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Research Article

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Formulation, Development and Characterization of Emulgel of a NSAID'S

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Abstract The objective of the current research work was to explore the potential of emulgel in enhancing the topical delivery of piroxicam. Emulgel formulations of piroxicam were prepared using three types of gelling agents: Carbopol 934, Xanthan gum and HPMCK15M. Based on solubility studies Tween-80 and Span-80 as emulsifiers and propylene glycol as co-surfactant were selected for preparation of emulgel. The persuade of the type of the gelling agent on the drug release from the prepared emulgel was investigated. The mentha oil is used as permeation enhancer. The formulated emulgel were characterized for their physical appearance, pH determination, viscosity, spreadability, *in vitro* drug release, *ex vivo* drug release, skin irritation test, anti inflammatory activity, analgesic activity and stability studies. All the prepared formulations showed acceptable physical properties, homogeneity, consistency, spreadability, viscosity and pH value. In-vitro release study demonstrated diffusion controlled release of piroxicam from formulation up to 8 h. The drug release profile exhibited zero order kinetics.

Keywords Emulgel, Carbopol, NSAID'S, Spreadability, Piroxicam

Introduction

Many extensively used topical agents like ointments, creams, lotions have numerous disadvantages. They are generally very sticky causing discomfort to the patient when applied. Likewise they also have a reduced amount of spreading coefficient and necessitate to apply with rubbing. They also show evidence of 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 [1-2]. 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. To overcome this curb an emulsion based approach is being used so that a hydrophobic therapeutic moiety can be fruitfully incorporated and delivered through gels. When gels and emulsions are used in united form the dosage forms are referred as emulgels. 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 [3-4].

Materials and Methods

Piroxicam was received as a gift samples from Torrent pharmaceuticals, Ahemdabad, India. HPMCK15M, Crabopol934 and Xanthan gum were generous gift from CP kelco Pvt. Ltd Mumbai, India. Light liquid paraffin, Span-80, Tween-80, Methyl paraben and Propyl paraben were purchased from Loba Chemie, Mumbai, India. All other chemicals and reagents used were of analytical grade. Deionised distilled water was used throughout the study.

Fabrication of Emulgel of Piroxicam

Dissimilar formulations were formulated using altering amount of gelling agent and penetration enhancer. The method only differed in the process of making gel in diverse formulations. The formulation of emulsion was same in all the formulations. The gel bases were prepared by dispersing Carbopol 934 and Xanthan gum in distilled water separately with constant stirring at a reasonable speed using mechanical shaker. Formulations EG1, EG2 and EG3 were formulated by Carbopol 934 and EG4, EG5 and EG6 by Xanthan gum as gelling agent. In formulations EG7, EG8 and EG9 the gel were prepared by dispersing HPMCK15M in heated distilled water (80 °C), and the dispersion was chilled and left overnight. The pH of all the formulations was adjusted to 6.2-6.7 using tri ethanol amine. The oil phase of the emulsion was equipped by dissolving Span 20 in light liquid paraffin while the aqueous phase was geared up by dissolving Tween 20 in purified water. Methyl and Propyl parabens were dissolved in propylene glycol and mixed with aqueous phase piroxicam, being hydrophobic was dissolved in oil phase. Mentha oil was also assorted in oil phase. Both the oily and aqueous phases were separately heated to 70 ° to 80 °C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The formulated emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel [5-7]. The composition of different formulations has been discussed in Table 1.

Table1: Composition of Emulgel of Piroxicam

Ingredients	**Formulation Code**								
	EG1	**EG2**	**EG3**	**EG4**	**EG5**	**EG6**	**EG7**	**EG8**	**EG9**
API (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 934	0.5	1.0	1.5	---	---	---	---	---	---
Xanthan Gum	---	---	---	0.5	1.0	1.5	---	---	---
HPMC K15M	---	---	---	---	---	---	0.5	1.0	1.5
Tween20	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Spam20	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Liquid paraffin	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Propylene glycol	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Methyl paraben	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Propyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Mentha oil	2	3	4	2	3	4	2	3	4
Deionised water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Characterization Emulgel of Piroxicam

Drug content: Weigh accurately 1 gm of emulgel and it was dissolved in 100 ml of phosphate buffer 7.4. The volumetric flask was kept for 2 h and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The absorbance was measured spectrophotometrically after appropriate dilution against corresponding emulgel concentration as blank. The drug content was determined using following formula [8-9].

Physical Examination: The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency, grittiness and phase separation [10].

Measurement of pH: The pH of emulgel formulations was determined by using digital pH meter. 1 gm of gel was dissolved in 100 ml of distilled water and it was placed for 2 h. The measurement of pH of each formulation was done in triplicate and average values were calculated [11].

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. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37±0.5 °C. Sample (5 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically and the cumulative % drug release was calculated [12-14].

Determination of viscosity: The viscosity of the formulated batches was determined using a Brookfield Viscometer with spindle 07. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature before the measurement was taken. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 12 rpm for 10 min. The viscosity reading was noted [15].

Spreadibility: 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 [16-17].

Skin Irritation Test: A set of 6 rats was used in the study. The emulgel was applied on the properly shaven skin of rat. Undesirable skin changes i.e. change in skin colour, change in skin morphology etc was checked for a period of 24 hr [18].

***In-vitro* drug release study:** The *in-vitro* drug release of piroxicam from prepared formulations 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 1 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 [19].

Release kinetics of selected formulatios (EG5 & EG1): To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), First order (log cumulative % drug retained v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time) and Peppas model (log cumulative % drug release v/s. log time) [20-22].

Stability Studies: The prepared emulgels were packed in aluminium collapsible tubes (5 gm) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties and drug content [23].

Result and Discussion

Apperance of emulgel: Emulgel formulations were yellowish viscous creamy preparation with a smooth homogeneous texture and glossy appearance.

Solubility: Utmost solubility of piroxicam was found in Tween 80 amongst surfactants and propylene glycol amongst co-surfactants. Hence these components are selected for formulation of emulgel system.

Table 2: Solubility of piroxicam with different solvents

Components	Solubility (mg/ml)
Water	0.15
Phosphate buffer 7.4	0.24
Propylene glycol	07
Tween 80	20

Spreadability Test: Spreadability test was carried out for all the formulations. Spreadability of the emulgel was diminishes with the augment in the concentration of the polymer. The spreadability is very much significant as show the behaviour of emulgel comes out from the tube. The data is shown in figure 1 below.

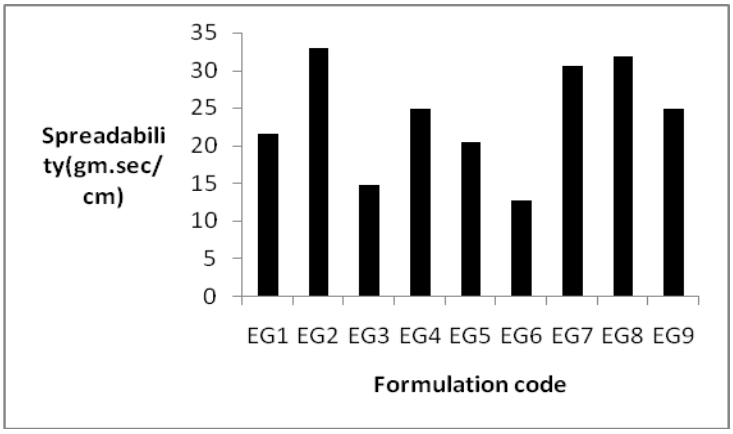

Figure 1: Spreading coefficient of different formulations (EG1-EG9)

Determination of viscosity: The emulgel was rotated at 50 rpm for 20 min with spindle 07. The analogous reading was noted. The viscosity of the emulgel was obtained, which is shown in figure 2. The viscosity of the formulations increases as concentration of polymer increases.

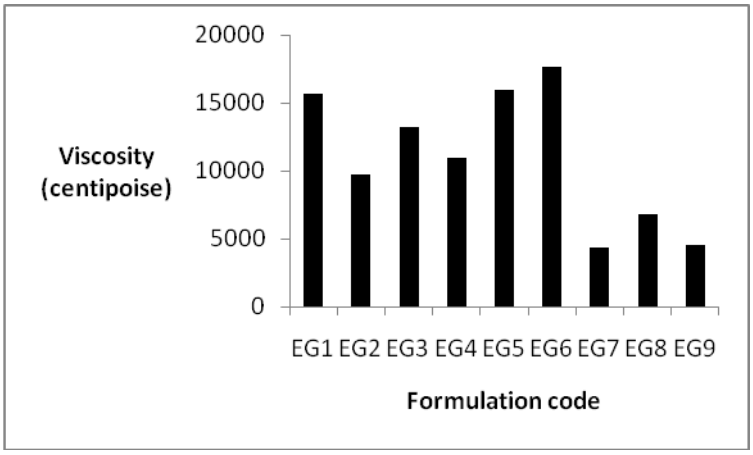

Figure 2: Viscosity of different formulations (EG1-EG9)

Determination of pH values: The pH of the emulgel formulations was in the range of 4.8 ± 0.4 to 5.8± 0.5, which lies in the normal pH range of the skin and would not fabricate any skin irritation. There was no considerable change in pH values as a function of time for all formulations, which is shown in figure 3.

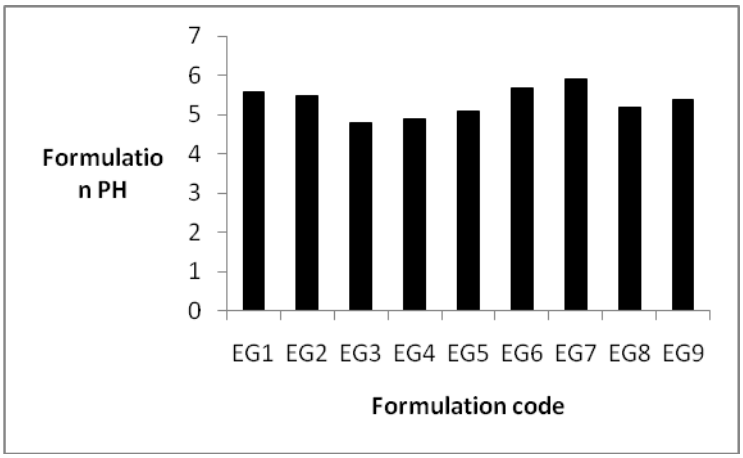

Figure 3: pH determination of different formulations (EG1-EG9)

Drug content: Drug content details of emulgel are shown in figure 4. Quantity of drug in the emulgel reveals the suitability of the system for sky-scraping entrapment in the internal phase.

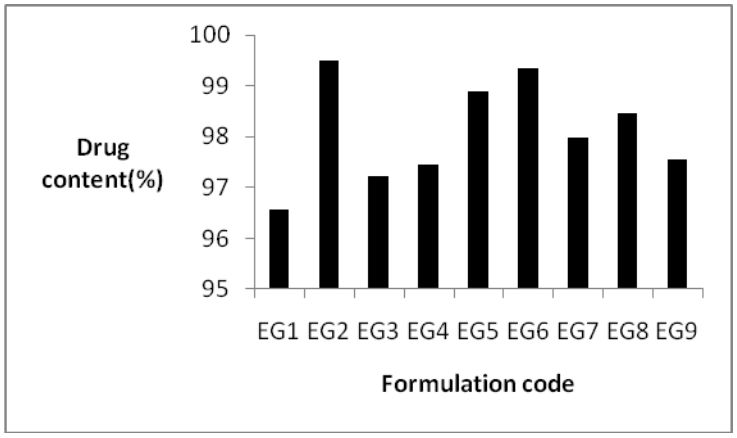

Figure 4: Drug content of different formulations (EG1-EG9)

Skin irritability test: No allergic symptoms like inflammation, redness, irritation witnessed on rats up to 24 h.

Table 3: *In-vitro* drug release of formulations EG1 to EG5

Time (h)	EG1	EG2	EG3	EG4	EG5
1	13.21±0.03	4.15±0.01	3.67±0.05	6.23±0.11	10.71±0.10
2	29.43±0.08	25.35±0.36	13.24±0.45	14.46±0.09	21.66±0.52
3	36.12±0.23	31.91±0.47	16.34±0.13	20.02±0.01	26.47±0.34
4	42.27±0.12	38.30±0.89	21.49±0.26	27.56±0.23	33.07±1.23
5	51.19±0.24	44.73±0.11	27.37±0.23	32.22±0.52	41.75±1.34
6	56.64±0.23	52.62±0.11	34.93±0.23	38.85±0.14	47.97±0.19
7	60.32±0.23	54.48±0.69	41.29±0.32	45.19±1.31	54.79±0.26
8	62.78±2.28	73.79±0.98	52.67±0.14	49.08±0.42	70.11±1.29

***In-vitro* drug release:** The release of active pharmaceutical ingredient from the emulgel was varied according to polymer concentration. The drug release from its emulsified gel formulation can be categorized in the following ascending order: EG4 < EG3 < EG8< EG6 <EG1 <EG9 < EG7 < EG5<EG2, Where the amounts of release of drug after 8 hours were 49.08%, 52.67%, 56.12%, 59.97%, 62.78%, 65.38%, 68.90%, 70.11%, 73.79% respectively. The

progressive augment in the amount of drug diffusion through memberane from formulation credited to gradual dwindle in the concentration of polymer. It has been recapitulated that, if we amplify the concentration of polymer, the diffusion of drug through the memberane also diminishes. The cumulative % of drug release profile of all the formulation batches has been shown in Table 2 and 3 and graph is plotted between cumulative % drug release versus time as shown in Figure 5.

Table 4: *In-vitro* drug release of formulations EG6 to EG9

Time (h)	EG6	EG7	EG8	EG9
1	7.36±0.12	4.92±0.09	9.93±0.07	8.43±0.14
2	14.07±0.08	14.75±2.63	21.46±0.11	16.09±0.27
3	22.87±1.23	23.37±0.33	26.12±1.34	25.38±1.04
4	29.45±0.24	29.5±1.96	33.08±1.23	31.53±0.45
5	33.63±0.17	34.37±0.25	38.98±0.43	38.59±0.17
6	38.64±2.10	40.56±0.28	43.16±0.31	43.52±0.31
7	46.32±0.13	47.37±1.50	47.59±0.23	47.94±0.34
8	59.97±2.15	68.90±1.23	56.12±0.27	65.38±0.23

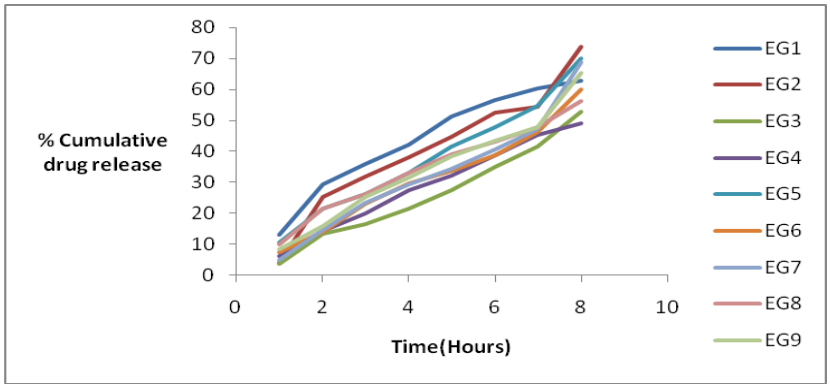

Figure 4: *In-vitro* drug release of different formulations (EG1-EG9)

Release kinetics of selected formulation (EG5 & EG1): The results obtained in in-vitro release studies were plotted in diverse kinetic models. Regression coefficient (R2) values of different kinetic models are shown in Table 5. This indicated that the release data was best en suite with Higuchi model kinetics because the value of R2 is superior in this model. Higuchi equation describes the diffusion release mechanism, so formulations track on the diffusion mechanism of drug release.

Table 5: Regression co-efficient (R2) values of kinetic models for formulation EG5 and EG1

Formulation code	Zero-order	First order	Higuchi model	Peppas model
EG5	0.9563	0.9487	0.9792	0.9653
EG1	0.8767	0.8489	0.9588	0.9328

***In-vivo study* of the emulgels (Anti-inflammatory activity):** This study was measured by applying emulgel EG5 topically at site of inflammation and also at a site away from inflammation because emulgels were showing elevated *in-vitro* release in comparison to marketed formulation whereas skin maintenance was found to be insignificant in emulgels. The anti-inflammatory action of formulation EG5 was intended and it was compared with marketed preparation (Pirox gel, Cipla). The percent reticence of marketed formulation and EG5 are given in table figure 5.

Table 6: Spreadability of the formulation

Formulation code	EG5	EG1	Marketed formulation
Diameter of circle (mean ± SD , n=3)	3.13 ± 0.11	3.77 ± 0.20	2.27 ± 0.25

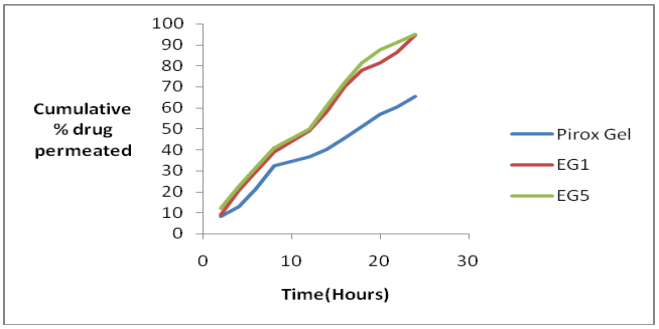

Figure 5: ***Percentage inhibition of inflammation***

Stability studies: Stability study was performed on optimized batches EG1 and EG5 at ambient conditions. The results obtained after 1 month time period are shown in table 7.

Table 7: Stability studies

Before			After		
Appearance	**pH**	**Drug content**	**Appearance**	**pH**	**Drug content**
yellowish white viscous creamy	5.98 ± 0.34	98.29 ± 1.11	yellowish white viscous creamy	6.07 ± 1.12	98.75 ± 0.98

Conclusion

Topical emulgels of piroxicam were formulated and characteized to physicochemical studies *i.e.* rheological studies, spreading coefficient studies and extrudability test, *in vitro* release studies and *ex vivo* release studies through rat skin. *In vitro* release of the tests formulations were performed to determine drug release rate from emulgel. *Ex vivo* drug release was also performed in which formulation EG1 and EG5 showed best release of 62.78% and 65.38% in 8 h respectively. The formulations EG1 and EG5 were comparable with marketed topical gel. So piroxicam emulgel can be used as an anti-inflammatory agent for topical drug delivery.

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