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Formulation Design & Development of Piroxicam Emulgel

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Abstract: The objective of this work is to develop emulgel of piroxicam which will increase skin penetration of drug in comparison with present marketed preparations of the drug. Based on solubility studies oleic acid as oil, Tween-80 and Span-80 as emulsifiers and propylene glycol and cetostearyl alcohol as co-surfactant were selected for preparation of emulgel. The emulgels were prepared using different combinations of oil, emulsifiers, co-surfactant and carbomer (Carbompol 940 and Carbopol 934). They were optimized using 3^2 full factorial designs to study the effect of independent variables, i.e. concentration of emulsifiers (X_1) and carbomer (X_2) on dependent variables like % drug release at 2 and 6 hours. The prepared emulgels were evaluated in terms of appearance, average globule size, drug content and *in-vitro* drug release. *In-vitro* release study demonstrated diffusion controlled release of piroxicam from formulation up to 8 hours. The drug release profile exhibited zero order kinetics. From the regression analysis, it was observed that all three independent variables had significant effect on response variables. Formulation was optimized using contour plot and response surface plot. The optimized formulations were found to be F3 and F12 containing lower concentration of Carbopol (0.5 %) and higher concentration of emulsifiers (6%). The optimized formulae ware evaluated for Zeta Potential, viscosity, spreadability, skin permeation and stability. Skin permeation (%) of optimized batches (F3 and F12) in 24 hours was found to be 87.89% and 89.09 % respectively. The formulation batch F12 had better anti-inflammatory activity than marketed preparation.
Keywords: Piroxicam, Emulgel, Carbopol.

Introduction

Piroxicam is a non-steroidal anti-inflammatory compound with analgesic and antipyretic effects, used for the treatment of rheumatoid arthritis, osteoarthritis and traumatic contusions. It is well absorbed following oral administration however its use has been associated with a number of undesirable side effects on the stomach and kidneys in addition to gastric mucosal damage[1,2]. Dermal delivery is an alternative route but requires a formulation which ensures deep skin penetration, allowing therapeutic effect at localized site[3,4]. Although piroxicam is not easily absorbed after topical application, some studies have been carried out to predict the percutaneous absorption of piroxicam using different substances as permeation enhancers[5-10].

Many widely used topical agents like ointments, creams, lotions have numerous disadvantages. They are usually very sticky causing uneasiness to the patient when applied. Moreover they also have less spreading coefficient and need to apply with rubbing. They also exhibit the problem of stability. Due to all these factors, within the major group of semisolid preparations, the use of transparent gels

has increased both in cosmetics and in pharmaceutical preparations[11,12].

A gel is colloid that is typically 99% by weight liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating substance present. In spite of many advantages of gels a major limitation is their inability to delivery hydrophobic drugs[12].

To overcome this limitation an emulsion based approach is being used so that a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels. When gels and emulsions are used in combined form the dosage forms are referred as emulgels.

Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, transparent with long shelf life & pleasing appearance[12].

The aim of this work was to develop an emulgel formulation of piroxicam using two different grades of carbomer (Carbopol 934 and Carbopol 940). The influence of type and concentration of the gelling agent and the emulsifying agent on the release of the drug from the prepared emulgels was investigated using 3^2 full factorial design.

Materials and Methods

Materials

Piroxicam was received as a gift sample from Torrent Pharmaceutical Ltd, Ahmadabad (India). Carbomers were purchsed from Corel Pharma Chem., Ahmadabad (India). Oleic acid, Span-80, Tween-80, methyl salicylate and propyl paraben were purchased from S.D Fine Chemicals Ltd., Mumbai (India) All other chemicals and reagents used were of analytical grade. Deionized distilled water was used throughout the study.

Methods

Solubility study

An excess amount of piroxicam was added to each solvent and was stirred magnetically. After stirring for 24 hours at 37ºC, the equilibrated sample was centrifuged for 10 min at 5000 rpm (rotations per minute) to remove excess amount of piroxicam. The supernatant was filtered and properly diluted with phosphate buffer pH 7.4. The concentration of piroxicam was determined by UV spectrophotometry[10].

Preparation of emulgel

The composition of piroxicam emulgel formulations is shown in table II and III. First cetostearyl alcohol is melted which was then mixed with oil, surfactant, co-surfactant and methyl salicylate in required quantity. Then 0.5% piroxicam gel was dissolved in this oil phase. Carbopols in required quantity as given in formulation table IV and V were dispersed in water phase. Both the oily and aqueous phases were separately heated to 50° to 60°C: then the oily phase was added to the aqueous phase with continuous stirring (up to 2 hours). The pH was adjusted to 6 to 7 using triethanolamine.

Table I. Selection of independent and dependent variables

Independent variables	**Variable level**		
	Low (-1)	**Medium (0)**	**High (1)**
Concentration of Emulsifiers (X1)	2	4	6
Concentration of Carbopol (X2)	0.5	0.75	1.0
Dependent variables			
1.	% Cumulative release at 2 hours (Q_2 in %)		
2.	% Cumulative release at 6 hours (Q_6 in %)		

Table II. Formulation of ingredients of emulgel using Carbopol 940

Ingredients(%w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Oleic acid (%)	20	20	20	20	20	20	20	20	20
Propylene glycol (%)	5	5	5	5	5	5	5	5	5
Methyl salicylate (%)	10	10	10	10	10	10	10	10	10
Cetostearyl alcohol (%)	4	4	4	4	4	4	4	4	4
Span-80 (%)	0.9	1.9	2.8	0.9	1.9	2.8	0.9	1.9	2.8
Tween-80 (%)	1.1	2.1	3.2	1.1	2.1	3.2	1.1	2.1	3.2
Carbopol 940 (%)	0.5	0.5	0.5	0.75	0.75	0.75	1	1	1
Water (%)	58.9	57.9	56.8	58.9	57.9	56.8	58.9	57.9	56.8
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Triethanolamine (%)	Adjust pH 6 to 7								

Table III. Formulation of ingredients of emulgel using Carbopol 934

Ingredients(%w/w)	F10	F11	F12	F13	F14	F15	F16	F17	F18
Drug (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Oleic acid (%)	20	20	20	20	20	20	20	20	20
Propylene glycol (%)	5	5	5	5	5	5	5	5	5
Methyl salicylate (%)	10	10	10	10	10	10	10	10	10
Cetostearyl alcohol (%)	4	4	4	4	4	4	4	4	4
Span-80 (%)	0.9	1.9	2.8	0.9	1.9	2.8	0.9	1.9	2.8
Tween-80 (%)	1.1	2.1	3.2	1.1	2.1	3.2	1.1	2.1	3.2
Carbopol 940 (%)	0.5	0.5	0.5	0.75	0.75	0.75	1	1	1
Water (%)	58.9	57.9	56.8	58.9	57.9	56.8	58.9	57.9	56.8
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Triethanolamine (%)	Adjust pH 6 to 7								

Table IV. *In-vitro* drug release study conditions

Apparatus	Franz diffusion cell
Diffusion medium (in receptor compartment)	pH 7.4 phosphate buffer
Diffusion medium volume	15 ml
Temperature	37 ± 0.5ºC
Speed	50 rpm
Sampling volume	3 ml
Sampling interval	1 hour

Table V. Experimental design for animal study

No.	Group	
1	**Control group**	Carrageenan (1%)
2	**Standard group**	Topical application of marketed formulation (Pirox gel, Cipla) on inflamed area (localized delivery)
3	**Standard group**	Topical application of marketed formulation (Pirox gel, Cipla) on dorsal area (transdermal delivery)
4	**Test group**	Topical application of F12 batch on inflamed area (localized delivery)
5	**Test group**	Topical application of F12 batch on dorsal area (transdermal delivery)

Experimental design

A 3^2 level factorial design was conducted to study the effect of independent variables (i) Concentration of emulsifiers (X_1) and (ii) Concentration of Carbopol (X_2) on dependent variables % cumulative drug release at 2 hour (Q_2) and % cumulative drug release at 6 hours (Q_6). The independent and dependent variables are listed in table I while all the batches ware prepared according to the experimental design **(**table II).

Two grades of Carbopol were taken. Same experimental design was applied for both grades.

Eighteen piroxicam emulgel formulations were prepared in all.

Characterization of emulgel

Appearance

Appearance of gel was evaluated on the bases of visual inspection.

Drug content

Drug content of emulsion was measured by UV spectrophotometer. 1 ml of emulsion was diluted to 20ml with methanol and volume was made up to 100ml using phosphate buffer 7.4. A volume of 2ml of this solution was further diluted to make 10 µg/ml solution of piroxicam.

Average globule size

Average globule size was measured by light microscope.

In-vitro drug release study

The *in-vitro* drug release of piroxicam from prepared formulations and marketed formulation (Pirox Gel, Cipla Pharmaceuticals) were studied through cellophane membrane using Franz diffusion cell. The cellophane membrane was previously treated with sodium hydroxide and soaked overnight in the phosphate buffer 7.4 at refrigeration temparature. The treated cellophane membrane was sandwiched between donor and receptor compartments of Franz diffusion cell. Formulation equivalent to 2 mg of piroxicam was added on the cellophane membrane. A magnetic bar was continuously stirred in diffusion medium to avoid diffusion layer effect. The withdrawn sample was analyzed by UV spectrophotometer. Study conditions were as shown in the table IV.

Kinetic study and mechanism of drug release

The diffusion profile of all the batches was fitted to Zero order, First order, Higuchi and Krosmeyer-Peppas models to ascertain the kinetics of the drug release[13,14].

Optimization of formulation

It was done by contour plot and response surface plot using Design Expert software 8.0.7.1 trial.

Characterization of optimized batch

Optimized batch was evaluated for all parameters previously described.

Additional evaluation parameters of optimized batch are given below.

Viscosity

The Viscosity of emulgel was carried out with Brookfield viscometer (LVDV II + prime model) using S64 spindle. The viscosity was measured at 12 rpm.

Globule Size and Zeta Potential

Globule Size and Zeta Potential of emulsions were determined by Zetatrac. Zetatrac determines Zeta Potential by measuring the response of charged particles to an electric field.

In a constant electric field particles drift at a constant velocity. Through the velocity, the charge and Zeta Potential are determined. Zetatrac utilizes a high frequency AC electric field to oscillate the charged particles. The Brownian motion power spectrum is analyzed with the Nanotrac controlled reference technique of particle sizing to determine the Modulated Power Spectrum, a component of the power spectrum resulting from the oscillating particles. Zeta Potential is calculated from the MPS signal. Also determined are the particle mobility (velocity per electric field), particle charge and particle size.

Photomicrography

Morphology of emulsion was studied under light microscope. Optimized batches of the emulgel were viewed under light microscope to study their shape. The emulgel was suitably diluted, mounted on glass slide and viewed by light microscope under magnification of 40 X.

Skin permeation and skin retention study

Skin permeation study was carried out with rat dorsal skin using modified Franz diffusion cell by the same method as described above in the *in-vitro* drug release study of emulgel. The skin was carefully checked through a magnifying glass to ensure that samples were free from any surface irregularity such as tiny holes or crevices in the portion that was used for permeation studies.

The ability of emulgel to help retain the drug within the skin (i.e. depot-effect) was investigated by determining the amount of drug retained in the skin samples employed in permeation studies. For this, remaining emulgel from the donor compartment was pipette out and dissolved in phosphate buffer. Absorbance was measured by UV spectrophotometer to determine amount of drug retained and remaining to diffuse.

Spreadability

One of the criteria for an emulgel 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 spreadability.

Spreadability of emulgel and marketed gel was measured in terms of diameter of emulgel circle produced when emulgel is placed between two glass plates of definite weight. A weighed quantity (350 mg) of emulgel or gels was taken on one glass plate and another glass plate was dropped from a distance of 5 cm. The diameter of the circle of spread emulgel was measured[15,16].

***In-vivo* Anti- inflammatory activity**

All the experimental procedures were carried out in accordance with committee for purpose of experiments on animal's guidelines (CPSCEA). The study was reviewed and approved by Institutional Ethics Committee (Protocol number: MPC/16/2012), Maliba Pharmacy College, India.

Edema was induced on the left hind paw of the rats by subplantar injection of 1 %(w/v) carrageenan. They were divided into 5 groups of 5 rat each (table V). Formulations i.e. F12 and standard (Pirox gel, Cipla) containing 0.25 mg of piroxicam were applied after carrageenan administration[17, 18].

The area to which gels were applied was kept constant (1 cm^2). The paw thickness was measured at intervals of 30, 90, 180, 360 and 1440 minute by measurement of diameter using Vernier callipers.

Table VI. Solubility study data

Components	Solubility (mg/ml)
Water	0.13
Linseed oil	5
Oleic acid	13.2
Phosphate buffer 7.4	0.20
Propylene glycol	6
Tween 80	16
Span 80	3.2

The % inhibition of paw edema in drug treated group was compared with carregenan control group and calculated according to the formula:

% inhibition of drug = **Dc-Dt/ Dc x 100**

Where, **Dc =** Rat paw diameter (in mm) of control group.

Dt = Rat paw Diameter of test group

Stability study

Stability study of selected formulation was done at room temperature for 1 month and formulation was finally evaluated for appearance, drug content and pH.

Result and discussion

Solubility

Solubility in various excipients is shown in table VI. From data shown in Table VI, highest solubility of piroxicam was found in oleic acid amongst oils, Tween 80 amongst surfactants and propylene glycol amongst co-surfactants. Hence these components are selected for preparation of emulgel system.

Appearance of emulsions and emulgels

All formulation batches were found to be homogenous yellowish milky emulsions while emulgels were found to be yellowish white viscous creamy preparation.

Drug content

Drug content details of emulgel are shown in table VII. Amount of drug in the emulgel indicates the suitability of the system for high entrapment in the internal phase.

Average globule size

Average globule size measurements are shown in table VII. The results indicate that globule size of droplet varies from 11 to 17 µm.

Table VII. % Drug content and average globules size

Batch No.	% Drug Content (n=3)	Average globules size (µm) (n=50)	Batch No.	% Drug Content (n=3)	Average globules size (µm) (n=50)
F1	98.29 ± 0.5	15.5 ± 0.25	**F10**	97.38 ± 0.64	13.42 ± 1.04
F2	97.21± 0.9	17 ± 0.75	**F11**	99.24 ± 1.43	12.75 ± 2.12
F3	101.23± 1.0	15 ± 1.0	**F12**	97.98 ± 2.29	11 ± 0.47
F4	99.01± 0.7	16.37 ± 0.35	**F13**	99.41 ± 0.28	11.9 ± 0.4
F5	97.69± 0.8	13.12 ± 1.06	**F14**	101.77 ± 2.88	12.75 ± 0.32
F6	100.13± 0.99	11.38 ± 0.56	**F15**	98.95 ± 0.83	12.5 ± 1.25
F7	99.1 ± 0.42	11 ± 0.95	**F16**	101.45 ± 1.66	12.9 ± 0.18
F8	102.59 ± 1.54	12.5 ± 1.25	**F17**	100.11 ± 1.75	12.5 ± 0.95
F9	101.7± 0.35	12.9 ± 1.3	**F18**	102.54 ± 0.59	12.1 ± 2

***In-vitro* drug release**

The results of *in-vitro* drug release study are shown in table VIII and comparative drug release is shown in figure 1.

Formulation batches F3 and F12 release drug faster than the other formulation due to the lower concentration of Carbopol and higher cocentration of emulsifiers. An increase in concentration of Carbopol leads to decreased drug release from formulation due to increase in viscosity of formulation.

Kinetic study and mechanism of drug release

The correlation coefficient value (R^2) of each formulation for zero order, first order, Higuchi, Hixon Crowell and value of release exponent from Korsmeyer Peppas model are shown in table IX.

The release kinetics data indicates that the release of drug from emulgels follows zero order kinetics because the correlation coefficient values are higher in case of zero order equation. The release rate is independent of the concentration of the drug. The release exponent value of Korsmeyer Peppas equation is near to 1, this suggests that the emulgel follows case II transport mechanism (zero order release).

Data analysis of 3^2 full factorial design

Multiple regression analysis of F1-F9 batches are shown in table X.

The response (Y_1 and Y_2) obtained at various levels of the 2 independent variables (X_1 and X_2) were subjected to multiple regression to yield a second-order polynomial equation (full model). Equation clearly reflects the wide range of values for response (Y_1 and Y_2).

$$\mathbf{Y_1 = 14.52 + 3.66\ X_1 - 6.282\ X_2 + 1.01\ X_1^2 - 0.525\ X_2^2 - 0.8425\ X_1X_2}$$

The amount of drug released at 2 hr from the F10-F18 batches of emulgel varied from 14.41% to 22.42%. Correlation coefficient was found be 0.940 suggesting best fit to model. From the P-value, it can be concluded that X_1 and X_2 have the prominent effect ($P < 0.05$) on the Q_2. Postive sign of X_1 in regression equation indicates that the response value increases as the number of factors increases. Negative sign of X_2 in regression equation indicates that the response value decreases as the number of factors increases.

$$\mathbf{Y_2 = 60.327 + 5.183\ X_1 - 3.377\ X_2 + 0.91\ X_1^2 - 0.57\ X_2^2 - 0.405\ X_1X_2}$$

The amount of drug released at 6 hr from the F1-F9 batches of emulgel varied from 52.52% to 69.64%. Correlation coefficient was found to be 0.9994 suggesting best fit to model. From the P-value, it can be concluded that X_1 and X_2 have the prominent effect ($P < 0.05$) on the Q_6. Postive sign of X_1 in regression equation indicates that the response value increases as the number of factors increases. Negative sign of X_2 in regression equation indicates that the response value decreases as the number of factors increases.

Similar results were found for F10-F18 bathes, multiple regression analysis of which is given in table XI.

Table VIII (a) *In-vitro* drug release of F1-F9 and marketed formulation (n=3)

Time (hours)	% Cumulative drug release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Pirox gel**
1	8.02	6.31	11.77	2.41	5.56	11.69	2.39	5.80	6.14	10.19
2	**17.64**	**20.32**	**24.89**	**10.66**	**13.41**	**21.50**	**6.25**	**8.78**	**10.13**	**22.90**
3	27.54	26.76	32.59	18.93	23.29	31.39	20.49	21.51	22.48	35.80
4	40.43	40.93	45.41	32.76	37.05	38.38	34.42	35.57	36.83	45.26
5	49.26	54.61	57.47	43.53	50.31	48.27	43.96	45.71	49.91	51.96
6	**58.49**	**63**	**69.73**	**56**	**60.56**	**66.24**	**52.53**	**56.28**	**62.15**	**67.23**
7	71.82	76.45	80.40	72.52	75.82	78.07	72.08	76.04	78.33	76.35
8	87.29	89.23	92.61	86.84	88.03	90.24	83.24	85.89	88.69	88.24

Table VIII(b) *In-vitro* drug release of F9-F18 and marketed formulation (n=3)

Time (hours)	% Cumulative drug release								
	F10	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
1	10.27	9.58	11.28	8.65	10.10	9.54	6.39	5.98	8.41
2	**19.16**	**20.76**	**22.20**	**17.73**	**19.23**	**21.87**	**14.70**	**16.71**	**17.98**
3	30.91	27.48	31.24	30.72	31.65	29.68	23.59	27.83	29.41
4	39.03	39.62	42.24	39.99	40.34	40.23	34.52	38.19	40.38
5	46.53	48.38	52.74	48.33	48.75	51.54	43.83	46.10	47.10
6	**58.60**	**62**	**65.42**	**57.56**	**60**	**63.87**	**55**	**58.54**	**61.63**
7	73.25	73.54	79.46	71.31	74.75	76.85	61.78	72.56	76.51
8	88.33	89.18	93.93	86.32	87.84	90.06	84.66	86.73	87.86

Table IX Kinetics and release mechanism of F1-F18 and marketed formulation

Batch	R^2 Value					Release exponent 'n"
	Zero order	**First order**	**Higuchi**	**Hixon Crowell**	**Korsemeyer Peppas**	
F1	0.994	0.918	0.963	0.936	0.998	1.123
F2	0.996	0.876	0.973	0.9525	0.985	1.266
F3	0.998	0.924	0.975	0.948	0.996	0.975
F4	0.989	0.872	0.944	0.928	0.991	1.74
F5	0.995	0.915	0.959	0.947	0.998	1.36
F6	0.987	0.956	0.945	0.926	0.990	0.926
F7	0.988	0.871	0.950	0.945	0.979	1.836
F8	0.985	0.929	0.941	0.937	0.960	1.366
F9	0.990	0.929	0.952	0.947	0.972	1.368
F10	0.987	0.943	0.947	0.915	0.997	0.967
F11	0.991	0.938	0.953	0.924	0.995	1.01
F12	0.994	0.945	0.957	0.908	0.999	0.968
F13	0.992	0.915	0.963	0.936	0.996	1.07
F14	0.993	0.933	0.959	0.935	0.998	0.997
F15	0.995	0.926	0.962	0.936	0.996	1.03
F16	0.980	0.924	0.939	0.903	0.999	1.20
F17	0.994	0.891	0.962	0.937	0.993	1.26
F18	0.993	0.923	0.959	0.940	0.998	1.10
Pirox gel	0.996	0.892	0.981	0.962	0.993	1.207

Table X. Multiple regression analysis for Y_1 and Y_2 (Full model) (batch F1-F9)

	$Q_2 = Y_1$		$Q_6 = Y_2$	
Dependent variables	**P value**	**Coefficients**	**P value**	**Coefficients**
Intercept	0.002526	14.52	$3.99*10^{-8}$	60.327
X_1	0.005007	3.66	$3.73*10^{-5}$	5.183
X_2	0.022568	-6.282	$1.03*10^{-5}$	-3.377
X_3	0.743054	1.01	0.032117	0.91
X_4	0.538926	-0.525	0.009023	-0.57
X_5	0.474354	-0.8425	0.031719	-0.405

Table XI. Multiple regression analysis for Y_1 and Y_2 (Full model) (batch F10-F18)

	$Q_2 = Y_1$		$Q_6 = Y_2$	
Dependent variables	**P value**	**Coefficients**	**P value**	**Coefficients**
Intercept	$1.21*10^{-5}$	19.58778	$1.85*10^{-07}$	60.36556
X_1	0.002699	1.745	0.000185	3.293333
X_2	0.001525	-2.12	0.001103	-1.80833
X_3	0.914296	0.038333	0.553409	0.166667
X_4	0.051985	-1.02667	0.347551	-0.27833
X_5	0.812491	0.06	0.805951	-0.0475

Results of Analysis of variance (ANOVA)

ANOVA was done using Microsoft Excel. Results of ANOVA for Q_2 and Q_6 are shown in Table XII.

Contour plot and response surface plot

Results of contour plot and response surface plot are shown in figure 1(a) and figure 1(b). From this F3 and F12 batches were selected as optimized batches exacting the maximum drug release from the emulgel formulation.

Table XII. ANOVA for dependent variables for F1-F18

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	Significance F
For Q_2 = % drug release at 2 hours (F1-F9)					
Regression	322.5603	5	64.51206	15.12272	0.024448
Residual	12.79771	3	4.265903	-	-
Total	335.358	8	-	-	-
For Q_6 = % drug release at 6 hours (F1-F9)					
Regression	232.575	5	46.51501	1030.867	$4.76*10^{-05}$
Residual	0.135367	3	0.045122		
Total	232.7104	8			
For Q_2 = % drug release at 2 hours (F10-F18)					
Regression	47.36198	5	9.472396	44.0774	0.005220422
Residual	0.644711	3	0.214904	-	-
Total	48.00669	8	-	-	-
For Q_6 = % drug release at 6 hours (F10-F18)					
Regression	84.9162	5	16.98324	135.3296	0.000992
Residual	0.376486	3	0.125495	-	-
Total	85.29269	8	-	-	-

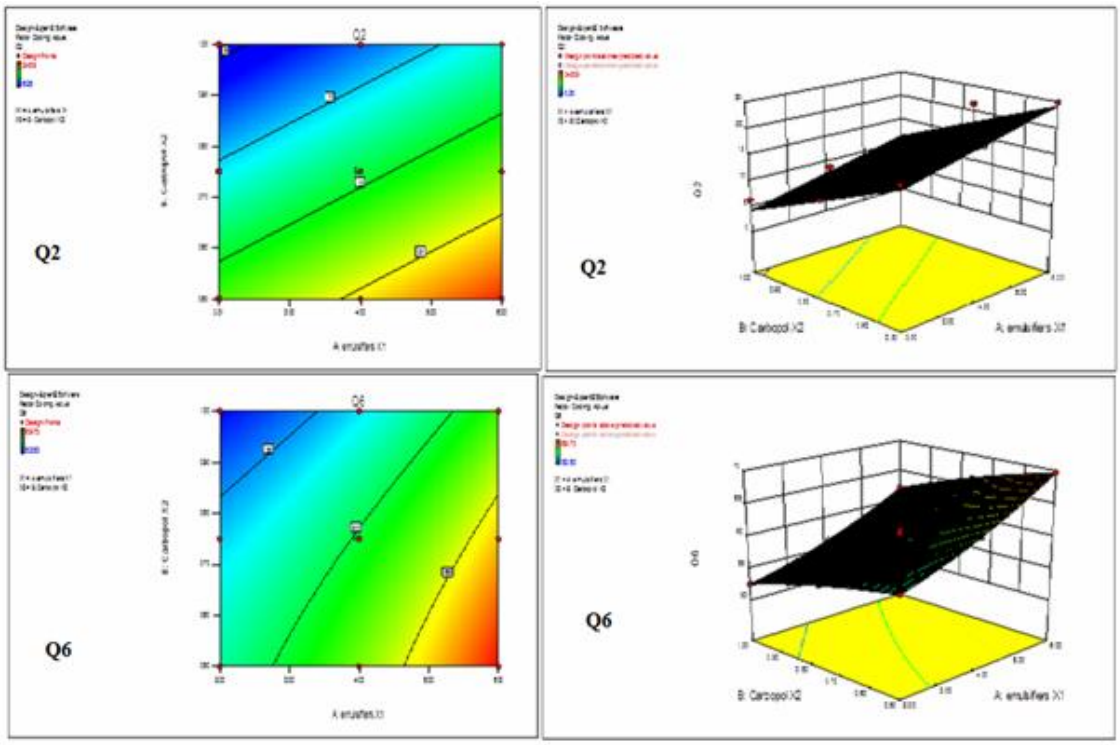

Figure 1 (a) Counter plot and Response surface plot for F1-F9

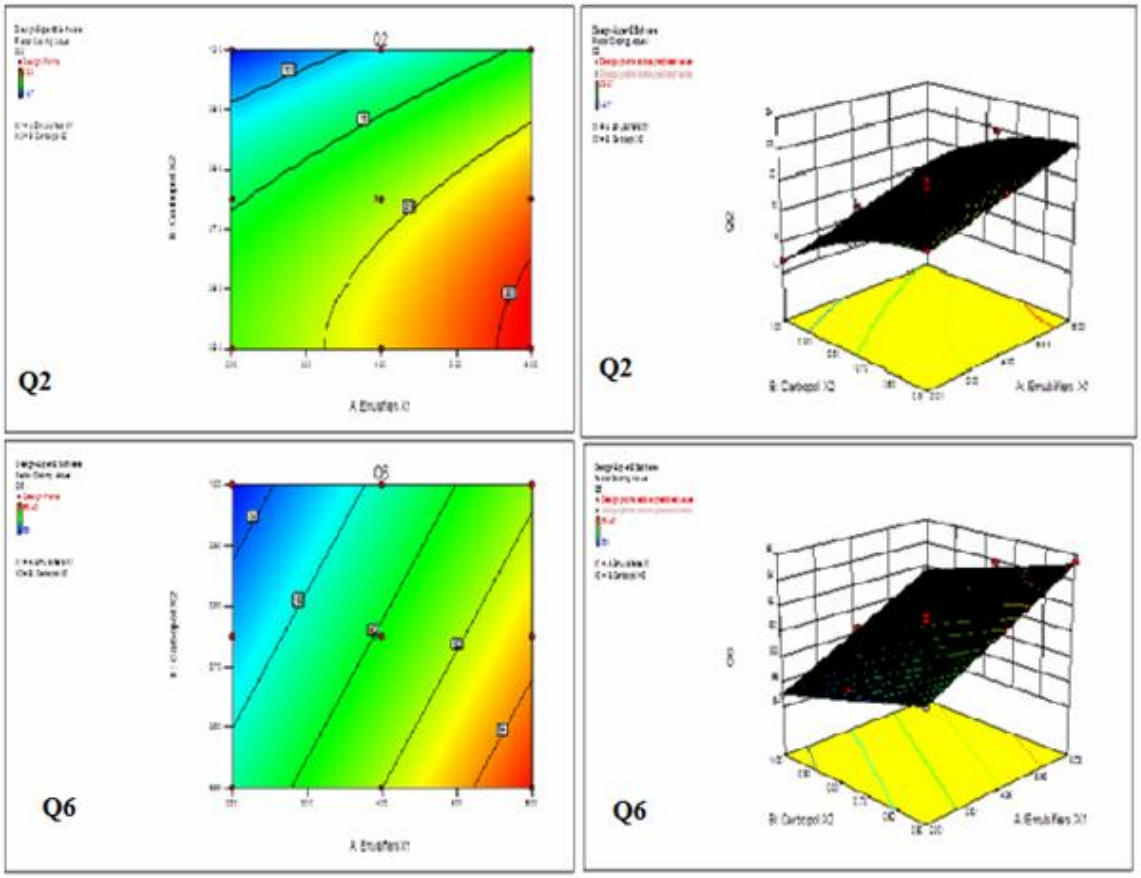

Figure 1 (b) Counter plot and Response surface plot for F1-F9

Evaluation of Optimization

Viscosity of optimization batch

Viscosity of the emulgel was measured at 12 rpm. Viscosity of F3 and F12 was found to be 21445 ± 0.59 cp and 19446 ± 0.74 cp respectively.

Globule Size and Zeta Potential

The results of Globule size and Zeta Potential measurement of the batch F3 and F12 emulgels are shown in figure 2 (a, b). Results revealed that both batches had reasonable globule size and PDI (Polydispersibility index).

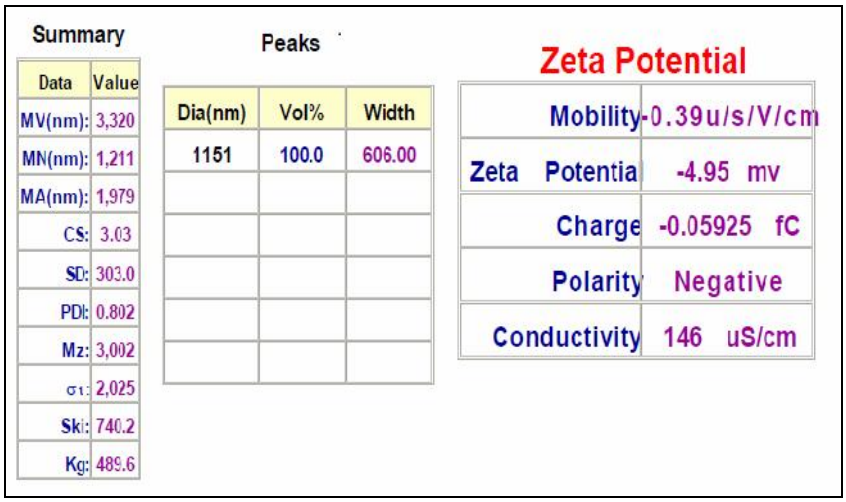

Figure 2 (a) Globule Size and Zeta Potential of F3

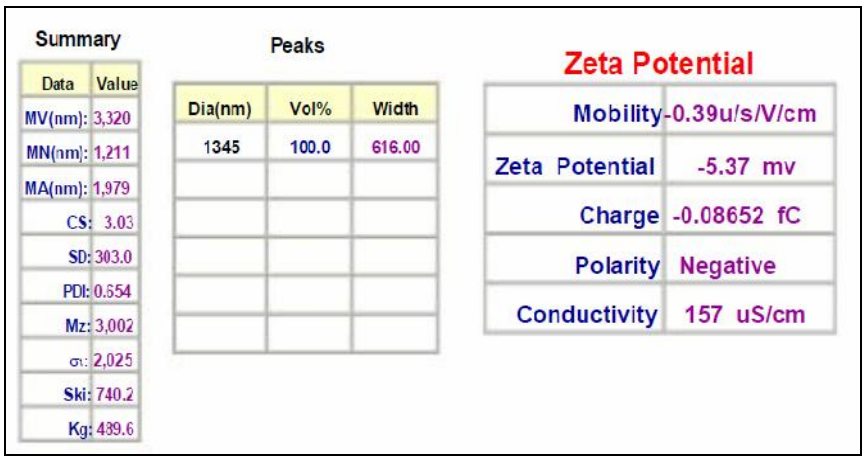

Figure 2 (b) Globule Size and Zeta Potential of F12

Photomicrography

The suitably diluted emulsions of optimized batches (F3 and F12) were observed under light microscope at 40X (figure 3). From the photomicrograph, nearly spherical globules of emulsion were observed. Though this study does not give any exact estimate of size however it gives a general idea about formation of emulsion and success of the method used.

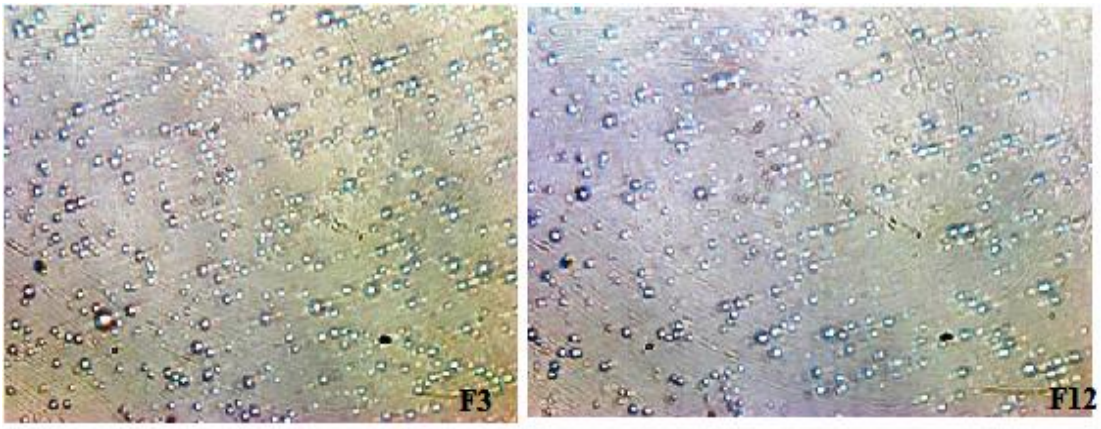

Figure 3 Photomicrographs of F3 and F12

Skin permeation and skin retention study

The skin permeation of Piroxicam from the optimized emulgel was studied through the rat's dorsal skin using a modified Franz diffusion cell. The diffusion medium used was phosphate buffer pH 7.4. The result of skin permeation for 24 hours of emulgel is as shown in figure 4.

Optimized batch F3 and F12 the amount of drug permeated through skin in 24 hours was 87.89% and 89.09 %. In marketed formulation, skin permeation was found to be 60.56% where as drug retention in skin was found to be 28 %. It can be concluded that drug permeation is enhanced in the emulgels.

Spreadability

Spreadability of the formulations is shown in table XIII. Spreadability of emulgel is an important parameter. Results of spreadability indicate that spreadability of emulgel is better than the marketed gel.

***In-vivo study* of the emulgels (Anti-inflammatory activity)**

This study was conducted by applying emulgel F12 topically at site of inflammation and also at a site away from inflammation (transdermal application) because emulgels were exhibiting high *in-vitro* release in comparison to marketed formulation whereas skin retention was found to be negligible in emulgels. The anti-inflammatory action of formulation F12 was calculated and it was compared with marketed preparation (Pirox gel, Cipla). The % inhibition of marketed formulation and F12 are given in table figure 5.

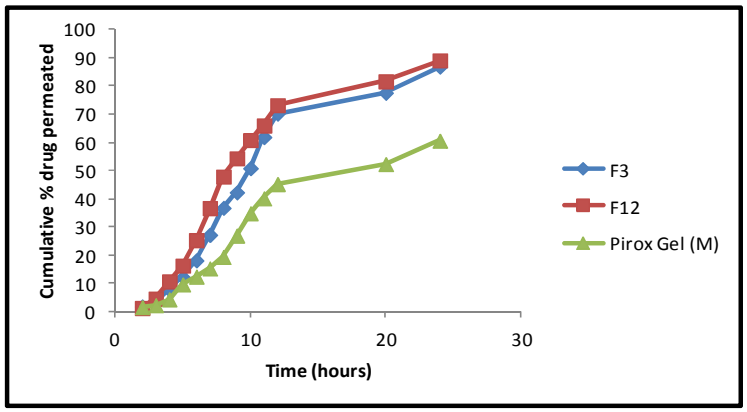

Figure 5. % Inhibition of inflammation

Table XIII Spreadability of the formulation

Batch	Diameter of circle (mean ± s.d. , n=3)
F3	3.13 ± 0.11
F12	3.77 ± 0.20
Marketed formulation	2.27 ± 0.25

Table XIV Results of stability study (mean ± s.d., n=3)

Before			After		
Appearance	**pH**	**Drug content (%)**	**Appearance**	**pH**	**Drug content (%)**
yellowish white viscous creamy	6.29 ± 0.53	99.45 ± 1.23	yellowish white viscous creamy	6.96 ± 0.73	98.00±0.64

Results show that the F12 formulation is more effective in inhibiting inflammation than marketed formulation. It is effective topically as well as transdermally.

Stability study

Stability study was performed on optimized batches F3 and F12 at ambient conditions. The results obtained after 1 month time period are shown in table XIV.

Conclusion

The present investigation deals with the formulation design and development of emulgel of piroxicam. Optimization was done using factorial design at 3 levels and 2 factors. From the polynomial equation and contour plots generated, both independent factors showed significant effect on dependent variables. The release of Piroxicam was good fit to the zero order and Higuchi model. The formulation batch F12 showed better anti-inflammatory activity than marketed preparation. Thus emulgel of Piroxicam is suitable to dermal delivery.

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