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Encapsulated hydrophilic polymer beads containing indomethacin as controlled release drug delivery systems

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Encapsulated hydrophilic polymer beads containing indomethacin were prepared by a combined technique of bead polymerization and phase separation. The drug delivery system consisted of the copolymer of 2-hydroxyethyl methacrylate and acrylamide as the core matrix and ethyl cellulose as the barrier membrane. The drug was incorporated into the polymer matrix during the formation of the beads. The system was found to be useful as a sustained release dosage form. Release of drug from the coated beads followed a zero-order rate up to 40% of the drug released. A linear relationship exists between the rate of release and the reciprocal amount of ethyl cellulose used for coating, indicating that the drug release was controlled by the coating thickness. Addition of polyvinyl pyrrolidone in the formulation significantly increased the amount of drug released. Blood level studies showed that drug absorption from the encapsulated beads was slower than that of indomethacin powder. It appeared that indomethacin was completely absorbed from the encapsulated beads.

In the search for effective controlled release drug delivery systems a novel procedure for the preparation of encapsulated hydrophilic polymer beads using a combined technique of bead polymerization and phase separation was developed (Suryakusuma & Jun 1984).

The preparation and testing of encapsulated hydrophilic polymer beads containing indomethacin are now described. Indomethacin was chosen as the model drug because of its known pharmacokinetic properties (Hucker et al 1966; Kwan et al 1976) and its effect of gastric irritation (Boardman & Hart 1967; Rothermich 1966; Alvan et al 1975).

MATERIALS AND METHODS

Indomethacin (Sigma Chemical Co., St Louis, Mo.), ethyl cellulose (Sigma Chemical Co., St Louis, Mo., viscosity 45 cps), azobisisobutyronitrile (Aldrich Chemical Co., Milwaukee, Wis.), polyvinyl pyrrolidone (PVP) (type K-90, GAF Corporation, New York, NY) and cyclohexane (J. T. Baker Chemical Co., Phillisburg, N.J.) were used as received. 2-Hydroxyethyl methacrylate and acrylamide (Aldrich Chemical Co., Milwaukee, Wis.) were also used without further purification.

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Methods

Preparation of encapsulated beads of indomethacin. The encapsulated hydrophilic polymer beads containing indomethacin were prepared by a combined technique of bead polymerization and phase separation (Suryakusuma & Jun 1984). In the present study azobisisobutyronitrile was used as the initiator. Monomers, 2-hydroxyethyl methacrylate and acrylamide (molar ratio of 1 : 1) were polymerized to form a hydrophilic matrix. In certain formulations, polyvinyl pyrrolidone was added to the monomer solution to modify the release rate of indomethacin. The composition, content of indomethacin and yield of the encapsulated products are presented in Table 1.

Determination of indomethacin in the encapsulated beads. Triplicate samples of 100 mg encapsulated beads of indomethacin were placed in a 100 ml volumetric flask containing methanol. The suspension was shaken vigorously to dissolve the ethyl cellulose coating and to release the drug from the beads. Aliquots were filtered and assayed spectrophotometrically for indomethacin at a wavelength of 318 nm until no increase in drug concentration was shown.

Dissolution studies. Dissolution rates of indomethacin from encapsulated beads and indomethacin powder were measured using the USP XX dissolution apparatus. The temperature was maintained at 37 ± 0·5 °C. Triplicate samples containing approximately 75 mg of indomethacin were tested for

dissolution rates of each formulation. The beads were placed and agitated at 100 rev min^{-1} in 900 ml of 1/15 M phosphate buffer, pH 6·5, containing 0·02% polyoxyethylene sorbitan mono-oleate (Tween 80). Five ml aliquots were removed at different times and assayed. An equal dissolution medium was made up to volume immediately after each sample was removed.

Bioavailability studies. Three male dogs, 20–25 kg, were randomly chosen for a cross-over design after an adequate wash-out time. Each dog received hard gelatin capsules containing indomethacin powder and encapsulated indomethacin on separate occasions. Immediately after swallowing the capsule, the dogs were given 40 ml of water. The animals were fasted for 12 h before and 4 h after dosing, water was freely available. Blood samples were collected from the jugular veins immediately before dosing and at 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after dosing. The serum was separated by centrifugation and frozen until analysis. Serum concentrations of indomethacin were assayed using an hplc technique (Jun & Suryakusuma 1982).

RESULTS AND DISCUSSION

Yield and size distribution of encapsulated beads

The average yield of beads from the various formulations was 93·2 ± 1·4% and the percent of indomethacin entrapped in the beads was 91·2 ± 2·2.

Under the conditions used, the size distribution of encapsulated beads containing indomethacin was:

Mean size diam. (μm):	>1000	920	715	505	359	254	<210
% sieve fraction:	3·2	4·8	12·9	41·0	27·4	5·9	4·8

Most beads fell in the range of 350–500 μm. Microscopic examination of the encapsulated beads suspended in cyclohexane (Fig. 1) shows them to be spherical and coated with a thin layer of ethyl cellulose. The electron micrograph of the encapsulated beads (Fig. 2) also shows that the surface of the coated beads is fairly smooth. However, some small particles appear to have adhered to the surface of the large beads.

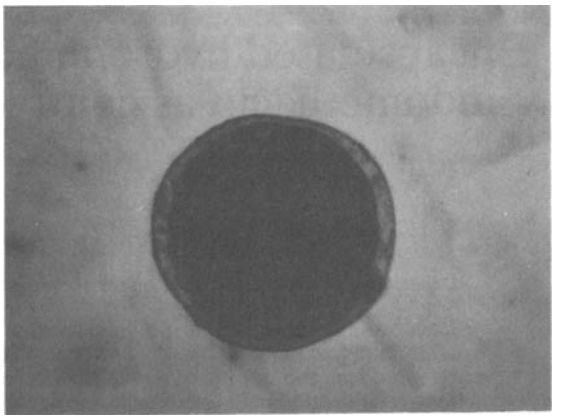

FIG. 1. Photomicrograph of an encapsulated bead with 15% ethyl cellulose and containing indomethacin, mean size 500 μm (×50).

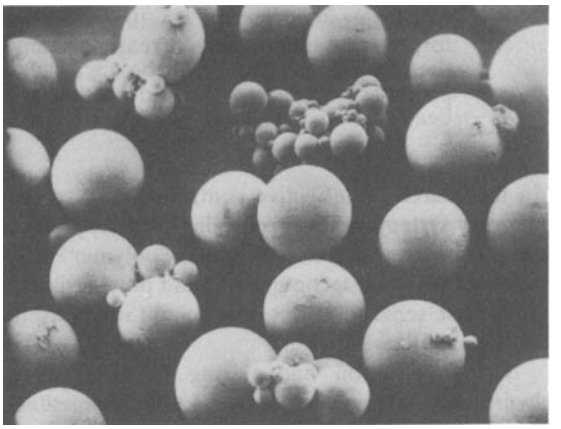

FIG. 2. Scanning electron micrograph of encapsulated beads with 15% ethyl cellulose containing indomethacin, mean size 500 μm (×30).

In-vitro dissolution studies

The rate of drug release from different formulations was measured for 8 h and compared with that of the

Table 1. Composition, content of indomethacin and yield of encapsulated beads formulations.

Formulation	Weight of each ingredient (g)				Yield of beads (%)	% Drug entrapped (amount in the beads/initial drug loading)
	Monomers	Ethyl cellulose	Polyvinyl pyrrolidone	Drug		
1	18·5	1·5		4·0	93·3 ± 0·17	91·2 ± 0·25
2	18·0	2·0		4·0	91·3 ± 0·37	87·9 ± 0·49
3	17·5	2·5		4·0	93·9 ± 0·31	90·3 ± 0·17
4	17·0	3·0		4·0	93·2 ± 0·29	89·1 ± 0·23
5	16·5	3·0	0·5	4·0	92·4 ± 0·20	94·3 ± 0·15
6	16·2	3·0	0·8	4·0	92·7 ± 0·43	86·8 ± 0·51
7	16·0	3·0	1·0	4·0	91·1 ± 0·23	92·5 ± 0·19

powder. The amount of encapsulated beads used for each dissolution test contained approximately 75 mg indomethacin, and the beads were in the range of 350–500 μm. Fig. 3 shows dissolution data of encapsulated beads with varying amounts of ethyl cellulose. The release of indomethacin from the encapsulated beads was slower than that of indomethacin powder. The release rate from the beads encapsulated with 15% (w/w) of ethyl cellulose was essentially linear over 8 h. The rate of release was about 4·5 mg h^{-1}. Although the drug was not completely released from the beads during the test, the results indicate that the ethyl cellulose coating served as a rate controlling barrier. The amount and rate of release of indomethacin from the coated beads were inversely proportional to the amount of ethyl cellulose added to the formulation. When 12·5% and 10% ethyl cellulose were added, the release rates for the first 4 h were 6·75 and 8·25 mg h^{-1}, respectively. When 7·5% ethyl cellulose was added to the formulation, the drug released during the same dissolution period was 80% of the total amount. However, the release rate, which was about 13·1 mg h^{-1}, deviated from linearity after 2 h.

It was previously reported that polyvinyl pyrrolidone increased the dissolution rate of indomethacin (Takayama et al 1980, 1981) in a solid dispersion of indomethacin in polyvinyl pyrrolidone, relative to the pure drug. As expected, the presence of polyvinyl pyrrolidone in the encapsulated bead formulations significantly increased the release of indomethacin from the encapsulated beads. Fig. 4 shows the dissolution data. All beads were coated with 15% ethyl cellulose. Initially, all formulations exhibited a constant rate of release until approximately 30% of drug was released. The total drug released was increased as the concentration of polyvinyl pyrrolidone increased. Encapsulated beads containing 2·5% polyvinyl pyrrolidone showed 50% of the drug released while encapsulated beads containing 4 and 5% polyvinyl pyrrolidone released 80 and 90% of drug, respectively, during the 8 h dissolution. The increase was probably due to an increase in wettability of indomethacin.

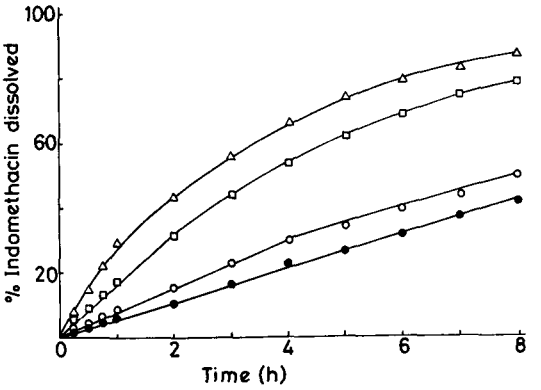

FIG. 4. Dissolution profile of coated hydrophilic polymer beads containing indomethacin. Mean coated beads size, 500 μm. Medium, 1/15 M phosphate buffer pH 6·5 containing 0·02% polyoxyethylene (80) sorbitan monooleate. The amount of polyvinyl pyrrolidone added, 0% ●; 2·5% ○; 4% □; 5% △.

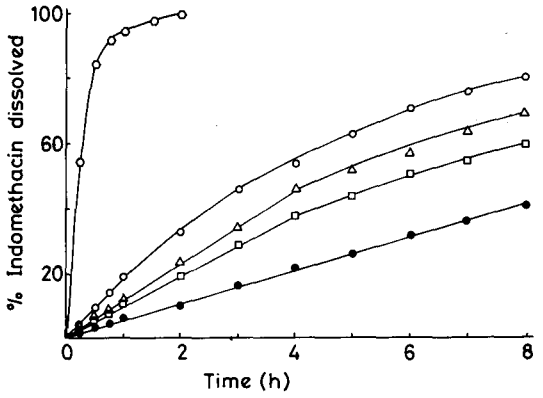

FIG. 3. Dissolution profile of coated hydrophilic polymer beads containing indomethacin. Mean coated beads size, 500 μm, Medium, 1/15 M phosphate buffer pH 6·5 containing 0·02% polyoxyethylene (80) sorbitan monooleate. Key: indomethacin powder, ◇; beads coated with 7·5% ethyl cellulose, ○; 10% ethyl cellulose, △; 12·5% ethyl cellulose, □; 15% ethyl cellulose, ●.

Correlation of release rate and amount of coating material

Reservoir systems as well as matrices are known to be susceptible to boundary effects and thus give a constant release in the early portion of the dissolution process. The rate of release of drug from a spherical reservoir system can be described by the equation (Baker & Lonsdale 1974):

$$\frac{dQ}{dt} = \frac{4\pi r_{in} r_{out} DKC_o}{r_{out} - r_{in}}$$

where: Q = the amount of drug released at time t, DK = the membrane permeability, C_o = the concentration of drug at the internal membrane surface, r_{out} and r_{in} = outside and inside radii of a sphere, respectively. For a given reservoir system, where DK, C_o and membrane thickness (h = r_{out} −

r_{in}) are constant, the apparent zero order rate constant may be obtained as:

$$k_o = \frac{4\pi r_{in} r_{out} DKC_o}{h}$$

This equation indicates that the apparent zero-order rate constant, k_o, should be inversely proportional to the thickness of the coating membrane. Assuming that coating thickness is proportional to the amount of ethyl cellulose added, it follows that the apparent zero-order rate constant, k_o, should be proportional to the reciprocal of amount of ethyl cellulose used. Thus, the slope of the linear regression line of the initial constant release rate of the beads coated with different amounts of ethyl cellulose was plotted against the reciprocal of the amount of ethyl cellulose added. It was found that a linear relationship (correlation coefficient: 0·9949) exists between the apparent zero order release rate and the amount of ethyl cellulose added. This result suggests that the encapsulated beads conform to the reservoir model.

Bioavailability studies

The potential of encapsulated beads as an oral sustained-release dosage form was studied by comparing the pharmacokinetic parameters following oral administration of indomethacin powder and the bead formulation coated with 7.5% ethyl cellulose because it gave the highest indomethacin release during dissolution tests. The dose of drug for powder and beads was adjusted so that each dog received a 7·5 mg kg^{-1} dose of indomethacin with 40 ml water. Fig. 5 shows the mean serum level profiles of indomethacin obtained. The means of the pharmacokinetic parameters that were used to measure bioavailability were: for powder and beads respectively AUC (μg h ml^{-1}) 16·25 ± 0·85, 16·20 ± 0·65; C_{max} (μg ml^{-1}) 4·30 ± 0·65, 1·6 ± 0·35; T_{max}(h) 2·0 ± 0·95, 4·0 ± 0·5; duration above 0·5 μg ml^{-1} (h) 5·5 ± 0·25, 9·0 ± 0·5. Peaks of mean serum concentration of indomethacin were 4·3 and 1·6 μg ml^{-1} following administration of indomethacin powder and the encapsulated bead formulation, respectively. The time of maximum concentration occurred at 2·0 and 4·0 h, respectively for the powder and the coated beads. Both the time and the peak of serum concentration, as shown in Fig. 5, suggest that indomethacin was more slowly absorbed from the encapsulated bead formulation. In addition, the duration at which the serum levels remained above 0·5 μg ml^{-1}, which is the minimum effective concentration of indomethacin (Bennet & Sheiner 1980), following administration of the encapsulated bead formulation was almost twice as great as that after indomethacin powder. As expected, the encapsulated bead formulation shows a longer serum concentration than the indomethacin powder. From the area under the serum concentration *vs* time curve the total amount of drug absorbed was essentially the same. Bechgaard et al (1982) reported that the frequency and severity of side-effects of indomethacin are well correlated with peak plasma concentrations. The results of the present study show that the initial high peak serum concentration disappeared after administration of the encapsulated bead formulation suggesting that side effects might also be reduced.

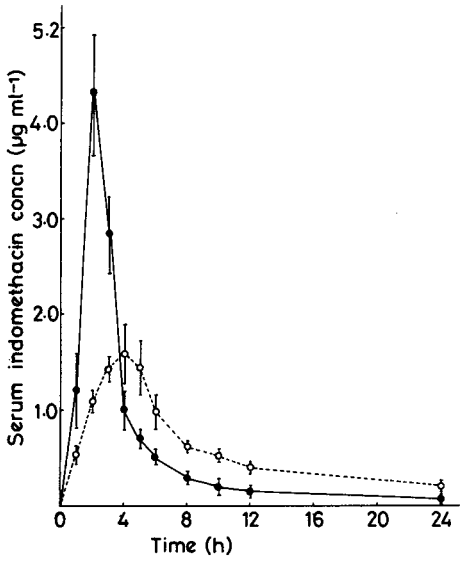

FIG. 5. Mean serum concentration in 3 dogs after oral administration of coated beads containing indomethacin 7·5 mg kg^{-1} dose ○, and indomethacin powder 7·5 mg kg^{-1} dose ●.

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