DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(2), 265-275 (1995)

PREPARATION AND IN VITRO EVALUATION OF MEFENAMIC ACID SUSTAINED RELEASE BEADS

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ABSTRACT

Sustained release beads of mefenamic acid 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 then formulated into capsule dosage form. The beads did not disintegrate in simulated gastric fluid; however, they disintegrated in simulated intestinal fluid. The dissolution profiles of mefenamic acid beads and capsule dosage form were conducted in phosphate buffer (pH 7.2) at 37° C. The beads containing Span 80 and a mixture of K 100 M and A 4 M Methocel resulted in prolonged drug release. 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 capsule dosage form yielded slower dissolution profiles compared to the beads alone. Aging for six months had no effect on dissolution of

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mefenamic acid beads. The release of mefenamic acid seems to be combination of diffusion and leaching. The release of mefenamic acid from beads can be modified by varying the polymer composition and their concentration.

INTRODUCTION

The basic goal of drug therapy is to achieve steady-state blood or tissue level for an extended period of time that is therapeutically effective and nontoxic. This goal can be achieved by formulating drugs in sustained release dosage form. Overall, administration of sustained-release formulations may increase reliability of therapy and improve compliance (1).

There are three approaches to preparing sustained-release beads. The first approach entails placement of the drug in an insoluble matrix. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case, the portion of the drug that has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid. The third approach is eroding beads in which drug is released as the bead matrix erodes or dissolves. In the first two cases, a constant area for diffusion together with a constant diffusional path length and constant concentration of drug can achieve a constant drug release rate.

Mefenamic acid, an anthranilic acid derivative, is a non-steroidal anti-inflammatory agent. The drug has a relatively short half-life of about 2 hours (2) and is, therefore, an ideal candidate for formulation as a sustained release dosage form. Cellulose acetate phthalate (CAP) is used as an enteric-coating material and the pH dependent solubility of CAP is due to the presence of ionizable phthalate groups (3,4). 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 (5). 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 (6). Recently, we have reported the preparation and drug release from sustained release beads of indomethacin and ibuprofen (7,8).

The objectives of this study were to prepare sustained-release beads of mefenamic acid, characterize beads in terms of size, shape and disintegration, and to study the release rates by performing dissolution studies.

MATERIALS AND METHODS

Materials

Mefenamic acid (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

Mefenamic acid beads were prepared by a coacervation method described previously (7). Solutions of CAP were prepared (9) 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. Mefenamic acid (2%) with various combinations of surfactants and polymers were added to the CAP solution to yield suspensions. Higher concentrations of polymers were not

possible 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 bead formulations, their composition, particle size distribution, and percentage drug incorporation are shown in Table 1.

Suspension (100 ml) of mefenamic acid along with polymers and surfactants was introduced into the receiver solution by means of a peristaltic pump that 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 per minute of the suspension into the acetic acid solution that 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 mefenamic acid content in beads

An assay for mefenamic acid 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 284 nm was measured by UV spectrophotometer (Beckman DU-65). The concentration of mefenamic acid was determined from the Beer's plot.

Formulation of capsule dosage form

The beads were formulated into capsule dosage form, by filling 100 mg of beads into No. 3 hard gelatin capsules. A total of 20 capsules were prepared from each bead formulation.

TABLE 1.

Composition of Mefenamic acid beads, Mean particle size and Drug incorporation.

Formulation	Surfactant	Polymer	Particle size Mean±S.D.	Drug incorporation (%)
I	1% Span 80	A	1.16±0.16	78.8
II	0.5% each of Tween 80 & Span 80	A	1.24±0.11	72.7
III	1% Span 80	B	1.11±0.14	73.3
IV	0.5% each of Tween 80 & Span 80	B	1.14±0.11	67.5
V	1% Span 80	C	1.02±0.09	62.2
VI	0.5% each of Tween 80 & Span 80	C	1.17±0.15	61.4
VII	1% Span 80	D	1.08±0.12	58.1
VIII	0.5% each of Tween 80 & Span 80	D	1.17±0.15	57.3
IX	1% Span 80	E	1.14±0.14	62.7
X	1% Span 80	F	1.14±0.15	52.7

All formulations contain 1% Na_2HPO_4, 2.5% CAP and 0.25% mefenamic acid.

A = 0.25% K 100 M Methocel

B = 0.25% A 4 M Methocel

C = 0.25% of K 4 M Methocel

D = 0.25% E 50 Methocel

E = 0.125% each of K 100 M and A 4 M Methocel

F = 0.125% each of K 4 M and E 50 Methocel

Dissolution Studies

The dissolution studies of beads alone 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 mefenamic acid beads 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 284 nm and the amount of mefenamic acid 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 mefenamic acid. A cumulative volume correction factor was applied to account for previously removed samples (10). Dissolution studies were performed in triplicate.

RESULTS AND DISCUSSION

Preparation of beads

To achieve uniform distribution of drug in beads it was necessary to prepare a satisfactory suspension of drug. An optimum concentration of CAP was found to be 2.5% to suspend surfactants, polymers and mefenamic acid during the process. Spherical beads containing mefenamic acid and excipients were obtained readily. The size of the beads varied from 1.02 to 1.24 mm with average size being 1.14 mm as shown in Table 1. The beads prepared using K 100 M Methocel were relatively larger compared to other polymers. No correlation was found between size of the beads and degree of incorporation of mefenamic acid in the beads. Some of the drug is expected to be lost during the process due to sticking to the glassware or tubing and solubility in the suspension medium. About 35% of the drug was lost during the preparation of beads.

The loss of drug is relatively greater than our previous reports with indomethacin (7) and ibuprofen (8). This may be due to the higher solubility of mefenamic acid in an aqueous phase.

Disintegration of beads

The beads did not disintegrate in simulated gastric fluid; however, they disintegrated in simulated intestinal fluid. Even though the beads contained surfactants and polymers along with CAP, did not appear to enhance the permeation of fluid at acidic pH. Since CAP is soluble only in an alkaline medium, this prevented the beads from disintegrating in an acidic medium. The beads prepared with Span 80 and K 100 M Methocel had the longest disintegration time of 65 minutes. The disintegration time for other formulations varied from 40 to 60 minutes.

Dissolution studies

The release profiles of mefenamic acid from beads and capsule dosage form of formulation I is shown in Figure 1. This formulation which contains Span 80 and K 100 M Methocel showed good sustained release property. The release of mefenamic acid from capsule dosage form was significantly lower than beads alone. Similar results were observed with formulation IX up to 6 hours as shown in Figure 2. This formulation also had good sustained release property and capsule dosage form had significantly lower release profile up to 6 hours. Beyond 6 hours there was no difference in the release profile from capsules compared to beads alone. This formulation was prepared using Span 80 and mixture of K 100 M and A 4 M Methocel. These results indicate Span 80 and K 100 M Methocel are necessary to formulate sustained release bead formulation.

Time required to release 60% of drug (T-60%) of all the formulations is given in Table 2. This value was higher for formulations I and IX compared to all other formulations. Time required for formulation I and IX were 2.46 and 1.69 hours, respectively. For other formulations it

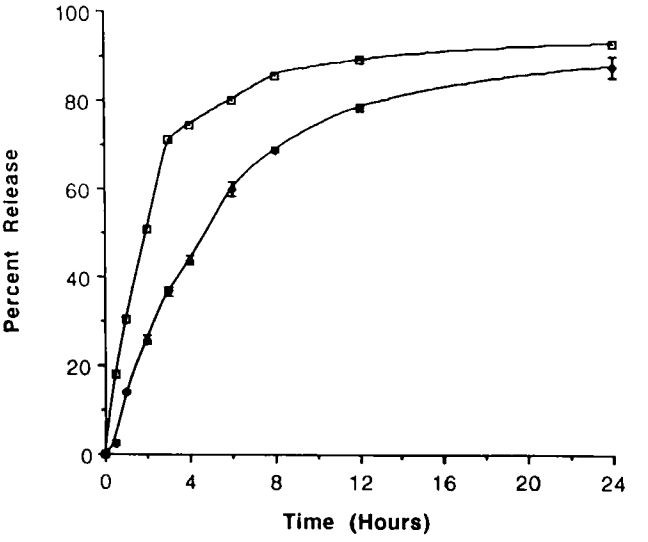

FIGURE 1.

Dissolution profiles of mefenamic acid from bead (⊡) and capsule dosage form (♦) of formulation I

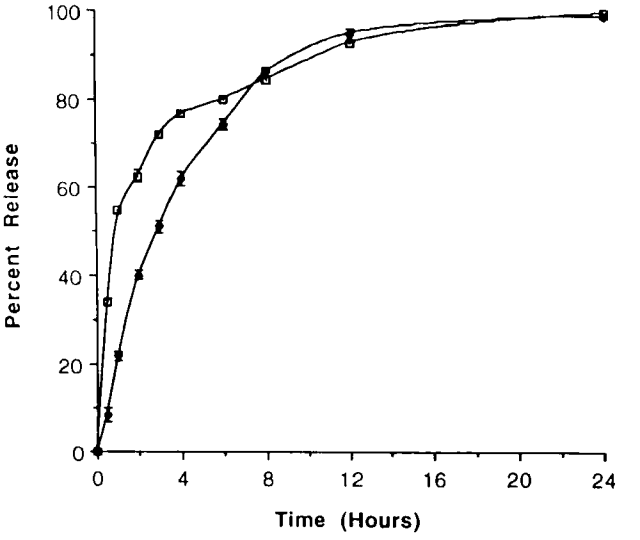

FIGURE 2.

Dissolution profiles of mefenamic acid from bead (⊡) and capsule dosage form (♦) of formulation IX

TABLE 2.

Time required to release 60% (T-60%) of mefenamic acid from bead formulations.

Formulation #	T-60%, Mean ± S.D. (Hours)
I	2.46 ± 0.01
II	0.73 ± 0.01
III	0.94 ± 0.01
IV	0.39 ± 0.01
V	0.83 ± 0.03
VI	0.39 ± 0.00
VII	0.48 ± 0.00
VIII	0.39 ± 0.00
IX	1.60 ± 0.14
X	0.80 ± 0.02

took less than an hour to release 60% of the drug, indicating no sustained release property.

Effect of aging on dissolution profiles

Bead formulations I and IX (sustained release property) were stored for 6 months and dissolution studies were repeated to determine the effect of storage on the dissolution behavior. No significant changes were

noticed for these two formulations with aging. For example, formulation I released about 50% of its drug content in 2 hours before aging and 47% after aging for 6 months. Similarly, the rate of release was about 86% in 12 hours before and after aging. A similar release trend was observed in case of formulation IX.

The rate of drug release from solid matrices has been studied extensively. Such an approach has been the basis for dosage forms that provide continuous release of drugs over relatively longer duration (11). Drug release profile data reported in the literature for several sustained-release formulations suggest linear pseudo first-order rates over the terminal portions of the data from about 0.5 hour to the time the study was completed (12,13).

The release of mefenamic acid 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 be released successively from the surface into the dissolution medium which acts as a perfect sink. Alternatively, leaching of the drug to 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.

In conclusion, controlled release beads of mefenamic acid can be prepared by coacervation technique. This process is very simple, and economical more over convenient to scale up to manufacture on large scale. The release profiles of these beads can be modified by varying the polymer composition and their concentration. In vitro dissolution studies showed that particularly K 100 M Methocel and Span 80 are required to achieve prolonged release of mefenamic acid from this type of beads.

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