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# PREPARATION AND EVALUATION OF SUSTAINED RELEASE IBUPROFEN BEADS

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## ABSTRACT

Sustained release beads of ibuprofen were prepared by a capillary method using cellulose acetate phthalate, surfactants (Tween 80 and Span 80), and polymers (K 100 M Methocel and K 100 LV Methocel). These beads were formulated into capsule and tablet dosage forms. The beads did not disintegrate in simulated gastric fluid; however, they disintegrated in simulated intestinal fluid. The dissolution profiles of ibuprofen beads and dosage forms of beads (tablets and capsules) were conducted in phosphate buffer (pH 7.2) at 37° C. The beads containing Span 80 and K 100 M Methocel resulted in prolonged drug release. The preparation containing Span 80 and equal quantities of both the polymers (K 100 M Methocel and K 100 LV Methocel), also showed good

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sustained release properties. The formulations prepared with Tween 80 and K 100 LV Methocel released over 90% of the drug in 2 hours indicating no sustained release properties. The beads in tablet dosage form yielded slower dissolution profiles compared to the beads in capsule form which, in turn, had slower release profiles compared to the beads alone. Release of ibuprofen was much slower from tablets after one year of storage compared to tablets immediately after their manufacture.



## INTRODUCTION

Ibuprofen is a non-steroidal anti-inflammatory agent that possesses analgesic and antipyretic activities. The drug has a relatively short half-life of about 2 hours and is therefore an ideal candidate for formulation as a sustained release dosage form (1). Cellulose acetate phthalate (CAP) is a physiologically inert polymer used as an enteric-coating material. The pH dependent solubility of CAP is due to the presence of ionizable phthalate groups (2,3). CAP is very commonly used as an enteric tablet-coating material. Coatings of CAP disintegrate due to the hydrolytic effect of the intestinal esterases, even when the intestinal contents are acidic. In vitro studies indicate that CAP will withstand the action of artificial gastric juices for long periods of time, but will disintegrate readily in artificial intestinal juices (4). Methocel has been used extensively as a rate-controlling polymer in oral sustained release dosage forms. Methocel has been evaluated as an alternate source of hydroxypropyl methylcellulose for use in a sustained-release tablet matrix (5). Recently, we have reported the preparation and drug release from sustained release beads of indomethacin (6).

The objectives of this study were to evaluate (i) the effect of polymers (K 100 M Methocel and K 100 LV Methocel) and surfactants (Span 80 and Tween 80) on the incorporation of ibuprofen in CAP beads, (ii) formulation of beads into tablet and capsule dosage forms and (iii) the drug release from beads, and dosage forms (tablets and capsules) prepared using beads.

## MATERIALS AND METHODS

### Materials

Ibuprofen (Sigma Chemical Co., St. Louis, MO), cellulose acetate phthalate (CAP, Eastman Kodak Co., Rochester, NY), polyoxyethylene 20 sorbitan monooleate (Tween 80) and magnesium stearate (Fisher Scientific Co., Fair Lawn, NJ), sorbitan monooleate (Span 80, City Chemical Corp., New York, NY), hydroxypropyl methyl cellulose (K 100 M and K 100 LV grades, Dow Chemical Co., Midland, MI), microcrystalline cellulose (Avicel, type PH 101, FMC Corporation, Philadelphia, PA) were used without further treatment. All other chemicals were reagent grade obtained commercially.

### Methods

### Preparation of Beads

Ibuprofen beads were prepared by a coacervation method described previously (6). Solutions of CAP were prepared by dissolving 1 g of dibasic sodium phosphate in 100 ml of distilled water, heating to 60° C, and then adding 2.5 g of CAP (7). Ibuprofen (2%) with various combinations of surfactants and polymers were added to the CAP solution to yield suspensions. Higher concentrations of polymers were not satisfactory due to solubility problems, high viscosity and unsuitable suspending properties. The receiver solution contained 30 ml of glacial acetic acid in 200 ml of distilled water. A list of various beads and their composition are shown in Table 1.

Suspension (100 ml) of ibuprofen along with polymers and surfactants, was introduced into the receiver solution by means of a peristaltic pump which was fitted with tubing. The tubing consisted of flexible plastic tubing (Fisher Scientific Co., Pittsburgh, PA inside diameter 0.031", outside diameter 0.094") which was fitted within a thick walled silastic tubing (Dow Corning Corp., Midland, MI, inside diameter 0.132", outside diameter 0.183"). The beads were formed by introducing 60 drops

TABLE 1.

Composition of Ibuprofen Beads, Mean Particle Size and Drug Incorporation (%).

| Formulation | Surfactant | Polymer | Particle size Mean±S.D | Drug incorporation |
|---|---|---|---|---|
| I | --- | A | 1.22±0.17 | 96.7 |
| II | 1% Tween 80 | A | 1.24±0.12 | 86.1 |
| III | 1% Span 80 | A | 1.22±0.19 | 85.7 |
| IV | 0.5% each of Tween 80 & Span 80 | A | 1.22±0.12 | 89.9 |
| V | --- | B | 1.09±0.13 | 90.2 |
| VI | 1% Tween 80 | B | 1.17±0.07 | 90.7 |
| VII | 1% Span 80 | B | 1.18±0.09 | 87.5 |
| VIII | 0.5% each of Tween 80 & Span 80 | B | 1.05±0.19 | 88.6 |
| IX | --- | C | 1.19±0.12 | 96.8 |
| X | 1% Tween 80 | C | 1.11±0.13 | 87.3 |
| XI | 1% Span 80 | C | 1.08±0.15 | 91.6 |
| XII | 0.5% each of Tween 80 & Span 80 | C | 1.12±0.12 | 88.3 |

All formulations contain 1% $Na_2HPO_4$, 2.5% CAP and 2% ibuprofen.

A = 0.5% K 100 M Methocel

B = 0.5% K 100 LV Methocel

C = 0.25% each of K 100 M and K 100 LV Methocel

per minute of the suspension into the acetic acid solution which was placed 3 cm below the tubing. The acetic acid solution was stirred at 80 rpm. After all the suspension had been introduced, the stirring was continued for an additional 10 minutes. The beads were collected, washed thoroughly with distilled water to remove traces of acetic acid, air dried in a fume hood for 24 hours and then dried in an oven at 50° C for 48 hours. The size range of beads was determined using a microscope fitted with a calibrated eye piece.

## Determination of ibuprofen content in beads

An assay for ibuprofen in the beads was performed by pulverizing 50 mg of beads in a mortar and dissolving the beads in 100 ml phosphate buffer (pH 7.2). Further dilutions of this stock solution were made with phosphate buffer and the absorbance at 221 nm was measured by UV spectrophotometer (Beckman DU-65). The concentration of ibuprofen was determined from the Beer's plot.

## Formulation of tablets and capsules

The beads were tableted with each tablet containing 300 mg of beads mixed with Avicel PH 101. After adding 1% magnesium stearate, the mixture was directly compressed on a rotary tableting machine equipped with a concave punch. Tablets weighed 600 mg, the thickness and diameter of the tablet were 2.5 and 13 mm, respectively. For capsule dosage form, 100 mg of beads were filled into No. 3 hard gelatin capsules. A total of 20 capsules and 15 tablets were prepared from each bead preparation.

## Dissolution Studies

The dissolution studies of beads alone and tablet and capsule dosage forms of beads were performed in 1000 ml round bottom flask using a USP dissolution apparatus (basket method). The dissolution medium consisted of 900 ml phosphate buffer (pH 7.2). The solution was maintained at 37±0.5° C and agitated at 100 rpm. The bottom of the basket was about 2 cm from the bottom of the flask. At the beginning of

the studies, either 100 mg of ibuprofen beads, one tablet or one capsule were introduced into the flask. The samples (5 ml) were withdrawn at fixed time intervals. After each sampling, 5 ml of fresh dissolution medium, maintained at 37±0.5° C, was added to the flask to keep a constant volume. The filtered samples were assayed at 221 nm and the amount of ibuprofen released at each time interval determined. The presence of CAP, Tween 80, Span 80 and Methocel, at concentration present in the samples, were found not to interfere with UV analysis of ibuprofen. A cumulative volume correction factor was applied to account for previously removed samples (8). Dissolution studies were performed in triplicate.

## RESULTS AND DISCUSSION

### Preparation of beads

To prepare beads containing a uniform amount of drug in the formulations it was necessary to prepare a satisfactory suspension of the drug. Although several concentrations of cellulose acetate phthalate (CAP) were tested, it was found that 2.5% CAP concentration had appropriate characteristics to suspend various quantities of surfactants, polymers, and drug during the process. Higher quantities of polymers and surfactants were not satisfactory because of high viscosity, solubility, and unsuitable suspending properties.

The size range of the beads varied from 0.83 to 1.46 mm with the average size being 1.1 mm as shown in Table 1. The beads prepared using K 100 M Methocel were relatively larger in diameter compared to beads prepared with K 100 LV Methocel. There was no correlation between bead size and incorporation of ibuprofen in the beads. More than 85% of ibuprofen was incorporated into the beads in all the formulations. Some of the drug is expected to be lost during the process due to sticking to the glassware or tubing. The amount of drug lost during the preparation of beads is, thus, reasonable.

### Disintegration of beads

The disintegration studies were conducted in simulated gastric fluid and then in simulated intestinal fluid. The beads did not disintegrate in

simulated gastric fluid even though they contained considerable amounts of excipients such as surfactants and polymers (K 100 M and K 100 LV Methocel). Since CAP is soluble only in alkaline medium, this may have prevented the beads from disintegrating in acidic medium. The inclusion of higher molecular weight polymer (K 100 M Methocel, 100,000 cps) prolonged the disintegration time considerably.

## Dissolution studies

Dissolution profiles of bead formulations III, VII and XI are shown in Figure 1. Release of ibuprofen from formulation III was the slowest compared to all the formulations in this study. Presence of Span 80 and K 100 M Methocel along with CAP provided slow release characteristics to the beads in this formulation. Formulations VII and XI also contain Span 80, which provides a hydrophobic property to the beads, also released ibuprofen slowly over the period of 10-12 hours. However, the rate of release of ibuprofen from formulations V, VI and VIII was much higher compared to all other formulations. Most of the drug (> 90%) was released within 2 hours, showing no sustained release property. Formulation V had no surfactant and K 100 LV Methocel was the polymer employed. However, formulations VI and VIII had Tween 80 along with K 100 LV Methocel. Tween 80 may increase the wetting of the beads and also K 100 LV Methocel is relatively less viscous due to low molecular weight compared to K 100 M Methocel.

The release profiles of formulation VII from beads, tablets and capsules is shown in Figure 2. The release of ibuprofen from the tablet dosage form was the slowest as compared to beads and the capsule dosage form. This is probably due to the reduction in surface area when incorporating beads into tablets. The release of ibuprofen from beads alone was faster than that from beads formulated into capsule dosage form. The effect of aging at room temperature on release of ibuprofen from tablets prepared using bead formulations III, VII and XI is shown in Figure 3. Release of ibuprofen was much slower from tablets after one year of storage compared to tablets immediately evaluated after their manufacture. For example, tablet formulation III released 80% of its drug

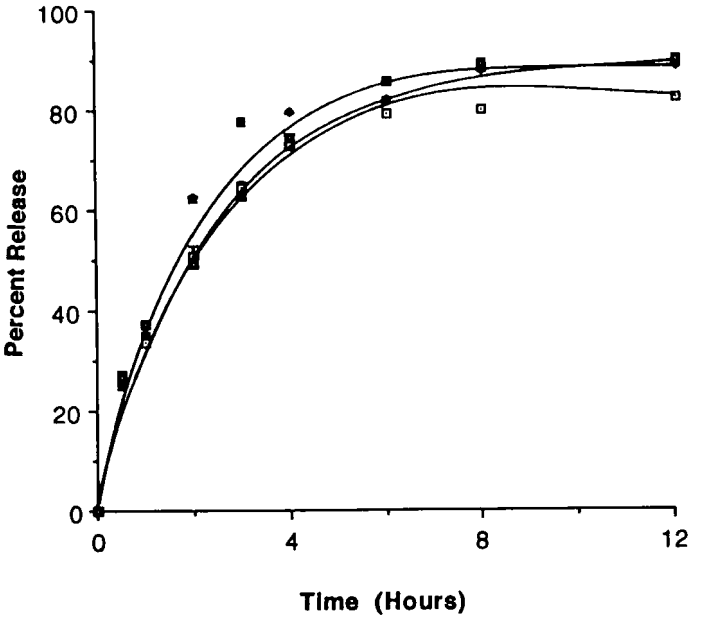


FIGURE 1

Dissolution profiles of ibuprofen from bead formulations: III (⊡), VII (♦) and XI (■).

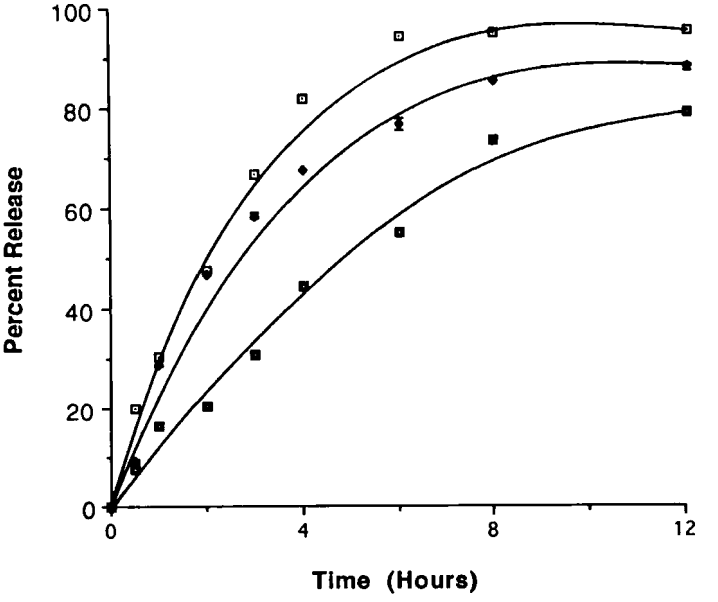


FIGURE 2

Dissolution profiles of ibuprofen from bead formulation VII: Beads (⊡), Capsules (♦) and Tablets (■).

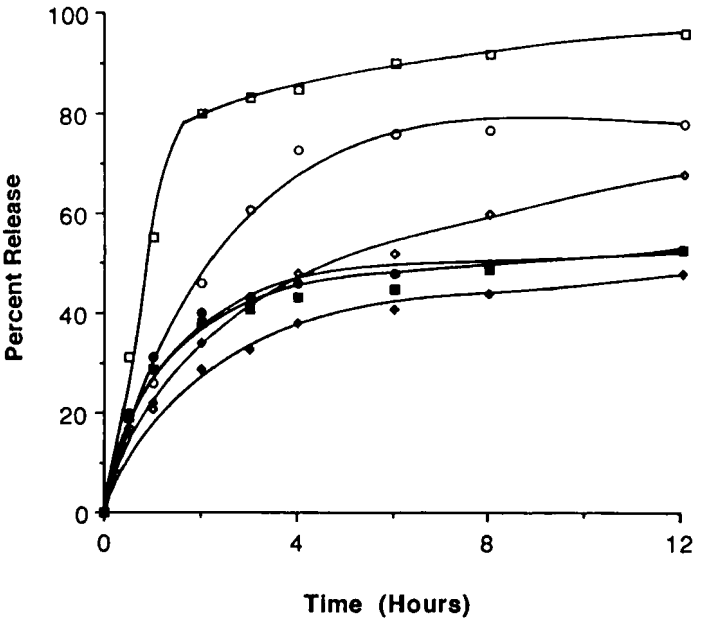


FIGURE 3

Dissolution profiles of ibuprofen from tablet formulations III (○, ●), VII (□, ■) and XI (◇, ◆). (Open symbols represent tablet formulations immediately after the manufacture and closed symbols represent tablets after a year of storage).

content in 8 hours. This same formulation after aging released only 52% of ibuprofen in 8 hours. Formulations VII and XI also followed similar pattern. These results indicate that after one year of storage, the compression forces in the tablets have consolidated, hence the release of ibuprofen was slower.

The rate of release of solid drugs randomly dispersed in solid matrices has been widely studied. This approach has been the basis for dosage forms which provide more or less continuous release of drugs over relatively long periods (9). Percent released-time data reported in the literature for many sustained-release preparations give linear pseudo (or apparent) first-order rates over the terminal portions of the data from about 0.5 hour to the time the test was completed (10,11).

The release of ibuprofen can be explained by two mechanisms. Extraction of the drug by a simple diffusional process through and from an enveloping, homogeneous matrix. The drug is presumed to go successively from the bead surfaces into the uniform matrix and out into the bathing solvent which in turn acts as a perfect sink. Alternatively, leaching of the drug by the bathing fluid which is able to enter the drug-matrix phase through pores, cracks and intergranular spaces may occur. The drug is presumed to dissolve slowly into the permeating fluid phase and to diffuse from the system along the cracks and capillary channels filled with the extracting solvent.

When beads are formulated into capsule and tablet dosage forms, these dosage forms may be complicated in their release of drug by (a) simultaneous break-up of the matrix (b) partial dissolution of the matrix substances (c) one fraction of the dose being in a different, non-matrix and readily available form and (d) drug on the surface being released more rapidly than drug in the matrix.



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