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Report

A Novel Approach to the Oral Delivery of Micro- or Nanoparticles

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A novel oral multiple-unit dosage form which overcame many of the problems commonly observed during the compression of microparticles into tablets was developed in this study. Micro- or nanoparticles were entrapped in beads formed by ionotropic gelation of the charged polysaccharide, chitosan or sodium alginate, in solutions of the counterion, tripolyphosphate (TPP) or calcium chloride ($CaCl_2$), respectively. The described technique did not change the physical properties of the microparticles, and it allowed a high microparticle loading (up to 98%). The ionic character of the polymers allowed pH-dependent release of the microparticles. Chitosan beads disintegrated and released the microparticles in 0.1 *N* HCl, while calcium alginate beads stayed intact in 0.1 *N* HCl but rapidly disintegrated in simulated intestinal fluids. Coating the calcium alginate beads with cellulose acetate phthalate resulted in an enteric drug delivery system. Scanning electron microscopy and dissolution and disintegration tests were used to characterize the microparticle-containing beads. The disintegration time of the beads was studied as a function of the solution viscosity of the polysaccharide, gelation time, counterion concentration, and method of drying.

KEY WORDS: chitosan; microencapsulation; microspheres; nanoparticles; oral drug delivery systems; sodium alginate.

INTRODUCTION

Drugs for oral use have been microencapsulated for a variety of reasons. Microencapsulation has been employed to sustain the drug release, to disguise the unpleasant taste of a variety of drugs, to reduce or eliminate gastrointestinal tract irritation, and to separate incompatible drugs (1,2). Tablets designed for controlled-release oral drug delivery are often nondisintegrating. This can cause local irritation and erratic absorption. Multiple-unit dosage forms spread out uniformly in the gastrointestinal tract. This results in a more reproducible drug absorption and reduces local irritation compared to single-unit dosage forms. In addition, unwanted intestinal retention of the polymeric material, which may occur with nondisintegrating tablets on chronic dosing, is avoided (3).

The formulation of microparticles into oral dosage forms, however, may encounter several problems. If microcapsules are to be compressed successfully, good flow properties are essential and the capsule wall must be capable of resisting the severe mechanical stress during compression. Poor flow properties can cause problems in content uniformity. Microcapsules, when compressed under high pressure, may rupture and lose their protective or sustained release action (4). The poor compressibility often requires the addition of large amounts of easily compressible excipients. This dilution could result in a drug content too low in the final dosage form. Fassihi studied the consolidation behavior of polymeric behavior and reported both plastic deformation and particle fusion to be operative during compression (5). The possible fusion of polymeric microparticles during compression could result in a nondisintegrating matrix with the loss of the character of a multiple-unit dosage form. Nixon and co-workers reported that the tableting of microcapsules resulted in a nondisintegrating matrix and in a reduction of drug release (6).

We overcame these problems by developing a delivery system for micro- or nanoparticles in bead form. Water-soluble polymers bearing positively or negatively charged groups can interact and form three-dimensional networks with molecules of opposite charges. Living cells were encapsulated in beads formed by gelling the anionic polysaccharide, sodium alginate, with $CaCl_2$ solutions (7). We entrapped water-insoluble drugs within beads prepared from the polycationic polysaccharide, chitosan, and tripolyphosphate (8). The same principle was used in this study to entrap drug-containing microparticles. Beads were formed by dropping dispersions of the microparticles in either chitosan or sodium alginate solutions into aqueous solutions of the counterions tripolyphosphate or $CaCl_2$.

MATERIALS AND METHODS

The following chemicals were obtained from commercial suppliers and used without further purification: chitosan with a viscosity of 2790 cps at 25°C (1%, w/w, in 1%, v/v,

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acetic acid) (Protan Laboratories, Redmond, Wash.), calcium chloride, ethylcellulose, propranolol, sodium alginate (three samples, supplier's specification; viscosities of 2% aqueous solutions at 25°C were 250, 3500, and 14,000 cps), tripolyphosphate (Sigma Chemical Co., St. Louis, Mo.), cellulose acetate phthalate NF (CAP) (Eastman Chemical Products, Inc., Kingsport, Tenn.), Aquacoat (FMC Corporation, Philadelphia, Pa.).

Drug-free ethylcellulose microspheres or microspheres containing propranolol (19%, w/w) were prepared by the solvent evaporation method as described previously (9). The microparticles were dispersed into aqueous solutions of either chitosan [1%, w/v, in dilute acetic acid (1%, v/v)] or sodium alginate (1%, w/v, in deionized water). The beads were formed by dropping the bubble-free dispersions (3 ml) through a disposable syringe onto gently agitated solutions of the counterion (30 ml), tripolyphosphate (TPP) or $CaCl_2$, respectively. The gelled beads were separated after a short period of time, rinsed with distilled water, and either freeze-dried (Labconco Model 75034, Kansas City, Mo.) or air-dried. The drug content of the microspheres and the drug content uniformity of the beads were determined spectrophotometrically after extraction in methanol (λ = 295 nm, N = 3, coefficient of variation < 3%).

The following preparative variables were investigated in this study: microparticle loading (solids content: 0, 75, 85, 90, 93, 95, and 98%, w/w), gelation or stirring time (1, 5, 15, 30, and 60 min), $CaCl_2$ concentration (1, 3, and 5%, w/v), and solution viscosity of sodium alginate. Calcium alginate beads were prepared from the medium viscosity sodium alginate sample, unless otherwise mentioned.

Disintegration studies were performed in 0.1 N HCl and simulated intestinal fluid (IF) (USP XXI) in a basket-rack assembly with disks complying with the experimental conditions described in the USP XXI (three beads per tube; N = 3).

In vitro drug release profiles of the beads (microsphere loading, 95%, w/w; counterion concentration, 1%, w/v; gelation time, 2 min) were obtained by the rotating bottle method (N = 3; 37°C, 26 rpm, 50 ml 0.1 N HCl or simulated intestinal fluid). The samples were assayed spectrophotometrically (λ = 295 nm for propranolol).

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 sec 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

In the present study, a novel oral multiple-unit delivery system of agglomerated microparticles is described. The interactions between the positively charged amino groups of chitosan and the negatively charged counterion, tripolyphosphate, and between the anionic sodium alginate and Ca^{2+} were used to entrap the microparticles. Beads were formed by dropping dispersions of the microparticles in either chitosan or sodium alginate solutions onto aqueous solutions of the counterions. The droplets instantaneously formed gelled spheres by ionotropic gelation. Strong spherical beads were prepared up to a microparticle content of 98%. A cross section of a calcium-alginate bead containing 95% ethylcellulose microspheres is shown in Fig. 1a. Smaller beads could be prepared by forcing the dispersion with compressed air through a nozzle onto the gelation medium (Fig. 1b). The droplet size could be varied by adjusting the air pressure. In addition to microparticles, colloidal particles can be entrapped by this technique. Drug-containing nanoparticles can be formed either by emulsion polymerization (10) or by emulsification of a drug–polymer solution in a water-immiscible organic solvent in water (11). The nanoparticles are generally kept in suspension or are freeze-dried. If it is desired to formulate the nanoparticles into an oral dosage form (12), an aqueous suspension may cause stability problems and the formulation of solid particles may encounter problems discussed under Introduction. A commercially available aqueous ethylcellulose latex (Aquacoat) was used as a model nanoparticle suspension. Beads containing the nanoparticles were formed either by dispersing spray-dried latex particles in the polysaccharide solution or by mixing the sodium alginate solution directly with the colloidal dispersion prior to gelation in $CaCl_2$ (Figs. 1c and d). If the nanoparticles are stabilized with ionic surfactants or ionic surface groups, compatibility with the polysaccharide solution is a prerequisite for successful bead preparation. When combining the ethylcellulose latex, which was stabilized with an anionic surfactant, with the positively charged chitosan solution, both latex coagulation and gelling of the polysaccharide solution were observed. This potential problem could possibly be overcome by stabilizing the nanoparticles with a polymeric, nonionic colloid.

The objective of this study was to develop a system which released the microparticles rapidly upon contact with either gastric or intestinal fluids. The disintegration time of the beads was a good measure of the time required for microsphere release. The disintegration of the beads depended upon the penetration of the dissolution medium and the subsequent hydration and dissolution of the polysaccharide matrix. The ionic character of the polysaccharides allowed pH-dependent release of the microparticles in the gastrointestinal tract. Chitosan beads which dissolved below pH 6 released the microparticles in 0.1 N HCl, while calcium alginate beads stayed intact in 0.1 N HCl but rapidly disintegrated in simulated intestinal fluids. Microparticles entrapped within calcium alginate beads did not disintegrate in 0.1 N HCl within 24 hr.

The disintegration time of the beads was studied as a function of the disintegration medium, the microparticle loading, microparticle size, the viscosity of the polysaccharide solution, the amount of counterion, and the method of drying (freeze- or air-drying). The disintegration time of calcium alginate beads in simulated intestinal fluid could be varied between 10 and 120 min. The disintegration time of chitosan beads in 0.1 N HCl varied between 5 and 100 min.

The effect of microsphere loading and $CaCl_2$ concentration on the disintegration time of calcium alginate beads is shown in Fig. 2. The disintegration time increased with increasing concentration of the gelling agent. The calcium ions reacted with the negatively charged carboxyl groups of the sodium alginate molecules and formed a gel by ionic cross-linking. The hydration and rate of drug release from hydro-

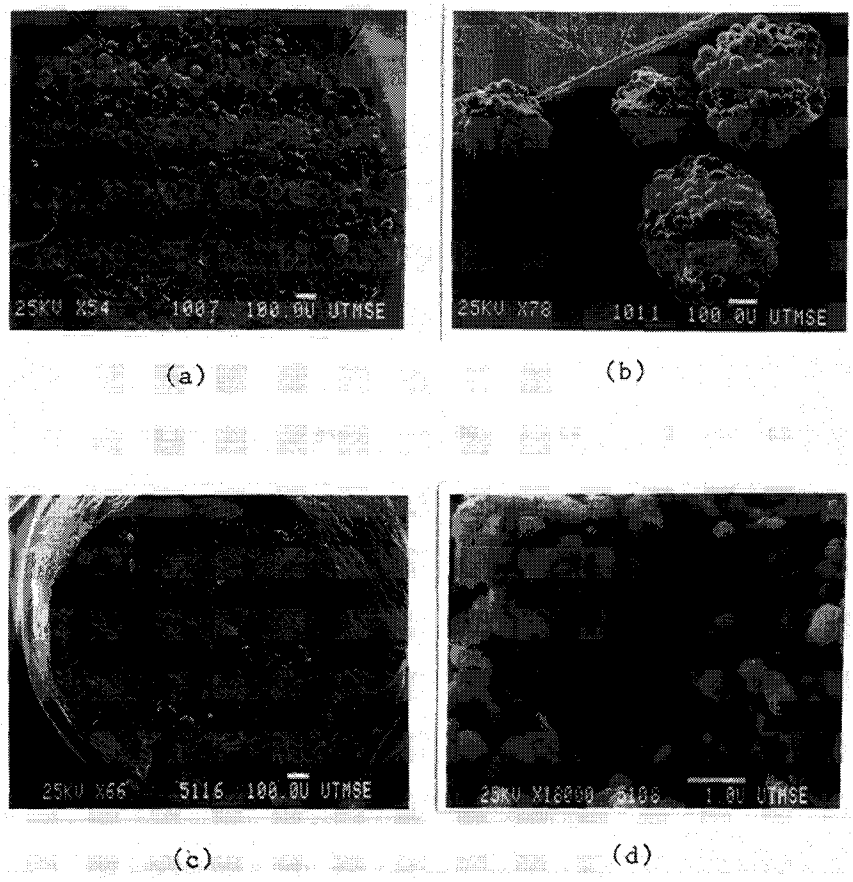

Fig. 1. Scanning electron micrographs of (a) a calcium alginate bead containing 95% (w/w) ethylcellulose microspheres, (b) small calcium alginate beads containing 95% ethylcellulose microspheres, (c) a calcium alginate bead containing 98% nanoparticles, and (d) a calcium alginate bead containing 98% nanoparticles.

gels decreased with increasing degree of cross-linking (13). The same trend was observed in this study. A higher degree of cross-linking resulted in slower disintegration times. As expected, the disintegration time decreased with increasing microsphere loading because of the increase in loading:matrix ratio. The effect of microsphere loading on disintegration time became less pronounced with decreasing $CaCl_2$ concentration. Similar tendencies were observed with chitosan beads in 0.1 *N* HCl (Fig. 3). The beads disintegrated in 0.1 *N* HCl but stayed intact in intestinal fluids.

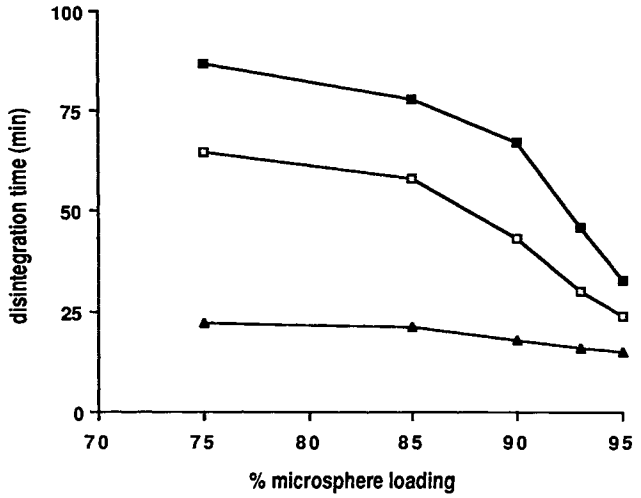

Fig. 2. Effect of $CaCl_2$ concentration and microsphere loading on the disintegration time of calcium alginate beads in simulated intestinal fluids (gelation time, 30 min): (■) 5% $CaCl_2$; (□) 3% $CaCl_2$; (▲) 1% $CaCl_2$.

The effect of gelation time on disintegration time is shown in Fig. 4. Longer exposure of the beads to the counterion solution probably increased the degree of cross-linking and hence the disintegration time. However, short gelation times of 1 to 5 min were preferred. They produced strong beads and resulted in both negligible extraction of the drug from the microspheres during bead preparation and rapid bead disintegration.

The disintegration time increased with an increase in the solution viscosity of the sodium alginate sample as shown in Fig. 5. Kohn reported that stable interchain junction zones form above a minimum critical sequence length for calcium-alginate gels (14). The interactions were individually weak and long arrays of noncovalent bonds acting together were required for gel stability. Stronger gels were apparently formed with the higher molecular weight samples.

Freeze-drying of the samples resulted in larger and hence more porous beads and slightly faster disintegration times compared to air-dried beads. Freeze-drying had the advantage of avoiding drug extraction by immediately freezing and removing the water present within the beads by sub-

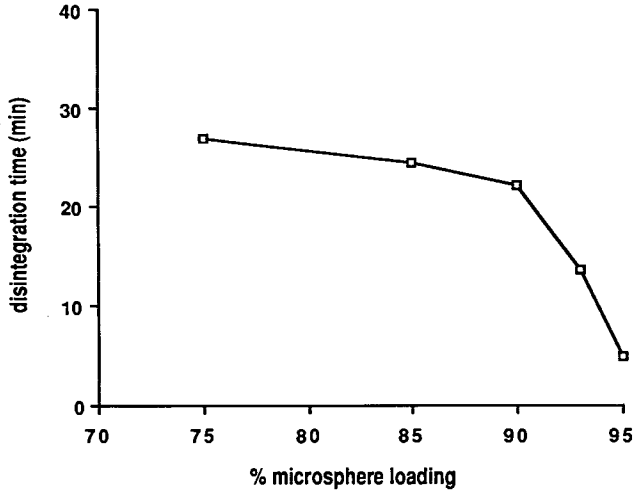

Fig. 3. Disintegration time of chitosan beads in 0.1 *N* HCl (3% TPP; gelation time, 30 min).

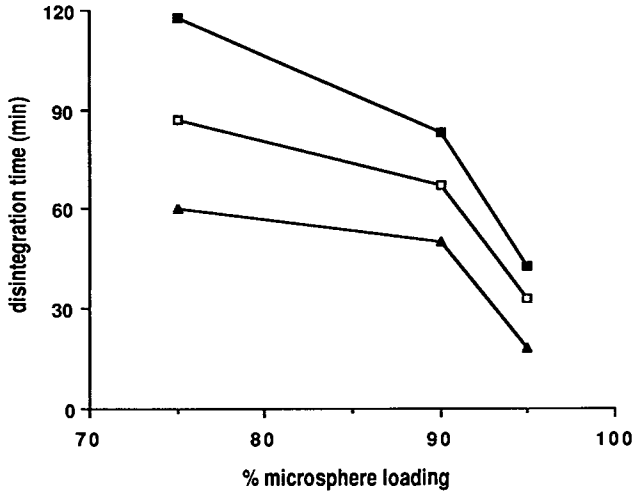

Fig. 5. Effect of sodium alginate solution viscosity on disintegration time of calcium alginate beads in simulated intestinal fluids (gelation time, 30 min; 3% $CaCl_2$; 90%, w/v, microsphere loading): (■) 14,000 cps; (□) 3500 cps; (▲) 250 cps.

limation. The microspheres were exposed to water within the gelled beads for longer periods of time when air-dried. Depending upon the drug solubility, this could result in drug extraction from the microspheres and a burst effect during the dissolution study.

Ethylcellulose microspheres containing propranolol were used as model drug-containing microparticles. The entrapment of microspheres within chitosan or calcium alginate beads resulted in an excellent drug content uniformity. Figures 6 and 7 compare the release of propranolol from ethylcellulose microspheres entrapped in alginate or chitosan beads to the drug release from nonagglomerated microspheres in 0.1 *N* HCl and intestinal fluids. Very little difference was seen between the propranolol release from nonagglomerated microspheres and the release from microspheres entrapped within the alginate or chitosan matrix. Although the calcium alginate matrix was insoluble in 0.1 *N* HCl and the beads did not disintegrate, propranolol was released. Calcium alginate was permeable to the acidic dissolution medium and did not form an enteric diffusion barrier. Cellulose acetate phthalate has been widely used as an enteric coating material (15). To develop an enteric drug delivery system with sustained release properties in intestinal fluids, the calcium alginate beads were dip-coated with a solution of cellulose acetate phthalate in acetone (10%, w/v). As can be seen in Fig. 6, the enteric coating eliminated the drug release in 0.1 *N* HCl. The coated beads disintegrated rapidly in intestinal fluids and drug release was similar to the release from the uncoated beads and microspheres (Fig. 7).

In conclusion, the proposed method is simple, rapid, and mild and overcomes many problems observed during the tableting of microparticles. It results in high micro- or nanoparticle loading, good flow properties, and does not change

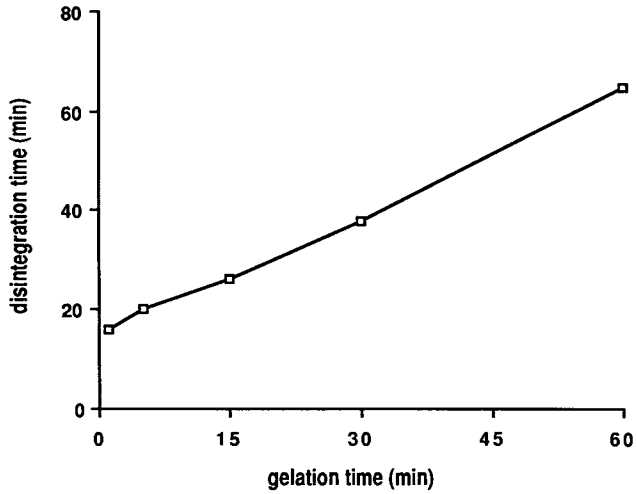

Fig. 4. Effect of gelation time on disintegration time of calcium alginate beads in simulated intestinal fluids (3% $CaCl_2$; 90%, w/v, microsphere loading).

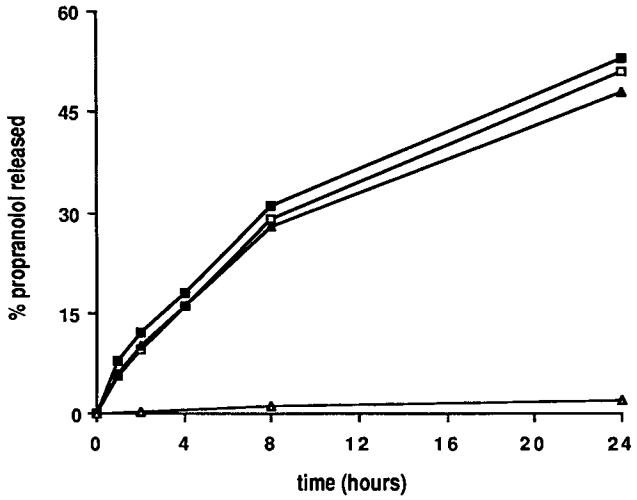

Fig. 6. Propranolol release from beads (95%, w/v, microsphere loading; counterion concentration, 1%, w/v; gelation time, 2 min) in 0.1 *N* HCl from (■) microspheres entrapped within chitosan beads, (□) microspheres, (▲) microspheres entrapped within calcium alginate beads, and (△) microspheres entrapped within calcium alginate beads and coated with cellulose acetate phthalate.

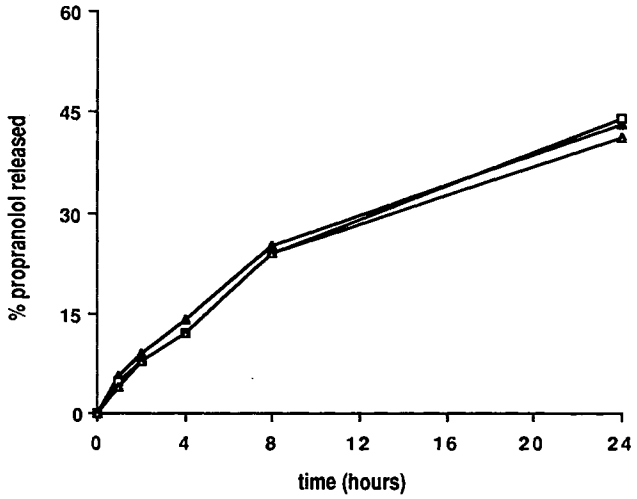

Fig. 7. Propranolol release from beads (95%, w/v, microsphere loading; counterion concentration, 1%, w/v; gelation time, 2 min) in simulated intestinal fluids from (▲) microspheres entrapped within calcium alginate beads, (□) microspheres, and (△) microspheres entrapped within calcium alginate beads and coated with cellulose acetate phthalate.

the physical properties of the microparticles. The ionic character of the polysaccharides allows pH-dependent release of the microparticles in the gastrointestinal tract. Considering the final dosage form, the beads could be administered as prepared or be filled into capsules.

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