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# DEVELOPMENT OF CONTROLLED RELEASE FORMULATIONS OF KETOPROFEN FOR ORAL USE

Muhammad J. Habib* and Roland Mesue
College of Pharmacy and Pharmacal Sciences
Howard University, Washington, D.C. 20059

## ABSTRACT

Microencapsulated forms of ketoprofen were formulated using polymers and polymer combinations and their in-vitro release characteristics were evaluated against pure ketoprofen using Vanderkamp 600 dissolution test apparatus. Suspensions of cellulose acetate phthalate were prepared and various quantities of drug, glycerin, tween 80, span 80, methocel and avicel were added and the resulting solution was passed through a peristaltic pump into a hardening solution. Beads were formed, dried and the release of the drug was studied at various time intervals in a dissolution medium of simulated intestinal pH. The dissolution studies of the ketoprofen demonstrated differences in drug release properties depending on composition and method of preparation. A formulation of Methocel beads with equal proportions of the two surfactants released its drug content over a period of 12 hours in a zero-order fashion. Rapid drug dissolution was seen when the formulations contained Tween 80 as a surfactant. Varying the drug to CAP ratio in the suspension from 0.1 to 0.4 did not appear to alter dissolution. It is concluded that proper control of the formulation can give any desirable release from ketoprofen formulations.

## INTRODUCTION

Ketoprofen is used as an antiinflammatory and analgesic agent in the symptomatic treatment of acute and

*to whom inquiries should be directed

chronic rheumatoid arthritis and osteoarthritis. It is also used to relieve mild to moderate pain and in the management of primary dysmenorrhea (1). The drug is normally administered orally as rapid release tablets available as 25mg, 50mg and 75mg capsules. The maximum daily dose of ketoprofen is 300mg and the mean plasma elimination half life is 2-4 hours (2). The therapeutic range has been suggested to be between 0.4-6.0 μg/ml and there is considerable inter-individual variation in plasma concentration attained with a given dosage. However, acute lethal dose of ketoprofen in humans is not known (1). This is due in part to the large inter-patient variability in regard to the bioavailability, distribution, metabolism and elimination of Ketoprofen. Ketoprofen is rapidly and completely absorbed from the gastrointestinal tract. Absolute bioavailability of commercially available ketoprofen is approximately 90%. Average peak plasma concentration following 50mg oral dose of 4.1μg/ml occurred after 1hr in fasted state compared to 2.4μg/ml after 2hrs in the unfasted state (3). Also, following the above dose, analgesic activity persists for approximately 3-4hrs (1). Because of the relatively rapid absorption and elimination of the drug, it must be given 3-4 times a day when administered as ordinary tablets in order to avoid fluctuations in plasma concentration outside the desired range .

The 6 hour dosing schedule, however, disrupts the patient's sleep which is not only inconvenient but may also decrease compliance. In order to provide a better dosing schedule, a slow-release formulation may be designed which will have numerous advantages (4). Several controlled-release mechanisms are being suggested to achieve the desired release pattern of the drugs. Kawashima et al. in Japan studied controlled-release preparation of Microspheres of Ibuprofen with Acrylic Polymers (5). In another study, investigators used Eudragit R S for microencapsulation of Ketoprofen (6). Gangrade and Price in USA studied the release properties of "Poly(hydroxybutyrate-hydroxyvalerate) microspheres containing progesterone (7). All these controlled release preparations deliver a constant and slow release of drug for 6-8 hours but fail to provide adequate plasma levels in a therapeutic range at the end of 8 hours. An ideal case would be to maintain the plasma concentration for upto 12-14 hours. Moreover, all the three methods used organic solvents which needed to be evaporated during the process of the experiment. The evaporation process caused porosity in the microspheres which distorted the rate of drug release during dissolution. The residual solvent in

the microspheres can be hazardous to health of the patient. Also, a complex instrumentations are involved in the design of the apparatus used for quasi-emulsion diffusion process. This study was therefore undertaken to design a simple controlled-release formulation of ketoprofen which would release the drug at a faster rate initially and maintain the plasma concentration in the therapeutic range for a period of 12-14 hours.

## MATERIALS

Ketoprofen was obtained from Sigma Chemical Co. (St. Louis, MO). Glycerin, sorbitan monooleate (Span 80), polyoxyethylene 20 sorbitan monooleate (Tween 80), microcrystalline cellulose (Avicel), hydroxypropyl methylcellulose (methocel), Cellulose acetate phthalate (CAP) were purchased from Fisher Chemical Co. Glacial acetic acid and other chemicals and solvents were reagent grade. Water was deionized and glass-distilled.

## METHODS

### Preparation of simulated intestinal fluid

6.8 g of monobasic potassium phosphate was added and mixed to 250 ml of distilled water. 190 ml of 0.2 N NaOH and 400 ml of water was added, mixed and the pH of the resulting solution was adjusted to pH 7.5±0.1 with 0.2 N NaOH and finally diluted to 1000 ml.

### Preparation of suspension for beads

2 gm of dibasic sodium phosphate was dissolved in 180 ml of distilled water, heated to 60°C and 5 gm of Cellulose acetate phthalate (CAP), 1 gm of ketoprofen, 2% tween 80 (3.6 gm), 0.5% of glycerin (0.9 gm), 0.5% of Avicel (0.9 gm), and 0.5% of methocel (0.9 gm ) was added respectively. The suspension was mixed properly using a magnetic stirrer until the suspension is homogenous.

### Formation of beads

A hardening solution was prepared by mixing 30 ml of glacial acetic acid and 200 ml of distilled water. A flexible tubing was connected from the suspension through the peristaltic pump to the hardening solution. The flexible tubing of internal diameter, 0.132 inches and outer diameter, 0.183 inches hangs about 3 cm over the hardening solution. The peristaltic pump was regulated to introduce 60 drops per minute of suspension into the hardening solution which was stirred continuously. Stirring was continued for 10 minutes after

all the suspension is being transferred. The beads were collected on filter paper, washed with distilled water, air dried in a fume hood for 24 hours, and then they were dried in an oven at 50°C for 48 hours. A list of various beads and their components are given in Table 1.

Ketoprofen contents of beads

An assay for ketoprofen in the beads was performed by pulverizing 50 mg of beads in a mortar and dissolving the beads in 100 ml of pH 7.5 buffer solution. Further dilution of this solution with the buffer was made and the absorbance was measured at 276 nm using Spectronic 1201 Scanning spectrophotometer. The concentration of the drug was determined from the Beer's plot. From the results of these studies, weights of beads equivalent to 100 mg ketoprofen was calculated for dissolution experiments.

Dissolution procedures

The dissolution rate measurements were carried out using a Vanderkamp 600 dissolution test apparatus (paddle method). The dissolution flasks were immersed in a water bath maintained at 37°C with an external temperature control unit. The dissolution medium (900 ml) was continuously stirred by an USP standard paddle at a 200 rounds per minute. Samples were added to the stirred dissolution medium and at different time intervals 3 ml samples were taken by a syringe to a Milton Roy Spectronic 1201 Spectrophotometer to determine the amount of drug dissolved and 3 ml of the solution was replaced to the dissolution flasks.

Data analysis

The value T25% is the time required for 25% of the total ketoprofen content to be dissolved. Similarly, T50% is the time for 50% to be dissolved and T75% is the time for 75% of the drug to be dissolved. All the values were calculated separately for each replication by interpolation. Reported values are means of the replications for that specific preparation. Percentage of Ketoprofen dissolved in 1 hour (D1), 8 hours (D8), and 12 hours (D12) were also reported.

## RESULTS AND DISCUSSION

The formation of good quality microcapsules with uniform thickness of coat depends on a number of factors such as viscosity of coating polymer, rate of agitation, the time of addition of coat and core material, rate of

Table 1
Formulations of Ketoprofen Beads

| Drug No. | Surfactant | Viscosity Agent | Code |
|---|---|---|---|
| 0.5 g | 2% Tween 80 | 0.5% each of A, M, and G* | I |
| 1.0 g | 2% Tween 80 | 0.5% each of A, M, and G* | II |
| 1.5 g | 2% Tween 80 | 0.5% each of A, M, and G* | III |
| 2.0 g | 2% Tween 80 | 0.5% each of A, M, and G* | IV |
| 1.5 g | 2% Span 80 | 0.5% each of A, M, and G* | V |
| 1.5 g | 2% Tween 80 | 0.5 g K 1100 M Methocel | VI |
| 1.5 g | -- | 0.5 g K 1100 M Methocel | VII |
| 1.5 g | 1% each of Tween 80 & Span 80 | 0.5 g K 1100 M Methocel | VIII |

* A - Avicel, M - Methocel, and G - Glycerin
All formulations contain 5 g CAP

hardening, the surface characteristics of core material and amount of solid (w/v) utilized during the microencapsulation procedure. Various quantities of CAP, ethocel and methocel were used as the coating material in microencapsulation.

To produce beads containing a uniform amount of drug for the preparations, it was necessary to prepare a satisfactory suspension of the drug. Although several concentrations of CAP were tested, it was found that the 2.5% concentration had appropriate characteristics to suspend various quantities of the drug during the process. Linear calibration curve which obeyed Beers law over the concentration range of 0.003 - 0.22 mg/ml were obtained. Regression analysis of the experimental points yielded slope of 17.7, intercept of 0.022 and correlation coefficient, r, of 0.999.

Dissolution profiles of formulations I, II, III, and IV in intestinal fluid are shown in Figure 1. Most of the ketoprofen was released from these preparations in one hour. After this time period, all these formulations yielded similar plateau concentrations. Dissolution profiles of formulations IV, V, and VI are shown in Figure 2. Formulation IV, with Tween 80 as surfactant, gave a higher plateau compared to formulation V, which contained Span 80. The latter had a maximum dissolution of only 72% in 12 hours. Dissolution profiles of

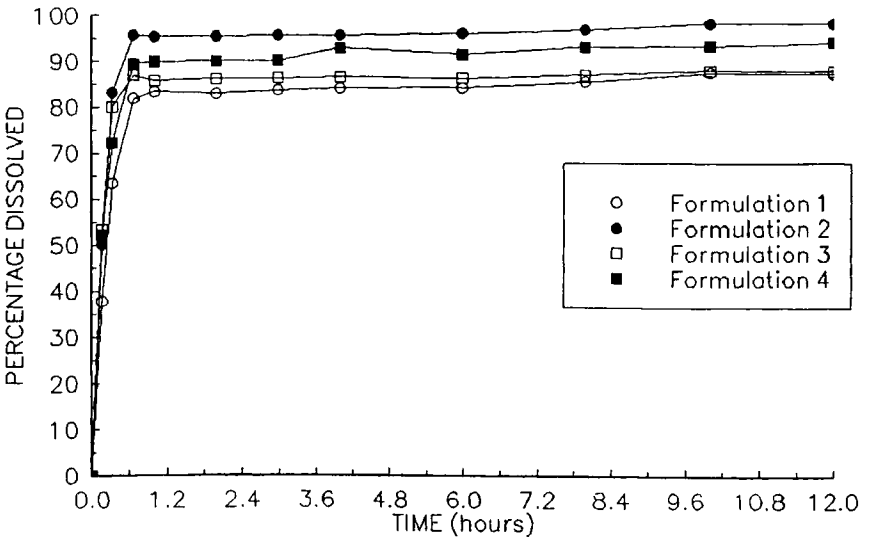


Figure 1 : Dissolution profiles of Formulations I, II, III and IV in simulated intestinal fluid at pH 7.5 and 37°C.

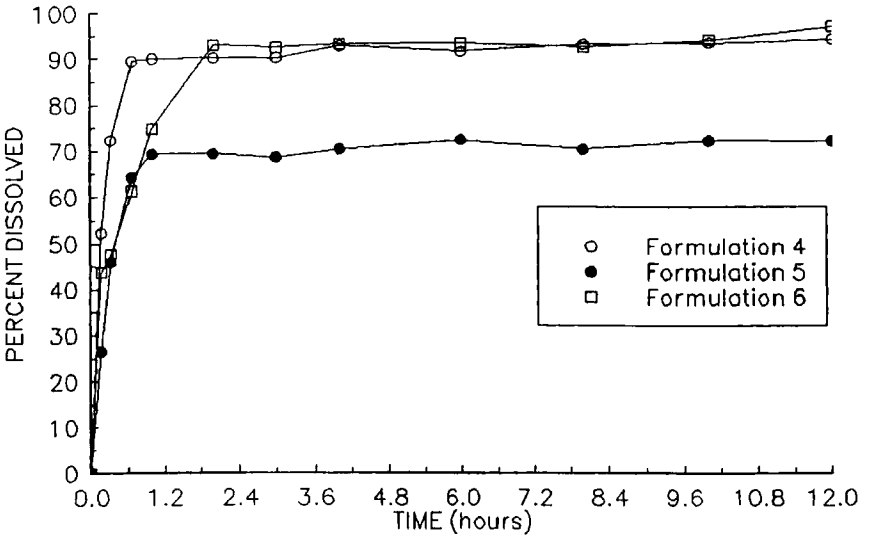


Figure 2 : Dissolution profiles of Formulations IV, V and VI in simulated intestinal fluid at pH 7.5 and 37°C.

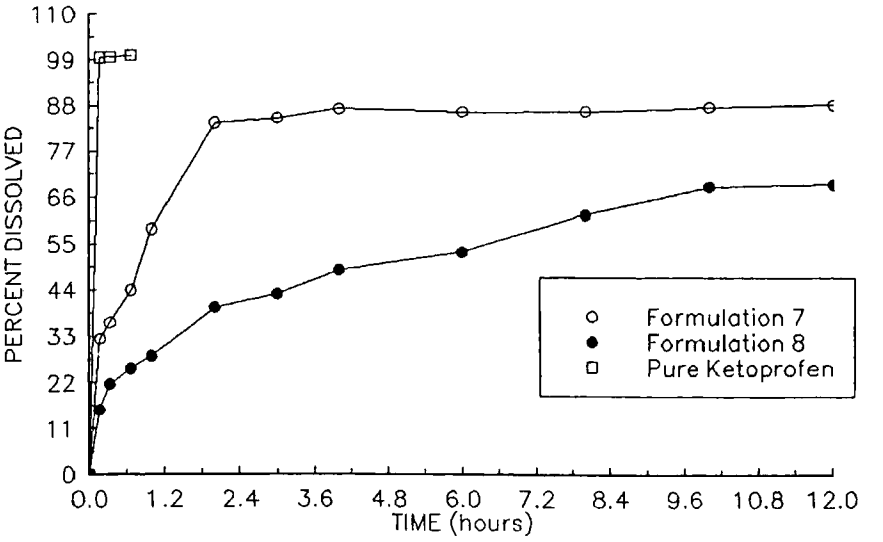


Figure 3 : Dissolution profiles of Formulations VII, VIII and pure ketoprofen in simulated intestinal fluid at pH 7.5 and 37°C.

formulations VII and VIII and that of pure ketoprofen are shown in Figure 3. Formulations VII and VIII showed differences in their dissolution patterns. The pure drug, ketoprofen, showed maximum dissolution in less than one hour. The dissolution pattern of formulation VIII appears to be zero-order upto 70% dissolved in 12 hours.

Values of T25%, T50%, and T75% for different formulations are shown in Table 2. As seen in Table 2, formulation VIII gave a T 25% of 39.4 minutes, which is significantly higher compared to other formulations. Similarly, the T 50% value is also longer for this formulation. Percentages dissolved reported as D1, D8, and D12 values for all the formulations are presented in Table 3. Formulation V, which contained Span 80 as surfactant, displayed D12 values of only 72.2% and is much lower than I, II, II and IV. This illustrates lower solubility of ketoprofen with Span 80 formulation. Again, formulation VIII showed gradual increase in drug release than any other formulations.

The dissolution profiles for formulations, in which Tween 80 was included with 0.5% each of Methocel, Avicel, and Glycerin (I, II, III and IV), had similar plateaus

Table 2
T 25%[1], T 50%[1] and T 75%[1] Values for the Formulations

| Formulation Code No. | T 25% minutes | T 50% minutes | T 75% minutes |
|---|---|---|---|
| I | 6.63 | 13.25 | 23.6 |
| II | 4.90 | 10.0 | 18.0 |
| III | 4.69 | 12.48 | 34.5 |
| IV | 4.79 | 13.83 | 33.6 |
| V | 9.4 | 31.19 | -- |
| VI | 5.82 | 21.16 | 60.0 |
| VII | 7.72 | 55.7 | 76.88 |
| VIII | 39.40 | 246.2 | -- |

[1]T 25%, T 50% and T 75% are the time required for 25%, 50% and the 75% of the total ketoprofen content to be dissolved respectively.

Table 3
D1[1], D8[1], and D12[1] Values for the Formulations

| Formulation Code No. | D1 % Dissolved | D8 % Dissolved | D12 % Dissolved |
|---|---|---|---|
| I | 83.3 | 84.3 | 87.6 |
| II | 95.3 | 96.2 | 98.5 |
| III | 85.7 | 86.4 | 88.2 |
| IV | 89.9 | 91.6 | 94.4 |
| V | 69.2 | 72.4 | 72.2 |
| VI | 74.7 | 93.5 | 97.2 |
| VII | 58.5 | 86.4 | 88.3 |
| VIII | 28.3 | 57.1 | 69.2 |

[1]D1, D8 and D12 are the % of ketoprofen dissolved in 1 hour, 8 hours and 12 hours respectively.

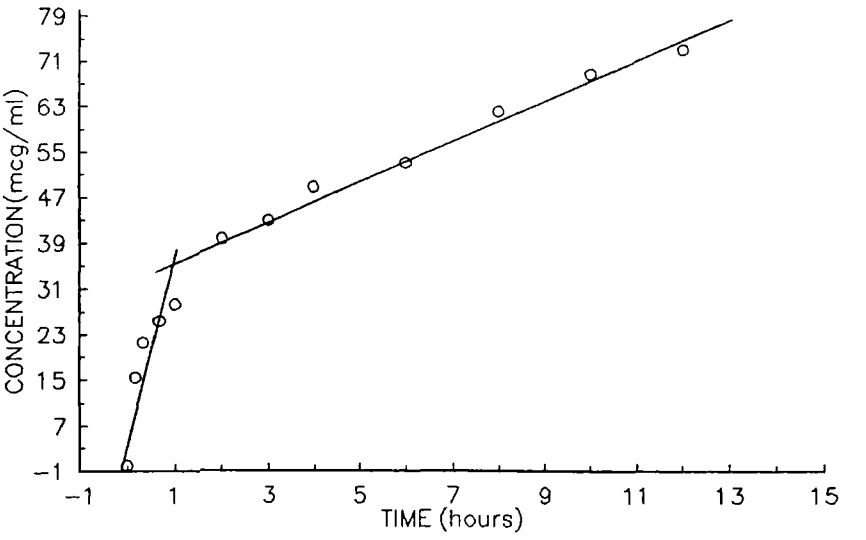


Figure 4 : Release pattern of ketoprofen from Formulation VIII in simulated intestinal fluid at pH 7.5 and 37°C.

and followed a similar pattern. Formulation II, which has a drug to CAP ratio of 0.2 to 1, released most of its ketoprofen content in a shorter period of time relative to other formulations. After about 1 hour, 80% of the ketoprofen was released from all four formulations. Varying the drug to CAP ratio from 0.1 to 0.3 did not appear to alter dissolution. All these formulations with Tween 80 and 0.5% each of Methocel, Avicel, and glycerin failed to show any sustained release properties.

Formulations V , which contained Span 80 as the surfactant, displayed lower plateau than formulation III. Span 80 has more lipophilic properties whereas Tween 80 has hydrophilic character. For these reasons, beads containing Span 80 dissolved slowly and released its drug content slower than formulations containing Tween 80. Since Tween 80 is a solubilizing agent, an increase in dissolution is expected. Formulation VIII, which contained both Tween 80 and Span 80 gave the perfect zero-order kinetics. Formulation VIII has been re-plotted in Figure 4 to show the behavior of zero-order release. As we can see from the graph a biphasic pattern was observed. The initial high rate constant of release

can be attributed to the drugs which are close to the surface and a combined diffusion controlled and dissolution controlled process could account for this high release of drugs. The correlation coefficient of this portion of the curve is 0.89 and the zero-order rate constant is 38.3 mcg/ml/hr. The second biphasic curve releases the drug much more gradually with a correlation coefficient of 0.98 and rate constant of 4.6 mcg/ml/hr. It shows that a zero-order release can be obtained for as long as 16 hours. Further modification in the formulation could provide a zero-order release for as long as 24 hours.

## CONCLUSIONS

A formulation of Methocel beads with equal proportions of the two surfactants released its drug content over a period of 12 hours in a zero-order fashion. This is probably the most suitable formulation for the 12 to 20 hours of controlled release of the drug. Rapid drug dissolution was seen when the formulations contained Tween 80 as a surfactant. Varying the drug to CAP ratio in the suspension from 0.1 to 0.4 did not appear to alter dissolution.

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