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Ketoprofen: *In-vitro* release and percutaneous absorption in rats through polymeric gels

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ABSTRACT

Ketoprofen is a potent non-steroidal anti-inflammatory drug which is used for the treatment of rheumatoid arthritis. The oral administration of ketoprofen can cause gastric irritation and renal adverse effects. Topical application of the drug can bypass gastrointestinal disturbances and provide relatively consistent drug levels at the site of action. Since the efficacy of gels depends on the type of gel base and the concentration of the drug, four different polymers (carbopol 940, HPMC K_4M, sodium CMC and sodium alginate) were used at different concentrations and 1% concentration of ketoprofen. The general rank order of the drug release was found to be: carbopol > HPMC K_4M> sodium CMC > sodium alginate). The in-vivo percutaneous absorption of ketoprofen from different polymer gels was studied by carrageenan-induced paw edema in rats. The rank order of the percent edema inhibition was as follows: carbopol > HPMC K_4M> sodium CMC > sodium alginate.

Key words: ketoprofen, non-steroidal anti-inflammatory, carrageenan-induced paw edema test.

INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) with well established analgesic and antipyretic properties used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout [1]. Although ketoprofen is poorly water soluble it is rapidly absorbed, metabolized and excreted, it causes some gastrointestinal complaints such as nausea, dyspepsia, diarrhea, constipation and some renal side effects like other NSAIDs [2]. Topical NSAIDSs have several advantages over their systemically administrated counterparts they are simple to apply and deliver high drug concentrations locally into affected tissues while producing limited side effects at the application site for prolonged periods [3,4]. The main objective of this study is to prepare the topical formulations of ketoprofen and study the effect of different polymer bases on the *in-vitro* release and percutaneous absorption of ketoprofen.

MATERIALS AND METHODS

Ketoprofen was obtained from BEC Chemicals, Roha, Maharastra, HPMC K_4M from Colorocon, Goa, carrageenan from Sigma, triethanolamine from E. Merck, ethanol, glycerin, methyl-paraben and propyl- paraben, Carbopol 940, Sodium CMC and Sodium Alginate from S. D. Fine Chemicals, Mumbai.

Preparation of topical gels:
Topical gels were prepared by geometric dilutions using the dispersion method taking 1% w/w of ketoprofen using different gelling agents carbopol 940, HPMC K_4 M, sodium CMC and sodium alginate in varying concentrations using ethanol as a co-solvent, glycerin as a humectant, methyl-paraben and propyl-paraben as anti-microbial agents, triethanolamine was added in carbopol gels to adjust the pH of the formulations. The gels were prepared by

dispersing the specified quantity of polymer in distilled water with constant stirring at 900-1000 rpm [5]. During stirring 1% w/w of ketoprofen was dissolved in specified quantity of ethanol in a beaker, the other additives glycerine, SLS, methyl paraben, propyl paraben were also mixed, the liquid mixture was also added to the polymer dispersion. Finally a homogenous dispersion of the gels was obtained. In case of carbopol gels only, triethanolamine was finally added to the polymeric dispersion for formulating the gels; this is done to neutralize the pH of the carbopol which is necessary for gelling. The preparations were air cooled for 12 hours for setting and then packed in wide mouth plastic jars covered with screw capped plastic lid after covering the mouth with an aluminum foil. After complete dispersion the solutions were kept in dark for 24 hours for complete swelling of the polymers.

In- *vitro* drug release studies:
The release of ketoprofen from gels was studied at 37 ± 2^{o}C using a modified K.C cell with side-arm. The sortious cellulose acetate membrane was clamped between the donor and receptor compartments. The receptor compartment was filled with 75 ml of medium (phosphate buffer 7.4). The medium was stirred by external driven teflon coated magnetic bead. The temperature in the diffusion cell was maintained at 37 ± 2 ^{o}C by the hot water circulating in the surrounding water jacket. Gel 2 gm was placed on the membrane in an area restricted by a teflon ring ensuring no air between gel and membrane surface. For the next 6 hours, 2 ml. aliquots of sample were withdrawn at intervals of 30 minutes for 6 hours and analyzed for ketoprofen contents spectrophotometrically at a wavelength of 260 nm. The sample removed was immediately replaced with an equal volume of fresh phosphate buffer [6]. Studies were performed in triplicate runs and the mean values were used for the analysis of the data.

Mathematical evaluation:
Mathematical analysis of the release of ketoprofen from different gel formulations were carried out using the Higuchi equation for solution types of ointments [7].When the amount of drug released was plotted against the square of time, a straight line was obtained.

The diffusion coefficient of drug (D) was calculated using equation 1

$$Q = 2C_0 \left(\frac{Dt}{\pi}\right)^{\frac{1}{2}} \quad (1)$$

where Q: amount of drug released per unit area (mg/cm^2)Co: initial concentration of drug in the ointment(mg/cm^3) D: diffusion coefficient (cm^2/s); t: time (s).

The permeability coefficient [8]of Ketoprofen was calculated using equation2

$$P = \frac{q}{A \cdot C_0 \cdot t} \quad (2)$$

where P: permeability coefficient (cm/s); q: amount of drug released (mg); A: area of diffusion membrane (cm^2); Co: initial concentration of drug in the base (mg/cm^3); t: time (s).

The partition coefficient[9] of Ketoprofen between the gel base and the receptor medium was calculated using equation 3 where

$$K_{p=} \frac{P \cdot h}{D} \quad (3)$$

where Kp: partition coefficient; P: permeability coefficient (cm/s); D: diffusion coefficient (cm^2/s); h: thickness of the membrane (cm).

In-vivo percutaneous absorption of ketoprofen in rats:
Young male rats were used for the test of the anti-inflammatory activity of ketoprofen gels by the carrageenan-induced paw edema method [10, 11]. The edema induced by the injection of carrageenan solution is measured using a plethysmometer [12]. Six rats weighing 200 - 330 g were used to evaluate the effect of gels without and with the drug on the percutaneous absorption of Ketoprofen. 10 mg gel was applied to the plantar surface of the left hind paw of the mice by gently rubbing 50 times with finger. After three hours, the paw volume was measured before carrageenan injection and recorded as control (E_c). 0.01 ml of a 1% carrageenan solution was injected subplantarly into the same paw. Three hours after the carrageenan injection the paw was measured again and recorded as edema induced by carrageenan injection (E). The percent swelling of the paw was determined using equation 4.

$$\%\, Swelling = \frac{E - E_c}{E_c} \times 100 \quad (4)$$

Ec: control; E: paw edema induced by carrageenan injection.

Control group of the rats was treated only by the gels without the drug through the same procedure and the percent edema inhibition was determined using equation (4) which is the ratio of average swelling of the drug treated group to the average swelling of the control group.

$$\% \, Inhibition = \left(\frac{1 - \% \, Swelling \, of \, drug \, treated \, group}{\% \, Swelling \, of \, control \, group}\right) \times 100 \quad (5)$$

Statistical analysis:
The differences in the results of in-vivo studies were evaluated using one-way ANOVA.

RESULTS AND DISCUSSION

***In-vitro* drug release studies:**
The *in-vitro* data were subjected to various kinetic models like zero order, first order and Higuchi to determine the mechanism of drug release from the polymer matrix. The Higuchi plots were linear after an initial lag time which indicates diffusion controlled release from gels. The amount of ketoprofen released from different polymeric gels is shown in Figure1. The rank order of drug release from different gels was found as: carbopol > HPMC K4M> sodium CMC> sodium alginate.

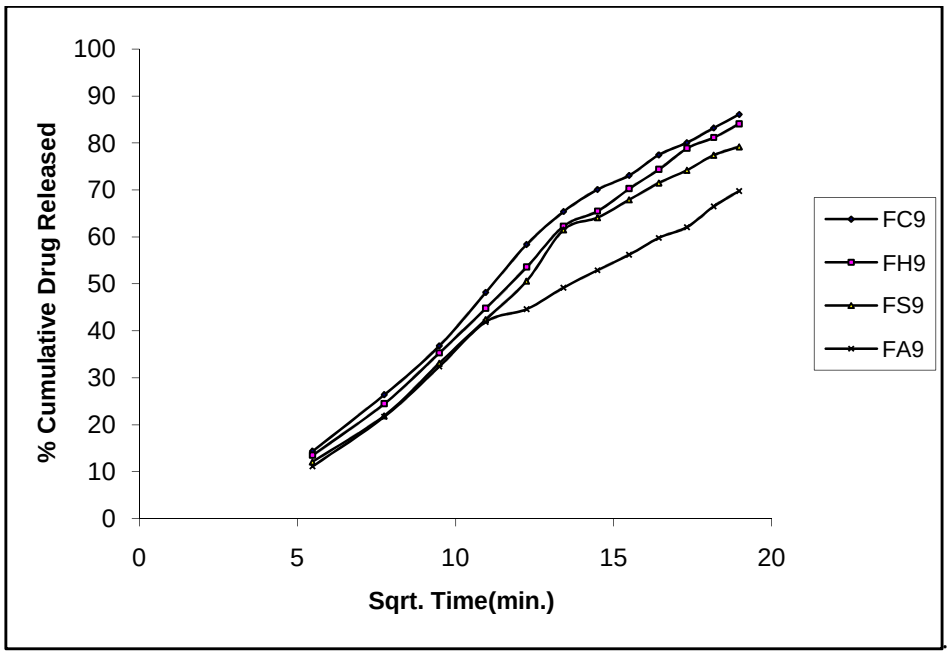

Figure 1: *In-vitro* release of ketoprofen from gels

Mathematical evaluation:
The calculated diffusion coefficient, permeability coefficient and partition coefficient of ketoprofen from the gels are as shown in table 2. It can be seen that the diffusion coefficient and permeability coefficient are highest in carbopol gels and lowest in Sodium Alginate gels. The partition coefficient values show that the affinity of ketoprofen for the polymer base is highest in sodium alginate gels.

Table2: Release kinetics of ketoprofen

Formulation	D* 10^{-9}	P*10^{-7}	K*10^{-2}
Carbopol	4477	81.3	3.6
HPMC	4275	79.5	3.7
Sodium CMC	3791	74.8	3.9
Sodium Alginate	2931	65.9	4.4

D= Diffusion coefficient (cm^2/sec.), P= Permeability (cm/sec.), K= Partition coefficient

In-*vivo* percutaneous absorption of ketoprofen in rats:

Gels of different polymers containing 1% concentration of ketoprofen were used to study the effect of polymers on percutaneous absorption of ketoprofen in rats paw. The effects of polymers on the percutaneous absorption of ketoprofen in rat paw are shown in Figure 2 & 3. The % inhibition of ketoprofen was 56.8, 37.05, 25.4 and 19.5 for carbopol, HPMC, sodium CMC and sodium alginate gels.

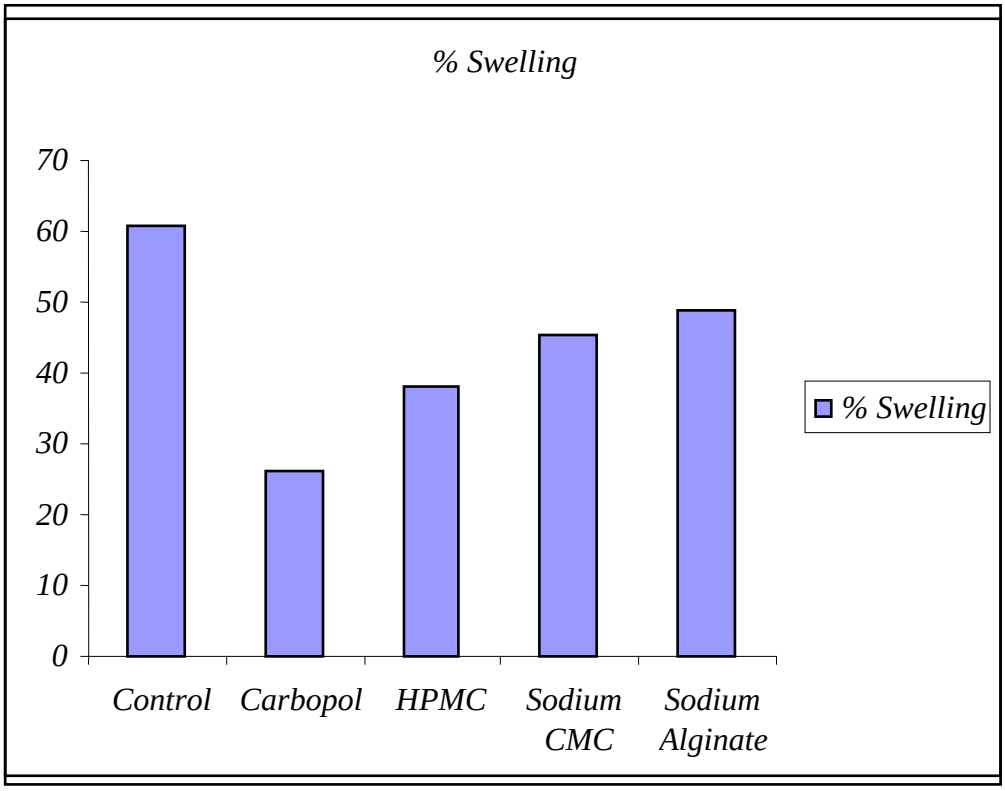

Figure 2: Graphical representation of % swelling with best gels.

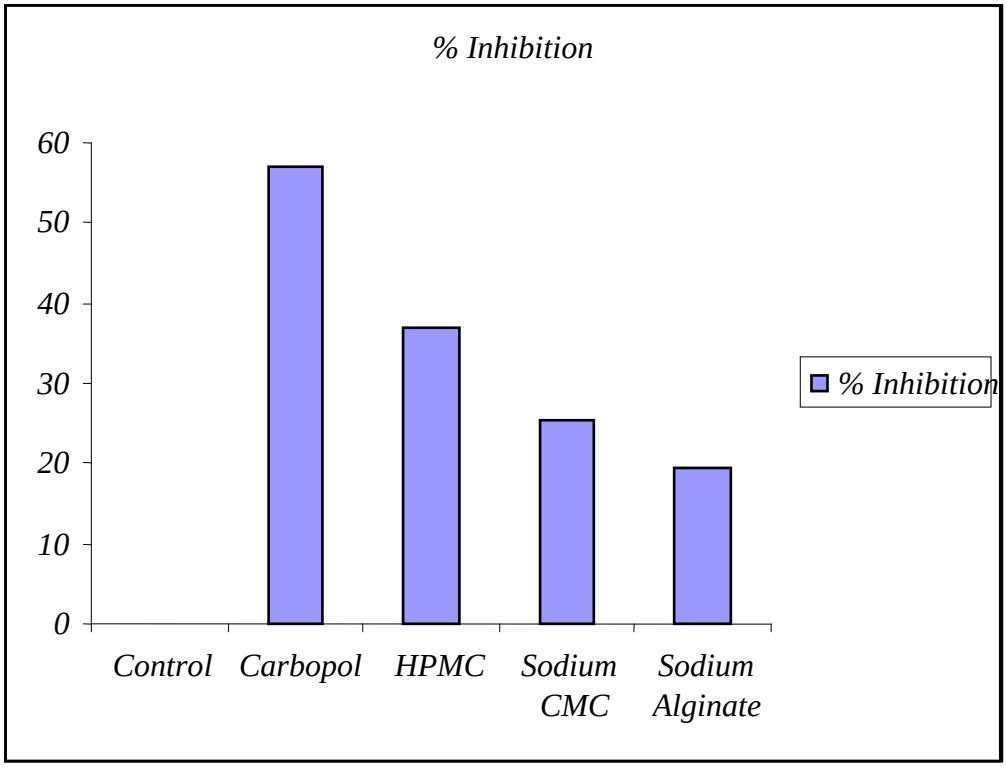

Figure 3: Graphical representation of % inhibition with best gels.

Table 3:Anti-inflammatory activity by carrageenan induced paw edema in rats.

S. No	Treatment	Percent Swelling	Percent Inhibition
1	Control	60.7 ± 5.79	-
2	Carbopol	26.1 ± 2.4	56.8 ± 5.4
3	HPMC	38.2 ± 3.14	37.05 ± 3.5
4	Sodium CMC	45.2 ± 4.2	25.4 ± 2.1
5	Sodium Alginate	48.8 ± 4.5	19.5 ± 1.5

Values are represented as ±SD (n= 6) in each group.

Statistical analysis of *in-vivo* release

Statistical analysis of *in-vivo* release was carried out using one - way ANOVA. The results as in table 5 show that significant difference was observed between the % swelling of all the different polymeric gels (F_{cal} 24.34 > F_{tab} 2.75 and P<0.05).

Table 4: *In-vivo* data of % swelling from different polymer gels

% Swelling				
Control	Carbopol	HPMC	Na CMC	Na Alginate
68.18	23.33	39.13	50.1	39.28
56.52	24.1	37.2	44.2	36.1
51.11	26.92	44.1	41.93	57.14
59.09	32.55	34.61	54.54	60.1
65.21	25.1	40.9	37.93	54.54
64.1	25.1	33.33	42.85	45.83

Table 5: One –way ANOVA for *in-vivo* release

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3928.081	4	982.02028	24.34165	0.0000000	2.75871
Within Groups	1008.58	25	40.343211			
Total	4936.661	29				

Normality Test: Passed (P = 0.761)
Equal Variance Test: Failed (P < 0.050)

CONCLUSION

There was a good correlation between the *in-vitro* release studies from the cellophane membrane and carrageenan-induced paw edema test in rats. Ketoprofen can penetrate to the skin easily. The best formulations for Ketoprofen was carbopol gel at 1% drug concentration.

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