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PREPARATION AND DISSOLUTION CHARACTERISTICS OF INDOMETHACIN SUSTAINED RELEASE BEADS

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ABSTRACT

Indomethacin is a nonsteroidal anti-inflammatory agent and has a short half life, and causes gastric irritation. Sustained release beads of indomethacin were prepared and dissolution profiles were investigated. Beads were prepared by allowing drops of a suspension of the drug and excipients in a solution of cellulose acetate phthalate to drop into an acetic acid solution by means of a peristaltic pump. In a previous study[1], sulfadiazine was used as a model drug to prepare beads by a similar method and the effects of various viscosity agents on the properties of these beads were assessed. Glycerin, polymers (Methocel and Avicel), and surfactants (Tween 80 and Span 80) were used as excipients. The incorporation of various viscosity agents and polymers into the suspension yielded beads with different disintegration and dissolution values. A high performance liquid chromatography method showed no indication of drug degradation during the preparation. The dissolution studies of the indomethacin preparations demonstrated differences in drug release properties depending on composition and method of preparation. The preparation with equal quantities of the two surfactants (Tween 80 and Span 80) released the drug at the slowest rate.

MATERIALS

The chemicals: Indomethacin, hydroxypropyl methylcellulose (Methocel, Sigma Chemical CO., St. Louis, MO), cellulose acetate phthalate (CAP, Eastman Kodak Co., Rochester, NY), polyoxyethylene 20 sorbitan monooleate (Tween 80),

glycerin (Fisher scientific Co., Fair Lawn, NJ), sorbitan monooleate (Span 80, City chemical corp., New York, NY), microcrystalline cellulose (Avicel, Type PH 101, FMC corp., Philadelphia, PA), hydroxypropyl methylcellulose (K 100 M grade, Dow chemical co., Midland, MI) were used without further treatment.

EXPERIMENTAL

Preparation of Beads

Solutions of CAP were prepared[2] by dissolving 2 g of dibasic sodium phosphate in 180 ml of distilled water, heating to 60^0 C, and then adding 5 g of CAP. Various quantities of drug, glycerin, Tween 80, Span 80, Methocel, and Avicel were added to CAP solution to yield suspensions. Higher concentrations of viscosity agents were not satisfactory due to solubility, high viscosity, and unsuitable suspending properties. The hardening solution contained 30 ml of glacial acetic acid in 200 ml of distilled water. A list of various beads and their components are listed in Table 1. Fifty ml of suspension was introduced into the hardening solution by means of a peristaltic pump which was fitted with tubing. The tubing consisted of flexible plastic tubing (Fisher Scientific Co, Pittsburgh, PA, id 0.031", od 0.094") which was fitted within a thick walled silastic tubing (Dow Corning Corp, Midland, MI, id 0.132", od 0.183"). The beads were formed by introducing 60 drops per minute of the suspension into acetic acid solution which was placed 3 cm below the tubing. The acetic acid solution was stirred at 80 rpm. After transferring the suspension, stirring was continued for 10 min. The beads were collected on filter paper, washed with distilled water, air dried in a fume hood for 24 hours, and then dried in a oven at 50^0 C for 48 hours. The size of 20 beads was determined microscopically using a calibrated eyepiece.

Indomethacin Content of Beads

An assay for indomethacin in the beads was performed by pulverizing 50 mg of beads and dissolving the beads in 100 ml of pH 6.5 solution. Further dilutions of this solution with the buffer were made and the absorbance at 318 nm was measured spectrophotometrically. 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 indomethacin were calculated for dissolution experiments.

TABLE 1

Formulations of Indomethacin Beads

Drug	Surfactant	Viscosity Agent	Code No.
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% Span 80	0.2 g K 100 M Methocel	VI
1.5 g	2% Tween 80	0.5 g K 100 M Methocel	VII
1.5 g	None	0.5 g K 100 M Methocel	VIII
1.5 g	1% each of Tween 80 & Span 80	0.5 g K 100 M Methocel	IX

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

Evaluation of Drug Degradation

Solutions of indomethacin obtained by dissolving beads were subjected to HPLC assay to evaluate possible degradation of drug during bead preparation. A diluted 10 μl sample was injected onto a Zorbax CN column (4.6 X 150 mm). The mobile phase consisted of 0.1% acetic acid : acetonitrile (65 : 35) and the detection wavelength was 340 nm.

Procedure for Dissolution Studies

The dissolution studies of beads were conducted in a 1000 ml round bottom flask containing 900 ml of pH 6.5 solution as dissolution medium. The solution

was maintained at 37 ± 0.5^0 C and agitated at 75 rpm by means of a sleeve stirrer connected to a motor. The tip of the stirrer was about 2 cm from the bottom of the flask. Then, beads containing 100 mg indomethacin were introduced into the flask at time zero. Subsequent to the introduction of beads, 5.0 ml samples were removed at time intervals of 0.167, 0.333, 0.667, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, and 24.0 hours. After each sampling, 5.0 ml of fresh dissolution medium maintained at 37 ± 0.5^0 C was added to the flask to maintain a constant volume. The samples were filtered through a 0.45 micron filter and were analyzed spectrophotometrically at 318 nm for the amount of indomethacin dissolved at each time interval. The presence of CAP, Tween 80, Span 80, Avicel, Methocel, and glycerin, in the concentrations present in the assay samples, were found not to interfere with the UV analysis of indomethacin. A cumulative correction factor was applied to account for previously withdrawn samples[3]. Dissolution studies were performed at least in duplicate.

Disintegration of Beads

The disintegration of the beads was determined by placing 50 mg of beads in a vial containing 10 ml of simulated gastric fluid without enzymes[4]. The vials were placed in a pre-equilibrated incubator, shaken at 100 oscillations per minute for 1 hr at 37 ± 0.5^0 C and observed for disintegrations. The vials were removed from the incubator shaker and the gastric fluid was decanted. They were rinsed quickly 3 times with distilled water, then 10 ml of simulated intestinal fluid without enzymes[4] was added, and the shaking was continued as described. The disintegration time was recorded when visible particles of the beads could no longer be observed. Three determinations were made for each set of beads.

Statistical Analysis

The values T 25% and T 75% are the times required for 25% and 75% of the drug to be dissolved, respectively. All the values were calculated separately for each replication. Reported values are means of the replications. Percentage of indomethacin dissolved in 1 hour (D1) and 8 hours (D8) were also reported. One way analysis of variance with a Tukey test[5] was used to determine significant differences ($p < 0.05$) among values for the different preparations.

RESULTS AND DISCUSSION

Indomethacin is unstable in alkaline pH conditions. For this reason, a HPLC method was used to evaluate the possible degradation of indomethacin. No loss of indomethacin could be reported based on identical peak shapes and areas and retention times obtained in the chromatogram and absence of extra peaks. Since this drug was for the most part insoluble in the suspension, drug degradation would be expected to be prevented. 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.

Percentage drug incorporated, disintegration values of the preparations and their particle size range in millimeters are reported in Table 2. Preparations composed of 0.5% each of Methocel, Avicel, and glycerin (I, II, III, IV, and V) gave similar disintegration values. Preparations with K 100 M Methocel (VI, VIII, and IX) had longer disintegration values of 125.0 ± 7.1, 130.0 ± 14.1, and 150.0 ± 0.0 minutes, respectively. Particle size values of the preparations are similar with very little variation.

Most of the drug was released from preparations I, II, III, and IV in two to three hours. After this time period, all these formulations yielded similar plateaus. Dissolution profiles of preparations III, V, VI, and VII are shown in Figure 1. Preparation III, with Tween 80 as surfactant, gave a higher plateau compared to preparation V, which contained Span 80. The latter had a maximum dissolution of only 74%. Preparation VII with Tween 80 as surfactant showed a much higher plateau than preparation VI, which contained Span 80. Dissolution profiles of preparations VIII and IX and that of pure indomethacin are shown in Figure 2. Preparations VIII and IX showed differences in their dissolution patterns. The pure drug, indomethacin, showed maximum dissolution in two hrs. The dissolution pattern of preparation IX appears to be zero-order upto 60% dissolved.

Values of T 25%, T 75%, D1, and D8 for different preparations are shown in Table 3. As seen in Table 3, preparation IX gave a T 25% of 190.64 ± 32.26

TABLE 2

Percentage Drug Incorporated, Disintegration and Particle Size Values for the Preparations

Preparation Code No.	Percentage Drug Incorporated	Disintegration Mean ± SD Minutes	Particle Size Range Min. - Mean - Max. Millimeters
I	81.2	42.5 ± 3.5	0.9684-1.2453-1.5789
II	91.0	37.5 ± 3.5	1.0526-1.2658-1.5158
III	88.0	47.5 ± 3.5	1.1474-1.2000-1.4737
IV	97.1	50.0 ± 7.1	1.1474-1.2568-1.5579
V	91.6	55.0 ± 7.1	0.9684-1.3495-1.6210
VI	95.4	125.0 ± 7.1	1.0830-1.3824-1.6900
VII	96.2	60.0 ± 0.0	0.9050-1.2045-1.5612
VIII	98.3	130.0 ± 14.1	1.1322-1.3560-1.6145
IX	93.4	150.0 ± 0.0	1.0345-1.3345-1.6210

minutes, which is significantly higher compared to other preparations. Similarly, the T 75% value is also longer for this preparation. Preparations III (with Tween 80) and V (with Span 80) did not show any significant differences in their T values. Preparations VI and VII with K 100 M Methocel also differ in their surfactant, but showed significant differences in their T values. Preparations III, V, VI, and VII showed significant differences in their D1 and D8 values. Preparations V and VI, which contained Span 80 as surfactant, displayed D8 values of only 73.00 ± 5.66% and 61.50 ± 2.12%, respectively. This illustrates lower solubility of indomethacin with Span 80 preparations.

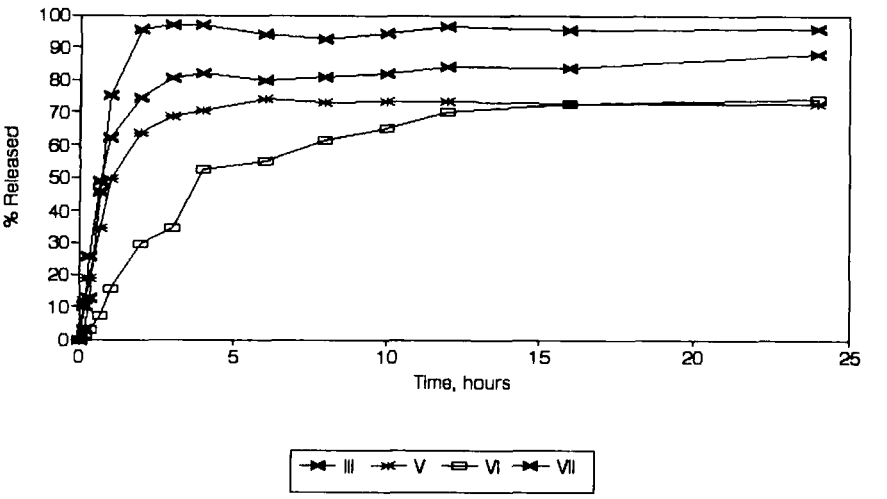

FIGURE 1

Dissolution Profiles of III, V, VI, and VII

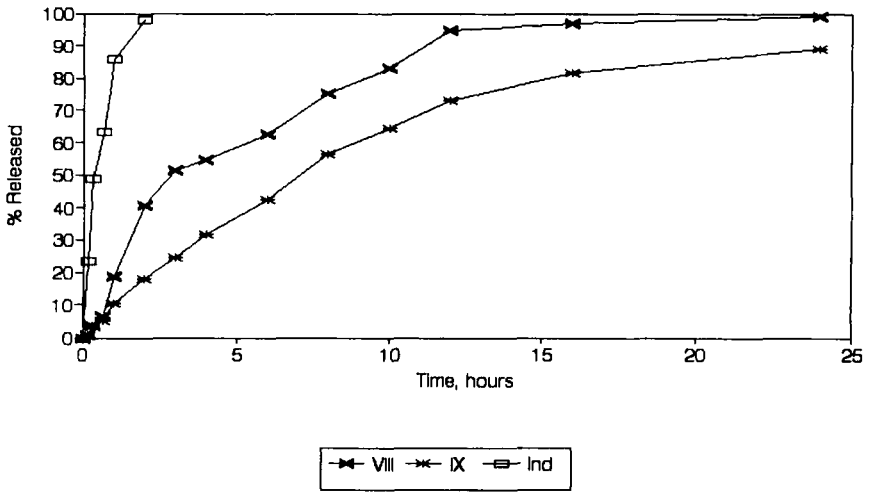

FIGURE 2

Dissolution Profiles of VIII, IX and Ind

TABLE 3

T 25% and T 75% & D1 and D8 Values for the Preparations

Preparation Code No.	T 25% minutes Mean ± SD	T 75% minutes Mean ± SD	D1 % Dissolved Mean ± SD	D8 % Dissolved Mean ± SD
I	14.64 ± 0.50	65.45 ± 7.72	74.00 ± 1.41	94.00 ± 0.00
II	20.14 ± 1.28	57.80 ± 1.24	76.50 ± 0.71	83.00 ± 0.00
III	19.66 ± 0.47	125.00 ± 7.07	62.00 ± 1.41	81.00 ± 0.00
IV	16.56 ± 0.44	66.25 ± 1.77	72.50 ± 0.71	95.50 ± 0.71
V	30.35 ± 6.56	----	49.50 ± 4.95	73.00 ± 5.66
VI	100.72 ± 3.03	----	15.50 ± 0.71	61.50 ± 2.12
VII	27.58 ± 0.11	60.00 ± 0.00	75.00 ± 0.00	92.50 ± 2.12
VIII	77.70 ± 0.79	480.00 ± 0.00	18.50 ± 0.71	75.00 ± 0.00
IX	190.64 ± 32.36*	780.00 ± 72.11*	10.67 ± 1.16*	56.33 ± 1.53*

* indicates IX is significantly different ($p < 0.05$) from all other preparations

The dissolution profiles for preparations, in which Tween 80 was included with 0.5% each of Methocel, Avicel, and glycerin (I, II, III, and IV), had similar plateaus and followed a similar pattern. Preparation IV, which has the highest drug to CAP ratio (0.4 to 1), released most of its indomethacin content in a shorter period of time relative to other preparations. After about 3 hours, 80% of the drug was released from all four preparations. Varying the drug to CAP ratio from 0.1 to 0.4 did not appear to alter dissolution. All these preparations with Tween 80 and 0.5% each of Methocel, Avicel, and glycerin failed to show any

sustained release properties. Preparations V and VI, which contained Span 80, displayed lower plateaus than preparations III and VII, respectively. Span 80 has more lipophilic properties whereas Tween 80 has more hydrophilic character. For these reasons, beads containing Span 80 dissolved slowly and released its drug slower than preparations containing Tween 80. Since Tween 80 is a solubilizing agent, an increase in dissolution is expected. None of the beads disintegrated in simulated gastric fluid even though some contained a considerable amount of excipients with surfactant or glycerin. The inclusion of K 100 M grade methocel prolonged the disintegration and dissolution times considerably. The correlations between T 25% and T 75% versus disintegration time were r = 0.844 and r = 0.939, respectively. In the future, bioavailability studies should be conducted to establish if in vitro disintegration and dissolution studies are predictors of in vivo drug release and absorption for this type of sustained release beads.

CONCLUSIONS

A preparation of K 100 M Methocel beads with equal proportions of the two surfactants released its drug content over a period of 12 hours. A similar preparation, which contained no surfactant, also gave sustained release profile, releasing drug over 10 hours. Rapid release was observed when the preparations contained Tween 80 as a surfactant. Varying the drug to CAP ratio in the suspension from 0.1-0.4 did not appear to alter dissolution. The inclusion of K 100 M grade Methocel into the formulations seemed to retard the rate of drug release. Correlations were observed between dissolution and disintegration values.

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