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Development and *In Vitro* Characterization of Piroxicam Loaded Emulgel for Topical Delivery

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ABSTRACT

Inflammation is the response to an injurious stimulus. It can be evoked by a wide variety of noxious agents (*e.g.*, infections, antibodies, or physical injuries). Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory anti-rheumatoid property. The purpose of this study was to develop an emulgel formulation of piroxicam, using methyl cellulose (MC) as gelling agent. The influence of the gelling agent and the concentration of both oil phase and emulsifying agent on the drug release from the prepared emulgels were investigated using 2^3 factorial designs. The formulation was found to be efficient with good physical appearance, spreadability, percentage drug content and release profile. The prepared formulations were characterized for various parameters like color, pH (5.5-6), spreadability, drug content and viscosity. All the formulations showed better rheological profile. *In vitro* drug release study was performed by locally fabricated membrane bag method and was found to be ~75 % in 24 hours.

1. INTRODUCTION

Piroxicam is a potent anti-inflammatory drug. It is used in treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gout disease. It has prolonged half life of about 45 hrs. It is a poorly water-soluble drug and when administered orally it may cause bioavailability problems due to its poor solubility and dissolution rates in biological fluids (Kiran *et al., 2010*). It also possesses analgesic and antipyretic properties. Although the drug is well absorbed following oral administration, gastric irritation is still the most serious adverse effect associated with conventional route of drug administration (Velmurugan *et al ., 2010*). Piroxicam is weakly acidic and highly lipophilic anti-inflammatory drug available for oral, parenteral and topical administration. The drug inhibits the synthesis of prostaglandins in inflammation (Moghimipour *et al., 2009*).

Delivery of drugs to the skin is effective for local dermatological disorders. This route of drug delivery has significantly improved due to its potential benefits including avoidance of first pass effect, gastrointestinal (GIT) irritation, and metabolic degradation associated with oral administration. Due to the first pass effect, only 25-45 % of the orally administered drug reaches the blood circulation. In order to bypass these limitations the emulgel formulation has been proposed for topical application (Jain *et al., 2010*). Use of topical agents requires a consideration of the factors that influence percutaneous absorption. Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, and through the sebaceous follicle.

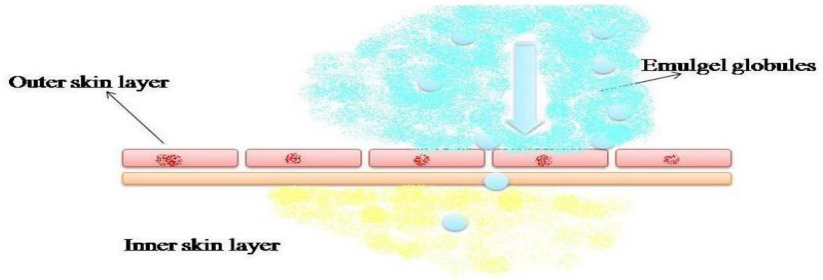

Fig. 1. Drug penetration through skin

The surface of the stratum corneum presents more than 99 % of the total skin surface available for percutaneous drug absorption. Passage through this outermost layer is the rate limiting step for percutaneous absorption including the establishment of a concentration gradient, which provides the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient) and drug diffusion across the layers of the skin (Patel *et al*., 2011).

There are primary three mechanisms for topical drug absorption: transcellular, intercellular, and follicular. Most of the drugs pass through the tortuous path around corneocytes and through the lipid bilayer to viable layers of the skin. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed onto the skin have been used to improve pain and anti-infective property at the site of action. It includes gels and creams for vaginal yeast infections, for skin infection and to control arthritic pain. New technologies for transdermal drug delivery allow other drugs to be absorbed through the skin. It can be used to treat not only various affected areas of skin but also for systemic drug delivery. In this context skin care and topical treatment of dermatological conditions a variety of vehicles ranging from solid to semisolid liquid preparation are available to clinician and patients. Within the major group of semisolid preparation the use of emulgels has expanded both in cosmetics as well as in pharmaceuticals (Khullar *et al*., 2011).

Emulgels are emulsions, either of the oil-in water or water in-oil type, which are converted into gel upon addition of a gelling agent. They have high patient acceptability since they possess the advantage of both emulsions and gels. Therefore, recently it is used as vehicles to deliver various drugs to skin in controlled manner. Emulgels are gaining importance owing to their better applicability in comparison to conventional formulation such as creams and ointments. Additionally they have faster and complete release of drug from the vehicle into the skin and therefore, better therapeutic efficacy as compared to creams, ointments (Magdy *et al.,* 2004). Furthermore, they offer ease for application on hairy skin due to absence of greasiness and lack of residues upon application. (Sachin et *al.*, 2011).

2. MATERIALS AND METHODS

Piroxicam (PCM) was kindly supplied as a gift sample by Pfizer Pharmaceutical India Pvt. Ltd (Mumbai, India). Methyl cellulose was purchased from Loba Chemie Pvt. Ltd. (Mumbai, India) and polyethylene glycol was purchased from Bengal Chemical and Pharmaceutical Ltd. (Kolkata. India). All other chemicals were of analytical grade and were used as received.

2.1 Preparation of emulgel

The gel was prepared by dispersing methyl cellulose (MC) in heated purified water (80°C), and the dispersion was cooled and left overnight. The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl paraben was dissolved in polyethylene glycol (PEG) whereas drug was dissolved in ethanol, and both solutions were mixed with the 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 cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel (Magdy *et al., 2004*). The composition of different emulgels is presented in Table 1. Eight piroxicam emulgel formulations were formulated.

Table 1. Composition (in %) of different emulgel formulations

Ingredient	Type	P1	P2	P3	P4	P5	P6	P7	P8
Piroxicam	Fix	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MC	Fix	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Liq. Paraffin	Variable	5	7.5	5	5	7.5	5	75	7.5
Tween 20	Variable	0.6	0.6	0.6	1	1	1	1	0.6
Span 20	Variable	0.9	0.9	1.5	0.9	0.9	1.5	1.5	1.5
PEG 400	Fix	5	5	5	5	5	5	5	5
Ethanol	Fix	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben	Fix	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Distilled water	Fix	100	100	100	100	100	100	100	100

Abbreviations: MC-methylcellulose, PEG-Polyethyleneglycol

2.2 Characterization

2.2.1 Color and pH

The prepared emulgel formulations were inspected visually for their color and pH. The pH values of 1 % aqueous solutions of the prepared emulgels were measured by a pH meter at working temperature of 27±1^{o}C.

2.2.2 Spreadability

Spreadability was determined by modified wooden block and glass slide apparatus. The apparatus consisted of a wooden block with fixed glass slide and a pulley. A pan was attached to another glass slide (movable) with string. A measured quantity of ointment was placed in the fixed glass slide, the movable glass slide with a pan attached to it, was placed over the fixed glass slide, such that the ointment was sandwiched between the two slides for 5 min. About 50 g of weight was added to the pan. Time taken for the slides to separate was noted. Spreadability was determined using the following formula (Akanksha et *al*., 2009).

Spreadability g/s =mass (gm)/time (s)

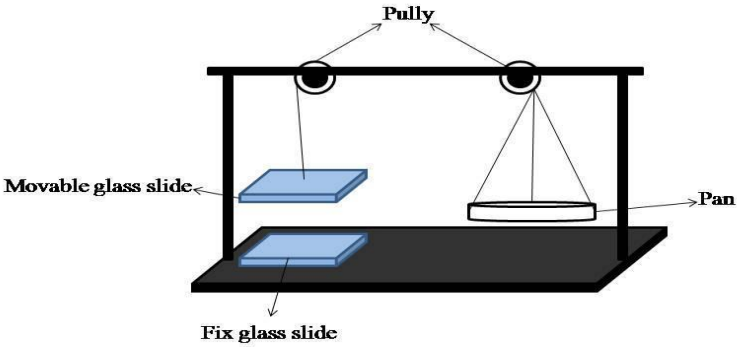

Fig. 2. Glass slide apparatus for determining spreadability

2.2.3. Drug content

One ml of prepared emulsion was taken and dissolved in 10 ml of solvent. The solution was filtered and analyzed spectrophotometrically at 352 nm.

2.2.4 Morphology of emulgel preparation

2.2.4.1 Optical microscopy

Morphological examination of emulgels was conducted by optical microscopy (Labomed, Leica ATC 2000, India) fitted with digital optical camera.

2.2.4.2 Transmission electron microscopy

The emulgel formulations were examined by transmission electron microscopy (CM12 Philips). The sample of emulgels was placed on carbon coated copper grids for visualization.

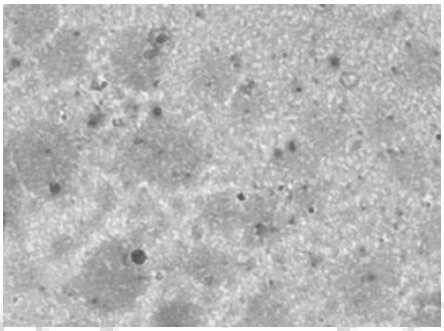

Fig. 4. TEM image of piroxicam emulgel

Table 2. Evaluation of emulgel formulations for different parameters

Formulation	Color	pH	Spreadability (g/s)	Drug content (µg/ml)
P1	White	5.5	5.50	33.6
P2	Pale yellow	6.0	0.38	33.4
P3	Light yellow	6.0	1.85	33.9
P4	White	6.0	25.00	33.5
P5	Light yellow	5.5	0.47	33.6
P6	White	6.0	25.00	33.9
P7	Pale yellow	6.0	1.16	33.9
P8	White	6.0	16.60	34.0

2.2.5 Rheological studies

The viscosity measurements of various formulations were performed using Brookfield digital viscometer (spindle: low viscosity -2) at 10, 20, 50 and 100 rpm.

2.2.6 *In vitro* release profile

This study was carried out by modified membrane bag method. The *in vitro* release was quantified as a function of time. An egg membrane was attached to the lower portion of glass cylinder tube. One gm of piroxicam emulgel formulation was placed in the modified membrane bag and this was coupled to diffusion cell containing receptor compartment filled with phosphate buffer saline (PBS, pH 7.4). The entire system was maintained at 37±0.5^{o}C with continuous stirring at 200 rpm. Samples were withdrawn from receptor compartment at predetermined intervals of time and replaced by fresh medium. The amount of drug release was quantified by UV spectrophotometer at 352 nm.

Fig. 3. In vitro release of drug from various emulgel formulations

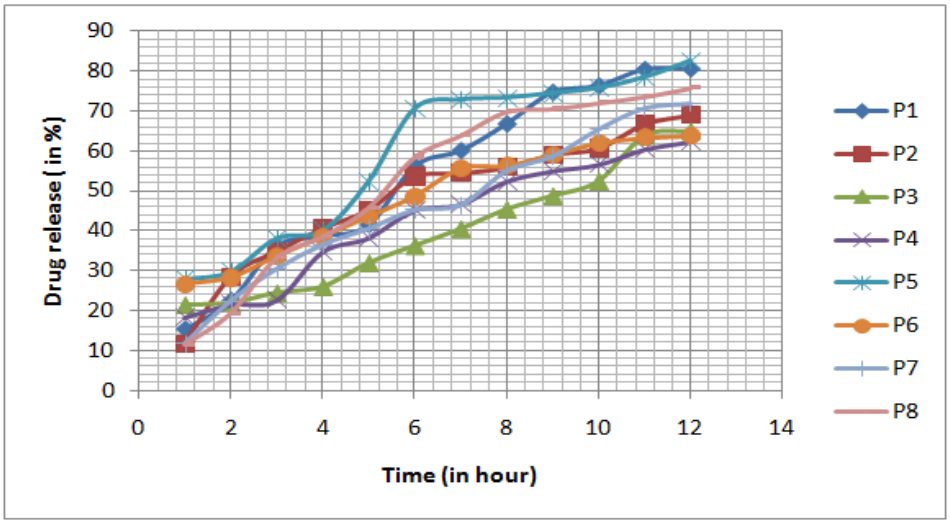

Table 3. Release kinetic data of different emulgel formulations

Formulation	Release kinetics				
	First order	Higuchi	Hixson	Peppas	
				R^2	N
P1	0.9790	0.9297	0.9810	0.9804	0.6874
P2	0.9120	0.9645	0.8458	0.9663	0.5277
P3	0.8799	0.8862	0.8720	0.9257	0.6684
P4	0.9337	0.9610	0.8953	0.9757	0.5874
P5	0.9210	0.9276	0.8758	0.9287	0.5214
P6	0.7669	1.9683	0.6592	0.9773	0.4477
P7	09819	0.9435	0.9702	0.9906	0.6783
P8	0.9172	0.9815	0.9683	0.9554	0.6564

2.2.7 Globule size

Globule size and size distribution was determined by Malvern zetasizer. One gm sample of emulgel was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetasizer and mean globule diameter and distribution was obtained.

2.2.8 Stability study

The stability studies were conducted by placing the prepared formulations at different temperatures and relative humidity for a period of three months.

Table 4. Stability profile of emulgel formulations (P8)

Sr. No.	Storage temp. (°C)	Duration (month)	Drug content(µg/ml)		Phase separation
			Initial	After 3 month	
1	25±2	3	34.0	32.04	Nil
2	4±2	3	34.0	31.19	Nil
3	42±2	3	34.0	29.42	Nil

3. RESULTS AND DISCUSSION

3.1 Physicochemical characterization

3.1.2 Compatibility studies of Piroxicam and methylcellulose

The procured sample mixture of Piroxicam (PCM), methyl cellulose (MC) was studied by using FTIR spectra. The major peaks were found at around 3338 for -NH stretching, around 1629 for amide carbonyl stretching with second amide bands at 1528 stretching, 1435 for CH_3, C=C stretch, 1350 cm^{-1} for CH_3 symmetric, 1180 cm^{-1} for $–SO_2$-N- did not changed in the mixture. Hence it could be concluded that Piroxicam, and methyl cellulose were compatible with each other.

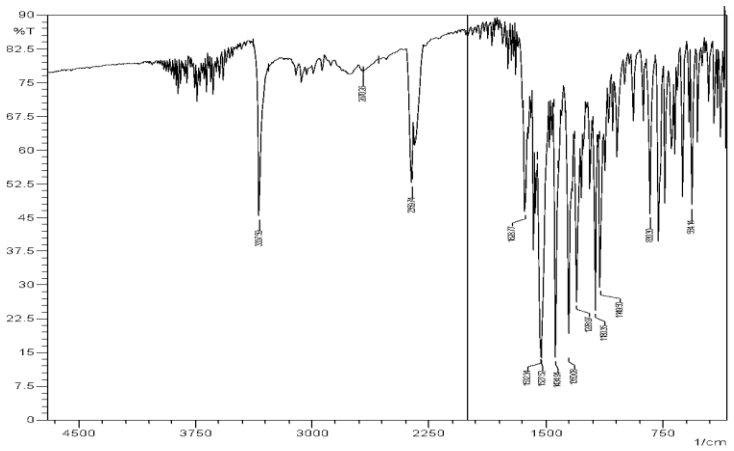

Fig. 5. IR spectra of piroxicam

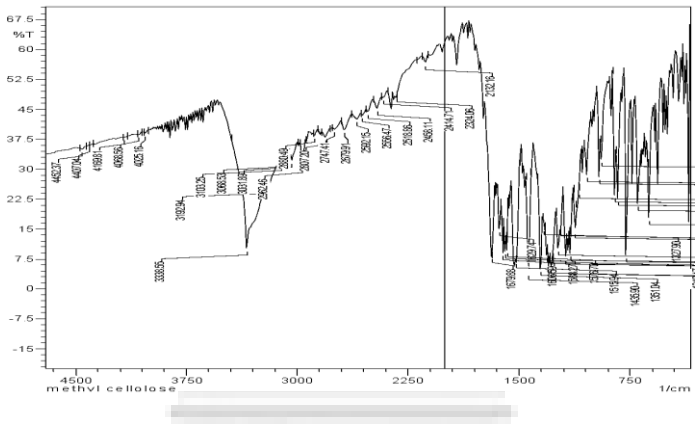

Fig. 6. IR spectra of methylcellulose

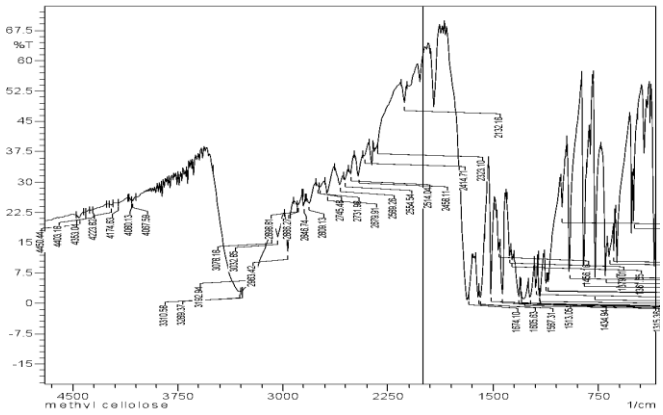

Fig. 7. IR spectra of methyl cellulose and piroxicam

3.1.3 Physical appearance

The prepared piroxicam emulgel formulations were found to be white viscous creamy preparation with a smooth and homogeneous appearance.

3.1.4 Color and pH of preparations

The pH values of all prepared formulations were found to be within the range 5.4-6.0 pH, which may be considered acceptable to avoid the risk of skin irritation and be compatible with skin (pH 5.5-6.0).

3.1.5 Spreadability

Spreadability denotes the extent of area where the gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. The spreadability of the emulgel formulations is presented in Table 2.

3.1.6 Rheological profile

All the prepared emulgel formulations exhibit a shear thinning behavior since the viscosity (the slope of the curve) decreased with increasing the shear rate. As the shear stress increased, the normally disarranged molecules of the gelling material are caused to align their long axes in the direction of flow. Such orientation reduces the internal resistance of the material and hence decreases the viscosity. All piroxicam emulgel formulations possessed thixotropic behavior. Thixotropy, or time dependent flow, occurs because the gel requires a finite time to rebuild its original structure that breaks down during continuous shear measurements. It is noteworthy that thixotrophy is a desirable characteristic in pharmaceutical preparations, in order to deliver an initially thick product as a thinner, easily spreadable material.

3.1.7 Drug content

The drug content of all the formulations was in the range of (33.0-34.0 µg/ml).

3.1.8 Morphology

Transmission electron microscopy displayed the morphological features of the emulgel formulation. TEM image confirmed that emulgel had globules with approximate diameter within the range of 1 µm and regular well identified and spherical shape of droplets were revealed.

3.1.9 Globule size in emulgel

Mean globule size of emulgel was found to be 656.0 nm and the polydispersity index (PDI) was found to be 0.982, indicating the homogeneity of the emulgel.

3.2 *In vitro* release profile

The release of the drug from its emulgel formulations can be ranked in the following order: F5 > F1 > F8 > F7 >F2 > F3 > F6 > F4, where the amounts of the drug released after 12 hours were 82.56 %, 80.66 %, 75.7 %, 71.98 %, 68.89 %,64.99 %,63.77 %, and 62.2 %, respectively. Thus, the greatest drug release was observed with formulations F8 according to drug release kinetic data. This finding may be due to the presence of liquid paraffin and the emulsifying agent at their high levels respectively, which leads to an increase in the hydrophilicity of the emulgel, which in turn facilitates penetration of the release medium into the emulgel and diffusion of the drug from the emulgel.

3.3 Stability studies

All the prepared emulgel formulations were found to be stable upon storage for 3 months, and no change was observed in terms of physical appearance, pH, rheological properties, and drug release.

4. CONCLUSION

Emulgel was successfully prepared by using methyl cellulose as gelling agent, Tween-20 and Span-20 as emulsifying agent, distilled water as aqueous phase and liquid paraffin as oil phase. The formulation was found to be efficient with good physical appearance, spreadability and percentage drug content, release profile and there is scope of scale up of the batches to the commercial level.

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