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DEVELOPMENT & CHARACTERIZATION OF KETOPROFEN EMULGEL FOR TOPICAL DELIVERY

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ABSTRACT

The major objective behind this formulation is to enhance the topical delivery of hydrophobic drug (ketoprofen) by formulating ketoprofen Emulgel using high molecular weight water soluble polymer of Hydroxypropyl methylcellulose (HPMC), Carbopol 940, CMC. with an objective to increase transparency and spreadability. The prepared emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, extrudability, *in vitro* drug release, Stability and pharmacokinetic studies. All the prepared emulgel showed acceptable physical properties, homogeneity, consistency, spreadability, viscosity and pH value. The formulation noted as F1 showed comparable percentage of drug release when they compared with standard diclofenac sodium emulgel. In addition to this, The *in vitro* release rate of emulgel was evaluated using Diffusion cell containing dialysis membrane with phosphate buffer pH 7.4 as the receptor medium. The results of the present study show that, the Emulgel was found to be stable with respect to physical appearance, pH, Rheological properties and drug content even at all temperature and conditions for three month and it is better suitable for topical delivery routes.

Keywords*:* Emulgel, Ketoprofen, Extrudability, Rheological properties.

INTRODUCTION

In the past, the most commonly applied systems were topically applied lotions, creams & ointments for dermatological disorders. But some of this formulation causes side effect which provided the path for other formulations like trans dermal drug delivery system. Trans dermal drug delivery system (TDDS) established itself as an integral part of novel drug delivery systems and it is defined as self-contained, discrete dosage forms which when applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation. Moreover, the TDDS obviates specific problems associated with drugs such as gastrointestinal irritation, low absorption and decomposition due to hepatic first pass effect[1-4].

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). It is widely used as analgesic for patients with rheumatic disease, joint disorders such as ankylosing spondylitis, osteoarthritis. Its molecular weight equal to 254.28, pKa of 5.94, partition coefficient of 0.97 and it is slightly soluble in water, freely soluble in solvents like acetone ,ethanol ,ether, chloroform, Ethyl acetate and di-methylformamide [5-6].

An emulgel is a jellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or oil-in-water (O/W) type with a gelling agent[7]. Due to solubility problems, most of lipophilic drugs cannot be formulated directly as hydro gel. [8, 9] For this reason; emulgel provide better stability and release of the lipophilic drug in comparison with simple hydrogel base. When gels and emulsions are used in combined form the dosage forms are referred as emulgels. In recent years, there has been great attention in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase [10-13].Hence, the aim of this work was to develop and characterize an emulgel formulation of ketoprofen, using Carbopol 940,CMC, Carbopol940+ HPMC and CMC+HPMC as gelling agent & penetration enhancer i.e.propylene glycol.

MATERIALS & METHODS

Drugs & Chemicals

Ketoprofen, Carbopol 940, CMC & HPMC K100M was procured from Yarrow chemical product.All other chemicals used were analytical grade and used without any further chemical modification.

Pre formulation study

The drug was characterized for the physiochemical and spectral properties and was compared with the standard. Drug identification was done by using the UV spectrophotometry whereas physical appearance of drug was observed and compared with the pharmacopeia specification.

Preparation of Emulgel

The oily phase of emulsion was prepared by dissolving span-80 in light liquid paraffin and the aqueous phase is prepared by mixing tween 80 in purified water. Ketoprofen was dissolved in ethanol where as methyl paraben was mixed with propylene glycol and both solutions were mixed with aqueous solution contains tween 80. The two emulsion phases were heated separately to 70^0C-80^0C, then adding the organic phase with continuous stirring with the aqueous phase .Then, Accurately weighed quantity of carbopol-940, CMC, Carbopol+ HPMC combination

and CMC+HPMC combination was taken in a previously dried beaker and 25 ml of distilled water was added to it. It was mixed well using mechanical shaker with constant stirring. More distilled water was added to it to maintain the consistency of the gel. The pH of the formulation was adjusted to 6.0 to 7.0 using triethanolamine. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Ketoprofen emulgel formulation [14].

Evaluation of Emulgel

The stable storage condition of prepared emulgel for drug in solid state and identification of compatible percipients for formulation was done by FTIR and observed for physical verification for their color, homogeneity, consistency and phase separation[15].pH of the formulation was determined by using digital pH meter [16].

Table 1 Composition of Ketoprofen Emulgel Formulation (%w/w)

Ingredients(%w/w)	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
	Emulsion											
Ketoprofen	1	1	1	1	1	1	1	1	1	1	1	1
Light Liquid paraffin	25	25	25	25	25	25	25	25	25	25	25	25
Tween 80	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Span 80	1	1	1	1	1	1	1	1	1	1	1	1
Propylene glycol	5	5	5	5	5	5	5	5	5	5	5	5
Ethanol	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Purified water	q.s											
Gel												
Carbopol 940	1	1.5	2									
CMC				3	3.5	4						
HPMC+CMC							1	1.5	2			
HPMC+Carbopol 940										1	1.5	2
Purified water	q.s											
Emulsion : Gel	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Triethanolamine was added to adjust the pH of all formulations from 5.5 to 6.5												

Measurement of viscosity [17]

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 63. Briefly, The formulations added to the beaker and allowed to settle down for 30 min at the assay temperature (25±1ºC) 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 50

rpm for 10 min and the viscosity reading was noted.

Extrudability

The prepared emulgel formulations were filled in clean, lacquered aluminum collapsible tubes with a 5 mm opening nasal tip. Extrudability was then determined by measuring the amount of gel extruded through the tip when a constant load of 1 kg was placed over the pan.

The extrudability of prepared Emulgel was calculated by using following formula.

$$\text{Extrudability} = \frac{\text{Amount of gel extruaded from the tube x 100}}{\text{Total amount of gel filled in the tube}}$$

Drug content study

Drug content study was done to determine the amount of the drug present in the certain quantity of the formulation. Briefly 1 g of the formulation into 10 ml volumetric flask added 1 ml methanol in it and shake well and make up the volume with PBS pH 7.4. The Volumetric flask was kept for 2 hr and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered the mixer then measured the absorbance by using spectrophotometer at 260 nm.

Drug Content = (Conc. × Dilution Factor × Vol. taken) × Conversion Factor

***In-vitro* Drug release study**

The *in vitro* drug release studies of the Emulgel were carried out on Diffusion cell using egg membrane. This was clamped carefully to one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was applied on to the surface of egg membrane dialysis to membrane. The receptor chamber was filled to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable time interval and analyzed for drug content by UV visible spectrophotometer at 260 nm after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug release across the egg membrane was determined as a function of time and calculated using standard calibration curve.

Details of dissolution testing:

- Dissolution media: Phosphate buffer saline pH 7.4
- Speed: 50 rpm
- Aliquots taken at each time interval: 1 ml
- Temperature: 37±20C
- Wavelength: 260 nm

Accelerated stability studies of Emulsion

The formulation were packed in aluminium collapsible tube and studies were carried out for 90 days by keeping at $40^0$to 2^0C and 75+5% RH samples were withdrawn on 30^{th} ,60^{th} and 90^{th} day and checked for changes in physical appearance ,viscosity ,drug content ,pH and *invitro* studies through dialysis membrane.

Comparison of selected formulation of ketoprofen Emulgel with Marketed Formulation (diclofenac sodium).

Marketed formulation was evaluated for *in vitro* drug release studies. The *in vitro* release profiles were compared with the selected formulation.

RESULTS AND DISCUSSION

Physical Appearance:

Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed

Table. 2 Physical parameters of Emulgel formulations

S.No	Formulation code	Colour	Phase separation	Homogeneity	Consistency
1	F_1	White	None	Excellent	+++
2	F_2	White	None	Excellent	+++
3	F_3	White	None	Excellent	+++
4	F_4	White creamy	None	Fair	+
5	F_5	White creamy	None	Fair	+
6	F_6	White creamy	None	Fair	+
7	F_7	White	None	Good	++
8	F_8	White	None	Fair	+
9	F_9	White	None	Fair	+
10	F_{10}	White	None	Good	++
11	F_{11}	White	None	Good	++
12	F_{12}	White	None	Good	++

Table. 3 Viscosity of Emulgel formulations

Formulation	viscosity
F_1	8482
F_2	17321
F_3	18241
F_4	1761
F_5	18120
F_6	1350
F_7	26450
F_8	27650
F_9	21720
F_{10}	2542

F_{11}	2252
F_{12}	18426

Table. 4. Extrudability of Emulgel formulations

Formulation	Extrudability
F_1	16
F_2	13.33
F_3	18.9
F_4	20.5
F_5	21.31
F_6	26.70
F_7	17.51
F_8	18.06
F_9	26.06
F_{10}	18.26
F_{11}	21.08
F_{12}	24.81

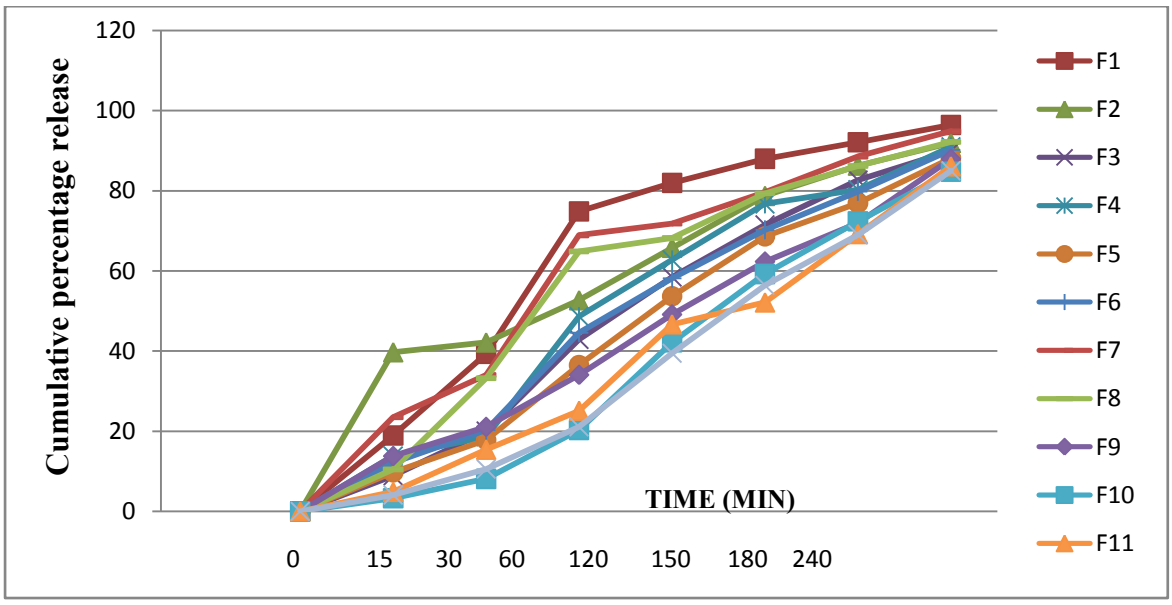
Table. 5 Drug content of Emulgel formulations

Formulation	Drug content
F_1	99.9
F_2	96.2
F_3	97.89
F_4	97.14
F_5	95.89
F_6	82.362
F_7	99.6
F_8	91.005
F_9	92.315
F_{10}	89.0012
F_{11}	90.96
F_{12}	98.13

***In-vitro* drug release study:**

The release of ketoprofen from the emulgel was varied according to concentration of polymer. The release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F1 > F7 > F8> F2 > F4>F6 > F3> F5> F9 > F11> F12> F10. The studies were performed at pH 7.4 using phosphate buffer. All the formulations were subjected to dissolution study for a period of 4hrs.Volume of dissolution medium used is 28ml and volume of sample withdrawn is 1ml.

Figure . 1.Drug content of Emulgel formulations



Stability Study

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

Comparison with Marketed Formulation

The cumulative percentage drug release of marketed formulation of diclofenac sodium emulgel is compared with our formulation (i.e.F1) by comparing the percentage of drug diffused.

Table. 6 Shows the cumulative percentage drug release

Time (min)	Test formulation (F1)	Marketed formulation (Volteran emulgel)
60	74.87%	61.56%

Conclusion

In the present study, Ketoprofen showed maximum absorption at a wavelength of 260 nm in pH7.8 using phosphate buffer. The value of correlation coefficient was found to be r^2 = 0.9959, which showed linear relationship between concentration and absorbance. Thus, it can be noted that, beer's law was obeyed. Preformulation study for drug excipients compatibility by FT-IR showed no interaction between drug and selected excipients. Viscosity studies of various formulations revealed that formulation F1 was better comparable to others. From all the developed formulation i.e. (F1 to F12), F1 shows better drug diffusion, good Rheological properties & good extrudability which more suitable for topical delivery as emulgel which is comparable with Marketed formulation of diclofenac Emulgel.

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