



Ketoprofen Emulgel: Preparation, Characterization, and Pharmacodynamic Evaluation

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ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory drug that has two major problems when administered orally; it is an insoluble drug and has irritant effect on GIT lead to ulceration and bleeding. The aim of this study was to overcoming these two problems through preparation of this drug as topical emulgel. Hydroxypropyl celluloses (HPC) and hydroxypropylmethyl celluloses (HPMC) were the two polymers used as gelling agents, the influence of type and concentration of them on the release of ketoprofen was investigated. Oleic acid, tween, carveol, terpene, and isopropyl alcohol were used as penetration enhancers, and effect of these enhancers on diffusion of ketoprofen a cross semi-permeable membrane was tested. The optimized formula was tested for its anti-inflammatory activity on carragenan induced rat paw edema model. Results revealed that the emulgel formulations exhibited high drug release especially at low polymer concentration and the release was follow diffusion controlled mechanism. All enhancers showed enhancement in ketoprofen penetration specially the optimized formula contain Ketoprofen 2%, HPC 2%, and 5% Oleic acid which exhibited improved anti-inflammatory activity compared to commercially available gel. So it can be concluded that topical emulgel enhanced permeation of ketoprofen and possessed an effective anti-inflammatory activity, with avoidance of GIT adverse effect.

Keywords: Ketoprofen, Emulgel, Penetration Enhancer, Rat paw, Oleic acid.

INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID). It is widely used as analgesic for patients with rheumatic disease¹, joint disorders such as ankylosing spondylitis, osteoarthritis. Its molecular weight equal 254.29, pKa of 5.94, partition coefficient of 0.97. It is practically insoluble in water, freely soluble in acetone, ethanol and methylene chloride².

Most of the ketoprofen adverse reactions are upper GIT complaints such as nausea, dyspepsia¹. Less frequent are CNS symptoms (headache, drowsiness, vertigo and insomnia)³. The risk of GIT bleeding and ulceration is increased when administered with corticosteroids⁴.

In order to eliminate the adverse effects of NSAIDs, the development of transdermal formulations was employed.

Several topical dosage forms may be utilized to deliver NSAIDs. One of the best topical dosage forms is emulgel⁵. The absorption of a drug in those formulation to the systemic circulation requires dissolution and release from formulation, partitioning and diffusion through SC, then partitioning from the SC into the aqueous epidermis⁶.

Addition of a chemical penetration enhancer to the delivery system will enhance drug partitioning into the SC⁷, these enhancer should be inert, non toxic, compatible with the drugs, and the onset of penetration-enhancing action should be immediate. Most common enhancers are alcohols, polyalcohols, amides, pyrrolidones, fatty acids, sulphoxides, esters, amines, terpenes, and surfactants⁸⁻¹⁰.

An emulgel is a gellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or O/W with a gelling agent¹¹. The main advantage of the emulgel that lipophilic drugs can be easily formulated into gels¹². Due to solubility problems, most of lipophilic drugs cannot be formulated directly as hydrogel¹³. For this reason; emulgel provide better stability and release of the lipophilic drug in comparison with simple hydrogel base. Other advantages for emulgel include; better stability, high loading efficiency, more production economical with low cost. The main constituents in emulgel preparation include water, oils mainly mineral oils as paraffin oil either used alone or mixed with vaseline or wax^{14,15}, emulsifiers, gelling Agent, and permeation enhancers¹⁶⁻¹⁷.

The aim of this work is to formulate the ketoprofen as emulgel in order to eliminate the GIT side effect, to incorporate this insoluble drug in a hydrophilic gel matrix, and to enhance the percutaneous absorption and pharmacodynamic of this drug.

MATERIALS AND METHODS

Materials

Ketoprofen was purchased from Sigma (St. Louis, MO, USA). Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Aqualon, U.K. Tween 80, Span 80, C.B.H. Lab Chemicals, Nottingham, U.K. Sodium chloride, disodium hydrogen phosphate and potassium dihydrogen phosphate, Prolabo, France. Cellulose nitrate membrane filter, diameter pore: 10 µm pore size, Albet Company, Spain. Isopropyl alcohol, Merck, Germany. Dimethylformamide, Merck, Germany. Oleic acid, Merck, Germany.



Methodology

Preparation of Ketoprofen Emulgels

The preparation of emulsion was same in all the formulations. The emulgel was prepared according to Jain et al.¹⁸. The aqueous phase prepared by mixing tween 80 in purified water, and the oil phase composed of span 80 in liquid paraffin. ketoprofen was dissolved in ethanol whereas propyl paraben was mixed with propylene glycol and both solutions [ethanolic solution and propylene glycol solution] were mixed with the aqueous solution contain tween 80. The two emulsion phases were heated separately to 70 °C–80 °C, then adding the organic phase was mixed with continuous stirring with the aqueous phase. The previously prepared gel base then mixed with the emulsion in 1:1 weight ratio to prepare the final emulgel formula. Different formulations were prepared using varying types and concentration of gelling agent according to the procedures mentioned below.

1) Preparation of Hydroxypropyl methylcellulose (HPMC) emulgel:

The weighed quantity [1 gm, 3 gm, and 5 gm] of hydroxypropyl methylcellulose powder will sprinkle gently, into the vortex of 50 ml purified water in 100 ml beaker, using homogenizer for stirring, until thin dispersion, without lumps will form. The solution will kept overnight in the refrigerator to form the emulgel.

HPMC concentrations of 2% in (F 1), 6 % in (F 2) and 10 % in (F 3).

2) Preparation of Hydroxypropyl cellulose (HPC) emulgels:

The weighed amount of HPC [1, 3, and 5 gm] will sprinkle gradually into the vortex of 50 ml purified water, placed in a 100 ml beaker, and mixed with a homogenizer at a high speed until complete homogenization and disappearance of any lumps.

HPC gel bases will prepare at concentrations 2%, 6 %, and 10 % in formulae (F 4, F 5, and F 6 respectively).

In-Vitro Release of Ketoprofen from Different Emulgel

This test was done by using modified USP Dissolution test (Apparatus I). A glass cylindrical tube (6 cm in length and 2.25 cm in diameter) containing the emulgel was hunged in place of the basket and was tightly covered with a semipermeable membrane (100 µm pore size)

1 gm of emulgel contain 2% ketoprofen was placed in the cylindrical tube covered with the semipermeable membrane. The glass tube dipped in a 500 ml 0.2M phosphate buffered saline (pH 7.4). The test was carried out at 37°C+ 0.5°C, and rotation speed of 50 r.p.m.

Aliquots of 2 ml were withdrawn from the dissolution medium at 5, 15, 30, 60, 90, 120 and 150 minutes time intervals, replaced at each time with 2ml of buffer to maintain a constant volume.

The sample diluted with equal volume with buffered and the absorbance of the collected samples was measured

spectrophotometrically at λ_{\max} 255 nm using phosphate buffered saline as a blank. For comparison a commercially available product namely ketoprofen emulgel was also tested.

Kinetic Analysis of the In-Vitro Release Data of Ketoprofen

The data were analyzed to establish the order of drug release. The linear regression was used for analysis of the released data according to:

$$A) C_t = C_o - Kt \quad \text{For Zero order kinetics}$$

$$B) \log C_t = -Kt/2.303 + \log C_o \quad \text{For First order kinetics}$$

$$C) Q = [Dt (2A - C_s) C_s]^{1/2} \quad \text{For Higuchi diffusion model}$$

Where

A =total amount of drug in base per unit volume. D =diffusion coefficient

Cs=drug solubility in the base. Q =amount released per unit area at time t

Effect of Addition of Different Penetration Enhancers to A selected Formula on Permeation of Ketoprofen

Permeation enhancers such as 0.5% carveol, 0.5% terpene, 5% oleic acid, 5% isopropyl alcohol, were incorporated separately into a selected emulgel prepared according to formula 4 (2% Ketoprofen+ 2% HPC) which gave the most optimum results in all previous tests.

Five different formulae containing enhancers were prepared:

Formula 4-A: containing Ketoprofen 2% + HPC 2% (Control emulgel)

Formula 4-B: containing Ketoprofen 2% + HPC 2% + 0.5% carveol

Formula 4-C: containing Ketoprofen 2% + HPC 2% + 0.5% terpene

Formula 4-D: containing Ketoprofen 2% + HPC 2% + 5% Oleic acid

Formula 4-E: containing Ketoprofen 2% + HPC 2% + 5% isopropyl alcohol

Different formulations then subjected to test effect of those permeation enhancers on permeability of ketoprofen across semi-permeable membrane (0.01 cm thickness). The membrane samples were mounted on diffusion cells (2.25 cm² surface area). Weighted amount of emulgel contain 10 mg of ketoprofen putted on a side that facing upward. The other side of the membrane directing toward the buffer compartment filled with 5 ml buffer, which kept at 37 °C and stirred at 50 r.p.m. Then samples were withdrawn at time intervals 15, 30, 60, 120, 150, 180 and 240 minutes and replaced with equal volume of fresh phosphate buffered saline to maintain a constant volume.

The absorbance of the collected samples was measured spectrophotometrically at λ_{\max} 255 nm using phosphate buffered saline as a blank. For comparison a commercially available product namely Fastum gel was also tested.

Calculation of the Permeation Parameters of Ketoprofen across Semi-permeable Membrane

The permeation parameters of ketoprofen (Permeability coefficient [P], partition coefficient [K], diffusion coefficient [D], Apparent steady state flux [J_{ss}], enhancing factor [F_{en}], lag time [t_L], relative permeation rate [RPR]) were calculated from the penetration data.

Plotting the cumulative amount permeated versus time, and the slope represent [J_{ss}]

$$P = J_{ss} / C_o$$

Plotting amount permeated versus square root of time [D] was calculated from the slope obtained according to the following equation

$$D = (\text{slope} / 2 C_o) \cdot 2 \cdot \pi$$

[K] was calculated from P and D using the penetration barrier L with known thickness of semipermeable membrane (0.01 cm) from equation :

$$K = P \cdot L / D$$

[t_L] was calculated from equation : $t_L = L^2 / 6 D$

[F_{en}] = Cumulative amount permeated from formula / Amount permeated from control gel

[RPR] = P of the formula / P of the Commercial product

Pharmacodynamic of Ketoprofen from Different Emulgel Formulae

Adult male albino rats weighing 150-200 gm will use. They will divide into 2 groups each of 3 animals. Inflammation was induced by a subcutaneous injection of 0.05 ml of 1% carageenan solution into the planter tissue of the two hind paws before the application of the topical drug to the animals.

The topical products were applied to the left hind paw only of the rats after a period of 15 minutes and leave for 30 minutes insure contact of the formulae to the inflamed left hind paw of the rats. The mean increase in the volume of carageenan injected paws of rats treated with the drug (V_t) as well as that of the control right paw (V_c) were calculated by subtracting the volume of the left hind paw from the Volume of the right hind paw. After 0.5 hr, 1 hr, 1.5 hr, 2 hr and 2.5hr.

The percentage inhibition of the inflammation for each group was calculated from the mean effect in control and treated paws according to the following equation:

$$\% \text{ Inhibition in Edema volume} = [(V_c - V_t) / V_c] \times 100$$

RESULTS AND DISCUSSION

In-Vitro Release of Ketoprofen from Different Emulgels in saline phosphate buffer pH 7.4

The release of ketoprofen from the prepared emulgels was performed in order to study the effect of different polymers types and concentration on the release of ketoprofen aiming to select the best formula. Figures (1,2) shows the results of *in vitro* release. It appear that formulae F1,F4,F5 enhanced release of Ketoprofen when compared the commercially available Fastum gel and the percentage of ketoprofen released after 150 minutes from these formulations was 49.4%, 90.2%, and 68.9% respectively, while formulae F2, F3, F6 decreased extent of ketoprofen released when compared to commercially available gel, the percentage of ketoprofen released after 150 minutes from these formulations was 29.13%, 15.3%, and 42.2%, respectively.

Thus the tested formulations can be arranged according to their efficiency in increasing release of ketoprofen as following: F 4 (90.2%) > F5 (68.9%) > F1 (49.4%)

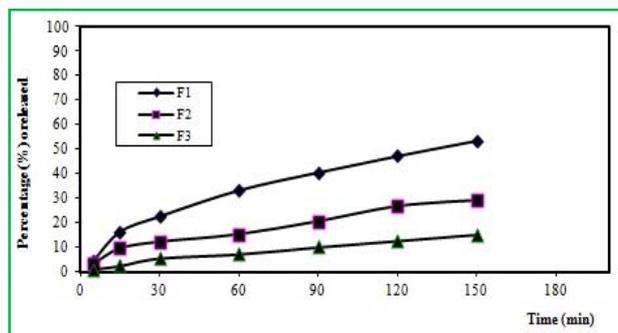


Figure 1: *In vitro* release profile of ketoprofen from HPMC emulgel in saline phosphate buffer pH 7.4

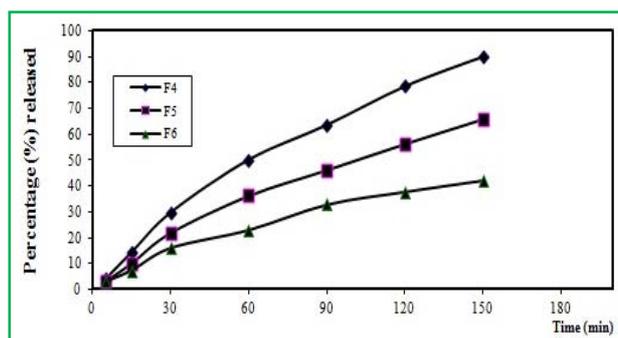


Figure 2: *In vitro* release profile of ketoprofen from HPC emulgel in saline phosphate buffer pH 7.4

It is clear from the above results that increasing polymer concentrations in formulae F3, F6 which contain polymers in their highest concentrations resulted in decreased percentage of drug release for all types of polymers. This is due to high viscosity, which will retard release of drug from emulgel base and by increasing concentration of polymer this leads to an increase viscosity of gel and thus retards release of drug. While formulae F1, F4 which contain polymers in low concentrations, resulted in low viscosity and higher release rate.

Kinetic Analysis of the Release Data

The data is illustrated in tables (1 and 2). It appears that the release of ketoprofen follows diffusion controlled mechanism. The cumulative amount of ketoprofen released from different emulgel bases was plotted against square-root of time. Linear plots ($r > 0.9$) for all formulations were produced, indicating that the release mechanism is in compliance with the Higuchi equation. The results are in agreement with Hassan et al.¹⁹ who reported that that the mechanism of release of ciprofloxacin and norfloxacin from gel bases obeyed Higuchi diffusion model mechanisms. Our findings are also in agreement with Fergany A²⁰, who reported that the mechanism of release of ketoprofen from NaCMC gel base follows Higuchi diffusion model mechanisms.

Table 1: Linear Regression of Release Data of Ketoprofen from Different Emulgel Bases.

Formulae	Linear Regression analysis Using correlation Coefficient (r^2) According to		
	Zero Order	First Order	Diffusion model
F1	0.9799	0.9012	0.9982
F2	0.9637	0.9557	0.9914
F3	0.9708	0.9896	0.9952
F4	0.9232	0.9670	0.9923
F5	0.9783	0.9821	0.9906
F6	0.9654	0.9730	0.9969

Table 2: Kinetic Analysis of Release Data of Ketoprofen from Different Emulgel Formulations.

Formula Number	Order of Release	R	K (mg%. min ^{-1/2})
F1	Diffusion	0.9982	4.694
F2	Diffusion	0.9914	2.486
F3	Diffusion	0.9952	1.390
F4	Diffusion	0.9923	8.739
F5	Diffusion	0.9906	6.319
F6	Diffusion	0.9969	4.073

Effect of Penetration Enhancers on Permeation of Ketoprofen A cross Semi-Permeable membrane

Figures (3) show the effect of incorporation of different permeation enhancers such as 0.5% carveol, 0.5% terpene, 5% oleic acid, 5% isopropyl alcohol on release of ketoprofen from emulgels prepared according to formula 4 (2% Ketoprofen+2%HPC) in comparison with commercial gel (reference). The cumulative amount permeated after 240 minutes were 2580, 2750, 2930, 3120, 2734, and 1814 $\mu\text{g}/\text{cm}^2$ for F4- A to E, and commercial gel, respectively.

It appears from the obtained results that all prepared formulation with enhancers gave higher results than control emulgel and commercial gel.

The maximal enhancement of ketoprofen permeation was obtained with formula F4-D (Contain Ketoprofen 2% + HPC 2% + 5% Oleic acid).

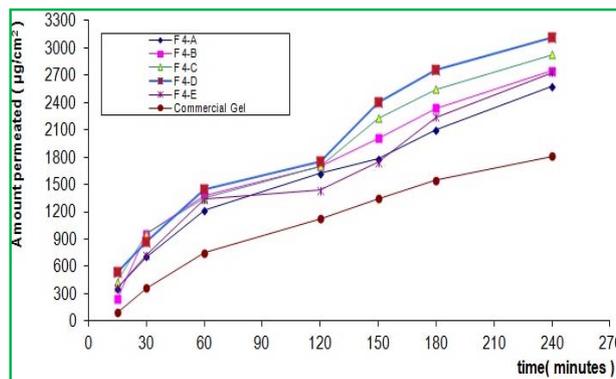


Figure 3: Cumulative amount of ketoprofen permeated across semi permeable membrane for formulae 4- A to 4- E, and commercial gel,

Table (3) shows the permeation parameters of ketoprofen from emulgels prepared according to formulae F4-A to E, in comparison with Fastum gel.

It appears that for all prepared formulae; the amount permeated at 240 minutes was higher compared to Fastum gel.

The tested formulae could be ranked in the following order: F4-D > F4-C > F4-B > F4-E > F4-A > Fastum gel.

The steady state flux [J_{ss}] was highest (12.134 $\mu\text{g}/\text{cm}^2\text{min}$) for formula F4-D and was lowest with Fastum gel (7.4421 $\mu\text{g}/\text{cm}^2\text{min}$).

The permeability coefficient [P] was highest (6.03 $\text{cm}/\text{min} \times 10^{-4}$) for formula F4-D and was lowest with fastum gel (3.77 $\text{cm}/\text{min} \times 10^{-4}$).

The Lag time [t_{lag}] was 2.12 min. for formula F4-D compared to 3.22, 2.68, 2.28, 3.21, 5.55 min. for Formula 4-A to C, F4-E, and Fastum gel, respectively. The decrease in the [Lt] of the tested formulae as in F4-D, lead to rapid onset of therapeutic effect.

Enhancing factor [F_{en}] was highest (1.21) for formula F4-D and was lowest with fastum gel (0.7). This may be due to highest enhancement of ketoprofen permeation was obtained with formula F4-D containing 5% oleic acid as enhancer.

Relative permeation rate [RPR] was >1 for all tested emulgels, which prove the usefulness and superiority of HPC as a base for ketoprofen specially for formula F4-D (Ketoprofen 2% + HPC 2% + 5% Oleic acid) which gave best results in all tests and results. Therefore, this formula [F4-D] was chosen for *in-vivo* investigation.

Pharmacodynamic of Ketoprofen From Different Emulgel Formulae

It is clear from table (4) that formula (F4-D) inhibited the carageenan-induced paw edema compared to the control group. In this respect the commercial gel form of Ketoprofen inhibited the carrageenan-induced paw edema by 38.341% compared to the control value (table 4). Formula (F4-D) showed a remarkable reduction in the paw edema by 65.198 % of the control value.



Table 3: Percutaneous Permeation Parameters of Ketoprofen across semi-permeable From Different Emulgel Formulations in Comparison with the Commercial Gel product

Formula	Cumulative amount at 240 min ($\mu\text{g}/\text{cm}^2$)	Jss $\mu\text{g}/\text{cm}^2\text{min}$	t_{lag} (min) $\times 10^{-4}$	P $\text{Cm}/\text{min}\times 10^{-4}$	K	D $\text{cm}^2/\text{min} \times 10^{-5}$	Fen	RPR
F4-A	2580	9.6435	3.22	4.88	0.94	5.161	—	1.29
F4-B	2750	10.645	2.68	5.34	0.86	6.22	1.09	1.41
F4-C	2930	11.435	2.28	5.76	0.79	7.293	1.17	1.52
F4-D	3120	12.134	2.12	6.03	0.76	7.859	1.21	1.59
F4-E	2734	9.8767	3.21	4.91	0.85	5.181	1.02	1.30
CommercialGel	1814	7.4421	5.55	3.77	1.25	3	0.7	—

Table 4: Antinflammatory activity of different formulation of Ketoprofen using carrageenan-induced paw oedema in rats

Formulation	Mean edema volume in ml	% Inhibition of control value
Control	0.931 \pm 0.03	0.000
Formula 4-D	0.324 \pm 0.04	65.198
Fastum Gel	0.574 \pm 0.02	38.341

CONCLUSION

On the basis of the previous finding the following could be concluded that the nature of the polymers used in preparation of gels and their concentrations showed an effect on release of ketoprofen from emulgel base. The maximal enhancement of ketoprofen permeation was obtained with formula F4-D (Contain Ketoprofen 2% + HPC 2% + 5% Oleic acid) which showed maximum cumulative amount permeated at 240 minutes, highest steady state flux [Jss], highest permeability coefficient [P], lowest Lag time [t_{lag}], highest Enhancing factor [Fen], greatest relative permeation rate [RPR], and significantly inhibited the carrageenan-induced paw edema and have superior ant-inflammatory activity.

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