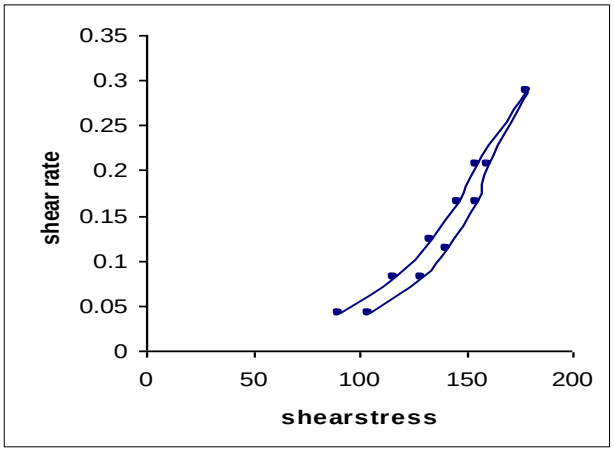

Fig 4: Rheogram of F1

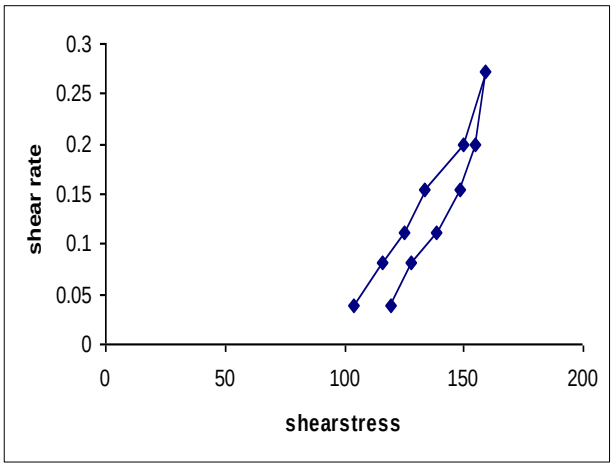

Fig 5: Rheogram of F2

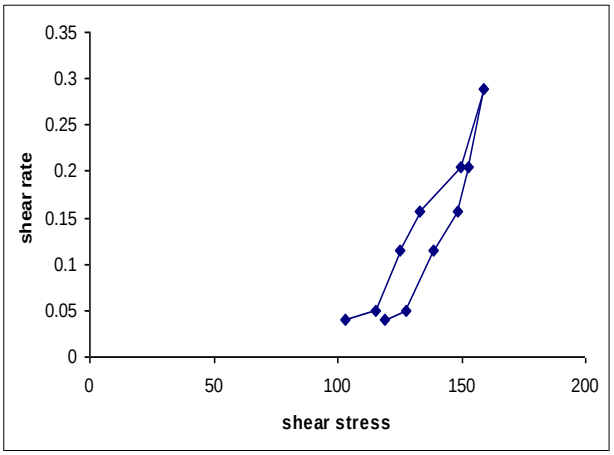

Fig 6: Rheogram of F3

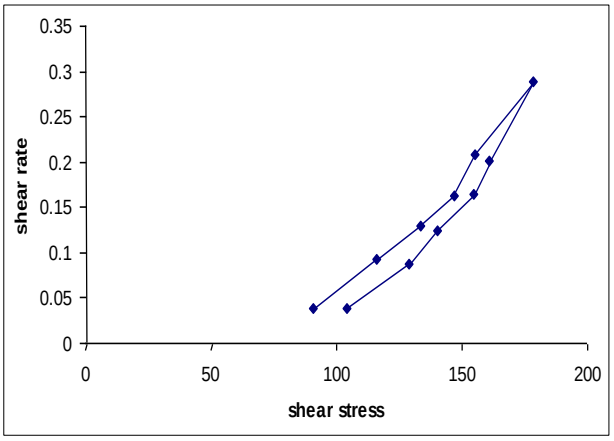

Fig 7: Rheogram of F4

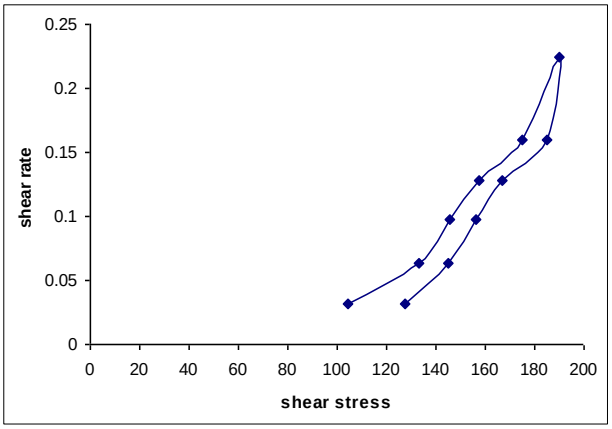

Fig 8: Rheogram of F5

The formulations were kept for stability studies there was no significant change observed in physical parameter i.e. (Drug content, pH, Spreadability) at 40 °C ± 2/75% ± 5 RH. There was negligible difference in the drug content observed after stability study suggested that all the formulations are stable under the given conditions for 90 days.

Table 5: Stability studies of F1

Sr. No.	Parameter	F1			
		Month			
		0	1	2	3
1.	Drug content	97 ± 0.027	96 ± 0.879	5.48	5.46
2.	pH	6.2	5.5	96 ± 0.327	95 ± 0.702
3.	Spredability	28.65 ± 0.507	29.23 ± 0.302	29.11 ± 0.411	29.89 ± 0.854

Conclusion

As per the results of the present study shows that the permeation rate of formulation C_1 and C_2 was enhanced without any significant change in the pH, Viscosity and Spreadability, it can be concluded that the formulation can be used to get the better effect of the drug. It is more worthwhile to evaluate the formulation at the clinical level as a further study.

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