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A Novel Multiple-Unit Sustained Release Indomethacin–Hydroxypropyl Methylcellulose Delivery System Prepared by Ionotropic Gelation of Sodium Alginate at Elevated Temperatures

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ABSTRACT

A multiple-unit indomethacin delivery system based on hydroxypropyl methylcellulose as the hydrophilic carrier material was developed by a novel technique using the insolubility of the cellulose ether at elevated temperatures and the ionotropic gelation of the polysaccharide, sodium alginate with calcium ions. Spherical beads were prepared by dropping hot sodium alginate solution (60 °C) containing dispersed drug and dispersed hydroxypropyl methylcellulose into the heated calcium chloride solution. Beads with a combined hydroxypropyl methylcellulose–indomethacin solids content of up to 98% could be prepared because of the processing of a hydroxypropyl methylcellulose dispersion rather than a solution. The beads were characterized by dissolution and scanning electron microscopy. The drug release was controlled by the viscosity grade of the hydroxypropyl methylcellulose and the rate of polymer gelation, and could be sustained over an 8-h period.

INTRODUCTION

Most oral sustained or controlled drug delivery systems have been based on insoluble drug carriers such as hydrophobic polymers (Baker, 1987) or waxes (Bodmeier *et al.*, 1990), to retard the drug release and absorption. In recent years, hydrophilic carriers (e.g. cellulosic and acrylic polymers, various polysaccharides), which swell upon contact with aque-

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ous media, have gained in popularity (Suryakusuma & Jun, 1984; Rao & Devi, 1988; Bodmeier *et al.*, 1989*a*). Depending on the drug solubility, the drug is released either by diffusion through a gel network or by erosion of the swollen matrix (Ford *et al.*, 1985*a*). With hydrophilic polymers, unwanted intestinal retention, as could occur with insoluble polymeric materials upon chronic dosing, is avoided because of erosion and dissolution of the polymer matrix within the gastrointestinal tract.

Hydroxypropyl methylcellulose has been the most widely used hydrophilic drug carrier. Matrix tablets were prepared by wet granulation (Lapidus & Lordi, 1966), slugging (Huber & Christenson, 1968), or direct compression (Huber & Christenson, 1966). The drug–polymer powder blend could also be filled into hard gelatin capsules (Dow Chemical Company Information, 1987). The drug release was controlled through variations in the molecular weight of the polymer, drug solubility, the drug:polymer ratio, the particle size of the drug and polymer, and the addition of different additives (Daly *et al.*, 1984; Ford *et al.*, 1985*a*,*b*, 1987; Baveja *et al.*, 1987; Feely & Davis, 1988; Shah *et al.*, 1989).

The major disadvantage of single-unit hydrophilic matrix systems such as tablets or capsules, has been the possibility of uncontrolled erosion as a result of mechanical stress during passage through the gastrointestinal tract, causing erratic drug release and absorption. This drawback could be overcome with multiple-unit dosage forms. The smaller size and the large number of individual particles would minimize unwanted effects due to irregular erosion. In addition, multiple-unit dosage forms spread out more uniformly in the gastrointestinal tract resulting in a more reproducible drug absorption and reduced local irritation with irritant drugs when compared to single-unit dosage forms.

These considerations led to the objective of this study: to prepare multiple-unit drug delivery systems based on hydroxypropyl methylcellulose as the hydrophilic carrier. Beads were prepared by a novel technique based on the solubility characteristics of hydroxypropyl methyl cellulose, being insoluble at higher temperatures, and the ionotropic gelation of sodium alginate with calcium chloride. Indomethacin was the model drug because of its frequent use in studies on hydrophilic matrix systems.

EXPERIMENTAL

Materials

The following materials were used as received from commercial suppliers: hydroxypropyl methylcellulose (Methocel E3, E5, E15LV,

E50, K4M, K15M, and K100M; Dow Chemical Co., Midland, MI); calcium chloride, ibuprofen, indomethacin, propranolol, theophylline, methylcellulose (supplier's specification: viscosity of a 2% w/v solution at 25°C were 100 and 4000 cps), sodium alginate (supplier's specification: viscosities of 2% aqueous solutions at 25°C was 3500 cps) (Sigma Chemical Co., St Louis, MO).

Methods

Hydroxypropyl methylcellulose (0·3–1·125 g) and the drug (0·06–0·625 g) were dispersed into aqueous solutions of sodium alginate (0·5% w/v in deionized water) heated to 60°C. Standard formulations contained a total amount of drug and polymer of 1·25 g or 0·60 g. The beads were formed by dropping the bubble-free dispersions (5 ml, 60°C) through a disposable syringe onto gently agitated calcium chloride (1% w/w) solutions (50 ml, 60°C). The gelled beads were separated after 5 min by filtration, rinsed with distilled water, and oven-dried at 60°C to a constant weight. The drug content of the beads was determined spectrophotometrically after extracting/dissolving the beads in pH 7·4 buffer (indomethacin-$\lambda = 265$ nm; ibuprofen-$\lambda = 224$ nm; theophylline-$\lambda = 273$ nm; propranolol-$\lambda = 290$ nm). The methylcellulose beads were prepared in a similar manner.

In-vitro drug release profiles of the beads were obtained by using the rotating paddle apparatus, USP XXII (Hanson Research, Northridge, CA; 50–100 mg beads, 37°C, 50 rpm, 500 ml, 0·1 M pH 7·4 phosphate buffer). All samples were assayed spectrometrically either directly or after appropriate dilution with the release medium. The polysaccharides did not interfere with the assay.

Scanning electron microscopy (SEM) was used to characterize the surface and cross section of the beads. Cross sections were obtained by cutting the beads with a razor blade. The samples were coated for 70 s under an argon atmosphere with gold–palladium (Pelco Model 3 Sputter Coater) and examined with a scanning electron microscope (Jeol JSM 35C).

RESULTS AND DISCUSSION

Water-soluble polymers bearing charged groups can interact and form three-dimensional networks with ions of opposite charge. Beads containing up to 98% water-insoluble drugs or polymeric micro- or nanoparticles were prepared by ionotropic gelation of the polysaccharide,

sodium alginate, with calcium chloride solutions (Bodmeier & Paeratakul, 1989; Bodmeier *et al.*, 1989*b*). The drugs or polymeric micro- or nanoparticles were dispersed into the polysaccharide solution, and dropped into the counterion solution to form gelled droplets. This was followed by either air- or freeze-drying to obtain solid beads.

In the present study, a similar technique was used to prepare a novel oral multiple-unit drug delivery system based on hydroxypropyl methylcellulose as the drug release-controlling polymer. The high viscosity of hydroxypropyl methylcellulose solutions at low polymer concentrations, especially with the higher viscosity grades, made the incorporation of large amounts of hydroxypropyl methylcellulose within the beads impossible. This problem was overcome by preparing dispersions of hydroxypropyl methylcellulose and the water-insoluble drug in heated sodium alginate solution rather than hydroxypropyl methylcellulose solutions in non-heated sodium alginate solution. It is well known that the viscosity of hydroxypropyl methylcellulose and other cellulose ethers such as hydroxypropyl cellulose or methylcellulose, decreases when the temperature is increased because of the dehydration of the polymer. The polymers do not dissolve in hot but only in cold water (Nicholson & Merritt, 1985). This temperature-dependent polymer solubility characteristic allowed the preparation of beads from hydroxypropyl methylcellulose dispersions with significantly higher solids content when compared to polymer solutions. Beads were therefore formed by dropping hot dispersions of hydroxypropyl methylcellulose and indomethacin particles in sodium alginate solutions onto heated aqueous solutions of calcium chloride (see Fig. 1). The droplets instantaneously formed gelled spheres. Strong spherical beads up to a combined hydroxypropyl methylcellulose and drug content of 98% could be easily prepared. A surface and cross section of a hydroxypropyl methylcellulose–indomethacin bead is shown in Fig. 2. If desired, smaller beads could be prepared by forcing the dispersion with compressed air through a nozzle onto the gelation medium (Bodmeier & Paeratakul, 1989). The droplet size could be varied by adjusting the air pressure.

Beads having the same amount but different viscosity grades of hydroxypropyl methylcellulose were prepared in order to study the in-vitro drug release characteristics. A wide range of hydroxypropyl methylcellulose grades characterized by solution viscosities or molecular weights is available (Dow Chemical Company Information, 1985). The viscosities of 2% w/v aqueous solutions at 20°C of the hydroxypropyl methylcellulose grades investigated varied between 3 and 50 cps for the Methocel E grades (E3, 5, 15, 50; the number corresponding to viscosity in cps) and 100 to 100 000 cps for the Methocel K grades (K100, 4M,

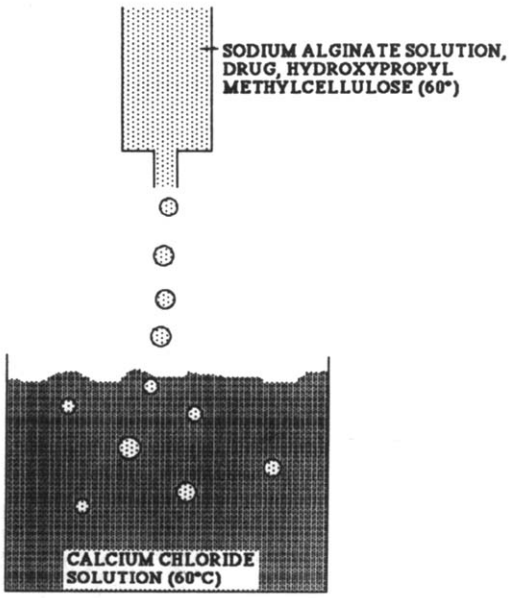

Fig. 1. Schematic diagram of the preparation of hydroxypropyl methylcellulose–indomethacin beads.

15M, 100M). As shown in Fig. 3, the drug release decreased with increasing viscosity grade up to a limiting viscosity above which no further reduction in drug release was seen. The drug release could be sustained over an 8-h period. After wetting the beads, the dissolution medium diffused into the polymer–drug matrix. The hydrophilic polymer, present throughout the beads, hydrated upon contact with the aqueous medium, swelled, and formed a visible gel layer around a solid, undissolved core. The dissolution medium continued to penetrate into the beads until drug and polymer were dissolved. Low viscosity grades released the drug faster because of faster drug diffusion through a less viscous gel layer and faster dissolution or erosion of the hydroxypropyl methylcellulose from the bead surface. Beads prepared with the high viscosity grades were still intact after the drug was completely released, indicating that the drug was released by diffusion through the gel network. When formulating hydrophilic matrix systems, a maximum in sustained release action could be reached after approaching the maximum gel viscosity (Ford *et al.*, 1985*a*; Dow Chemical Information, 1987). This was also observed in this study, as shown by similar drug release profiles with the K4000, 15000, and 100000 cps viscosity grades.

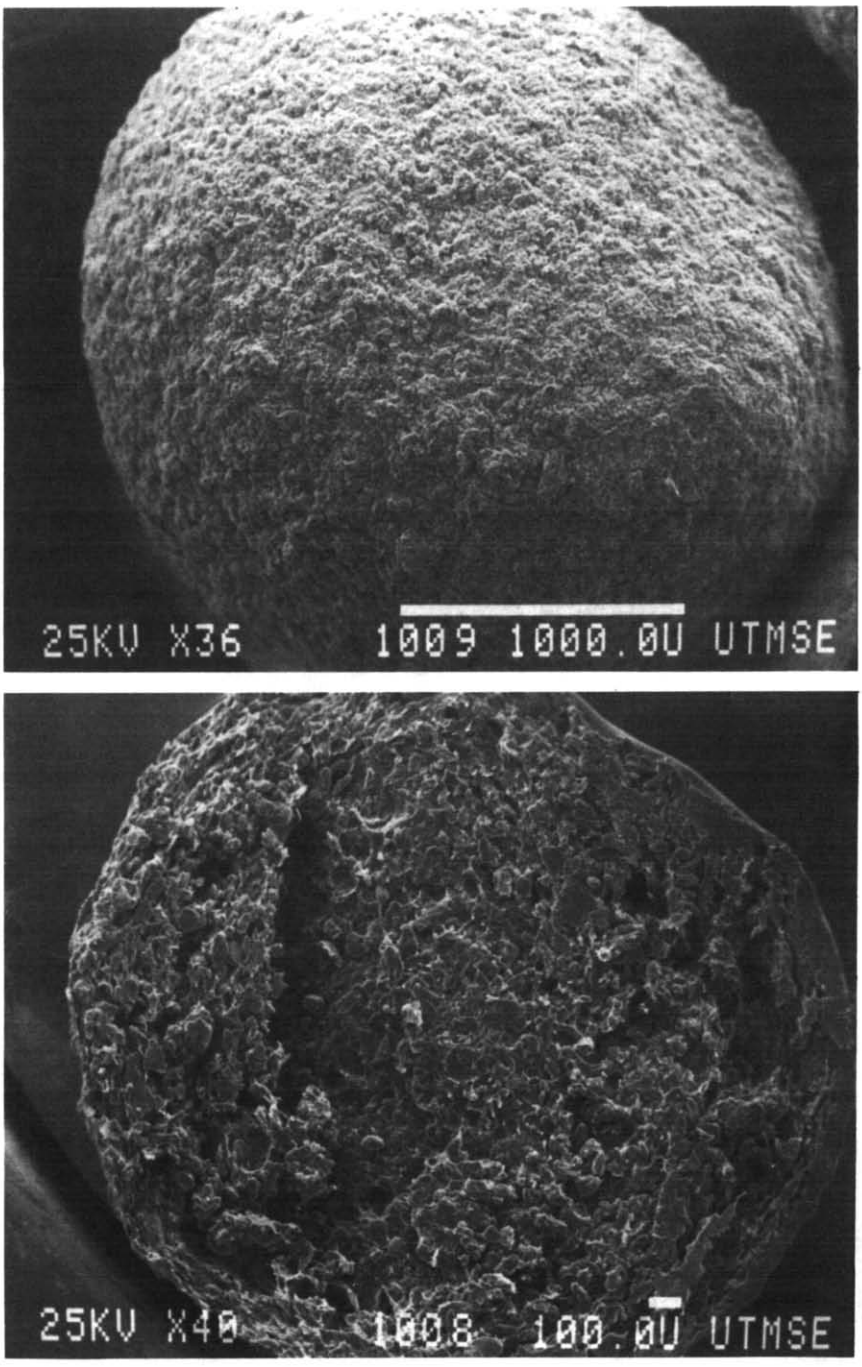

Fig. 2. Scanning electron micrographs of the (a) surface and (b) cross section of the hydroxypropyl methylcellulose–indomethacin bead.

Besides using different viscosity grades, the drug release could also be controlled by blending two viscosity grades as demonstrated with the E3 and 50 cps grades (Fig. 4). The release profiles were intermediate to the profiles of the pure polymers.

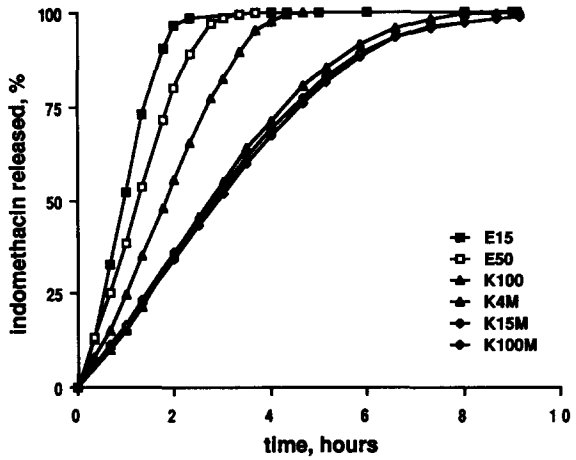

Fig. 3. Effect of the hydroxypropyl methylcellulose viscosity grade (E15, 50, 100, K4M, 15M, 100M; the number corresponds to the viscosity in cps) on the indomethacin release from beads (0·6 g total solids in standard formulation, 10% w/w indomethacin) in 0·1 M pH 7·4 phosphate buffer.

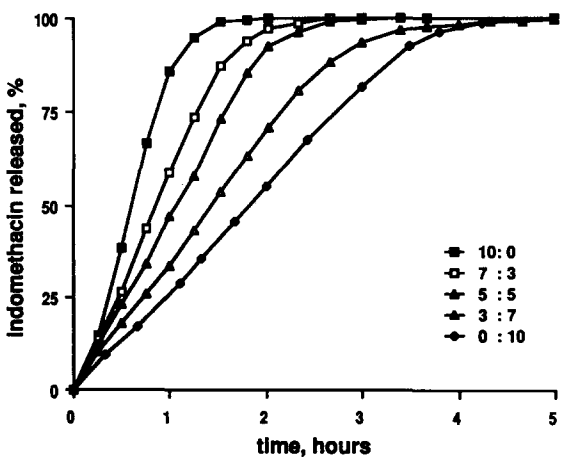

Fig. 4. Effect of the ratio of two hydroxypropyl methylcellulose viscosity grades (E3: E50 cps) on the indomethacin release from beads (1·25 g total solids in standard formulation, 10% w/w indomethacin) in 0·1 M pH 7·4 phosphate buffer.

The effect of drug loading (10, 20, 30, 40, 50% w/w theoretical indomethacin loading) on the drug release from beads prepared with a low viscosity grade hydroxypropyl methylcellulose (E50) is shown in Fig. 5. The actual drug loading was within 1% of the theoretical loading,

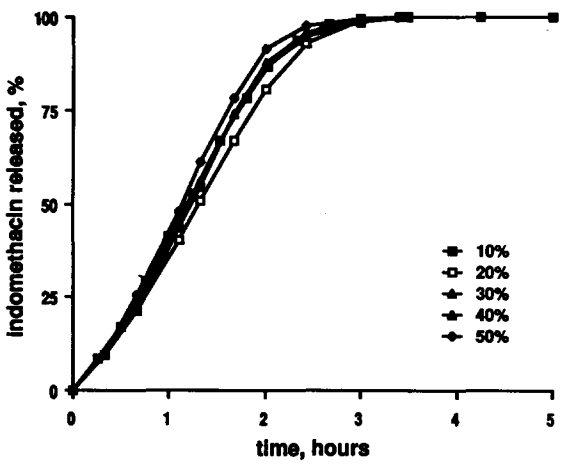

Fig. 5. Effect of the indomethacin loading (10–50% w/w) on the drug release from hydroxypropyl methylcellulose (E15) beads (1·25 g total solids in standard formulation) in 0·1 M pH 7·4 phosphate buffer.

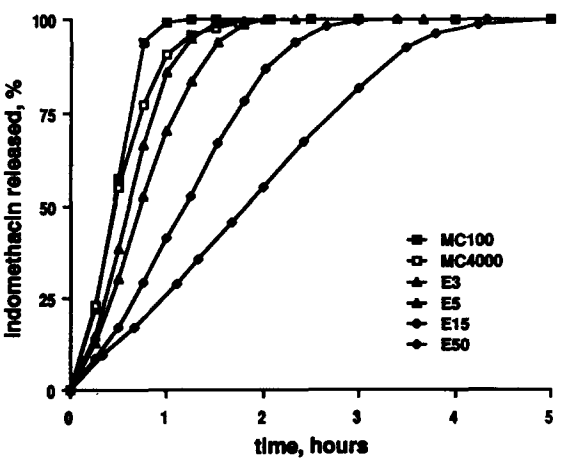

Fig. 6. Effect of the type of cellulose ether (methylcellulose, MC100 and 4000 cps; hydroxypropyl methylcellulose, E3, 5, 15, 50) on the indomethacin release from beads (1·25 g total solids in standard formulation, 10% w/w indomethacin) in 0·1 M pH 7·4 phosphate buffer.

indicating that indomethacin was not lost to the external calcium chloride solution during the preparation of the beads. It has been reported that water-soluble drugs are released both by diffusion through the polymer gel and by gel erosion, while water-insoluble drugs are released primarily by the erosion mechanism (Ford *et al.*, 1985*a*). With indomethacin, a water-insoluble drug, the drug release was insensitive to the drug loading with the low viscosity grade hydroxypropyl methylcellulose, indicating an erosion-controlled drug release mechanism.

In order to achieve sustained release with hydrophilic polymers, the polymer must hydrate and form a gel layer rapidly on the bead surface. The rate of gel formation is critical to prevent rapid penetration of the dissolution medium into and drug dissolution from the interior of the bead. This was evident when comparing the drug release from hydroxypropyl methylcellulose beads to that from beads prepared with methyl cellulose (Fig. 6). The drug release was rapid and complete within an hour with the methyl cellulose beads. The methylcellulose beads did not hydrate to form a gel layer, but disintegrated rapidly in the dissolution medium, thus explaining the faster drug release when compared with the hydroxypropyl methylcellulose beads.

In conclusion, a multiple-unit drug delivery system based on hydroxypropyl methylcellulose as the hydrophilic drug carrier was prepared by a novel technique based on the ionotropic gelation of sodium alginate, and the insolubility of the cellulose ether at elevated temperature. The beads had sustained release properties because of the rapid hydration and formation of a gel layer. Considering the final dosage form, the beads could be administered as prepared or be filled into capsules.

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