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Report

Controlled Gastric Emptying. II. *In Vitro* Erosion and Gastric Residence Times of an Erodible Device in Beagle Dogs

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An erodible gastric retention device fabricated from various polymeric blends was examined *in vitro* for its dissolution properties and *in vivo* in fasting dogs for assessment of its gastric retention potential. Dissolution studies were conducted with extruded rods of polymer blends to assess their potential as candidates for the erodible component of a gastrically retained device. Based on results from dissolution studies, rods of poly(ortho ester)/polyethylene blends (POE/PE) (45% erosion at pH 1.5 and 24 hr) were used to fabricate arms for tetrahedron-shaped devices. Corners for the tetrahedral device were fabricated from Silastic 382 loaded with 15% barium sulfate for X-ray visualization. Beagle dogs were dosed with tetrahedron-shaped test devices administered in gelatin capsules and gastric retention monitored by X ray over a 24-hr period. A comparison of *in vitro* erosion rates and *in vivo* performance of various polymer blends indicated a definite trend for increased gastric retention of devices made from the more slowly eroding blends. The results indicate that the blending of erodible and nonerodible polymers is a valid approach for obtaining materials that will provide the necessary structural properties to achieve gastric retention yet lose integrity within a desired time.

KEY WORDS: controlled gastric emptying; erodible device; physical parameters; dogs.

INTRODUCTION

Recent pharmaceutical developments have resulted in oral drug delivery systems which can control drug release in a predetermined pattern ranging from a few to >24 hr. Effective drug therapy depends not only on the drug release pattern from the formulation, but also on the kinetics of drug absorption from the gastrointestinal (GI) tract and presystemic metabolism. Some drugs are effectively absorbed in all parts of the GI tract (Metoprolol), while others are absorbed only in the small intestine (1). Small intestinal transit occurs over 3–5 hr and cannot be lengthened significantly by changes in the physical properties of the delivery system (2). Extension of the absorption period can most reliably be achieved via retention of the formulation in the stomach, where the drug can be released in a controlled fashion.

Previous work in beagle dogs (11–15 kg) has shown that a nondisintegrating, open, tetrahedral-shaped device administered in a hard gelatin capsule is consistently retained in the stomach for at least 24 hr (3). For practical use, a drug delivery device must also be designed to exit reliably from the stomach at the desired time. One method to allow programmed removal of the device would be to design a device which is erodible in the stomach. For such erodible materials to function appropriately under gastric conditions, the following characteristics are necessary: (a) pH-independent erosion at pH < 5.5, (b) sufficient material integrity against stomach contractile forces to retain the device in the stomach during erosion, and (c) disintegration or loss of mechanical integrity permitting passage from the stomach in a specified time range. Blends of erodible and nonerodible polymers have been examined *in vitro* and *in vivo* as potential candidates for the components of gastrically retained platforms.

MATERIALS AND METHODS

Extrusion Procedure

Poly(ortho ester)/polyethylene blends (POE/PE) with and without phthalic anhydride were extruded using a Custom Scientific Instruments Max-Mixing Extruder. Poly(ortho ester) powder (65% 1,6-hexanediol:35% t-cyclohexane-dimethanol; w/w) (POE) was obtained from SRI International. Phthalic anhydride was obtained from Aldrich Chemicals Co. The POE and PE were compounded by hand mixing and manually fed into the extruder hopper. Extrusion temperatures were 180°C (header) and 175°C (rotor). Take-up speed was 25 rpm.

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Poly(vinyl alcohol) (Air Products and Chemicals, Inc.), poly(propyleneacrylic acid) (Polysciences, Inc.), and hydroxypropyl methylcellulose phthalate (HPMCP) with 15% diethyl phthalate were extruded using a Custom Scientific Instruments Max-Mixing Extruder. Extrusion temperatures were set at 270°C (header) and 265°C (rotor), 170°C (header) and 165°C (rotor), and 185°C (header) and 170°C (rotor), respectively.

Tableting Procedure

Poly(acrylic acid), poly(3-hydroxybutyrate), poly(vinyl pyrrolidone), vinyl pyrrolidone/vinyl acetate copolymer, and vinyl alcohol/vinyl butyral copolymer were compressed into disks (100 mg) using a 3/16-in.-diameter flat-faced die in a Carver press under 1000 lb of force.

In Vitro Dissolution Study

The effects of pH on the erosion rate of polymeric rods (15.0 × 1.5 mm) or tablets were studied in a water/shaker bath maintained at 37°C and 60 oscillations/min. Each sample was placed in 5 ml of dissolution medium at pH 1.5 (simulated gastric juice 0.9% NaCl, adjusted to pH 1.5 with 1 *N* HCl), pH 4.0 (0.1 *N* sodium acetate, 0.1 *N* acetic acid), or pH 7.0 (0.9% NaCl, 0.47 m*M* NaH_2PO_4, 0.8 m*M* Na_2HPO_4, adjusted to pH 7.0 with 0.067 *M* NaH_2PO_4 and/or 0.067 *M* Na_2HPO_4 solution). At specified time intervals, a sample was removed from the dissolution medium, dried, and weighed. Percentage erosion was calculated from weight loss of the erodible component. After total erosion of the POE a spongy polyethylene ghost remained.

Tetrahedron Fabrication

Tetrahedron-shaped devices were formed by assembling two types of components (Fig. 1). Corners (3 mm thick) for the device were fabricated from Silastic 382 (Dow Corning) and were molded with openings for insertion of device arms at a 60° angle. For X-ray visualization, the Silastic 382 was loaded with 15% barium sulfate ($BaSO_4$). Arms for the device were fabricated from extruded rods (1.5 mm in diameter and 1.5 cm in length) of POE/PE blends. The arms were anchored into the corner with additional Silastic 382. The completed tetrahedron measured 2 cm/side.

In Vivo Dog Model

Twelve male and female Beagle dogs (11–15 kg) were used to study the feasibility of gastric retention of a platform (tetrahedron) for a drug delivery device. Food was withheld from 18 hr before to 36 hr after dosing, and water was available ad lib. An erodible tetrahedron was loaded in a No. 000 or smaller gelatin capsule, and after dosing, each dog was administered 15–50 ml of water. Standard X-ray techniques were employed to identify the *in vivo* location of the test device (CRG compact X-ray unit No. 726B951G). An X ray was taken at the time of dosing to assure the device was in the stomach. Gastric retention was monitored by X ray seven or eight times over a 24-hr period. Most of the devices were retrieved intact from the stools. If the device was retained longer than a 1-week period, it was retrieved endoscopically. The following materials were examined in this model for use as "arms" of the tetrahedron: (a) POE/PE, 50:50, with 0, 0.5, 1.0, 1.5, or 2.0% phthalic anhydride; (b) POE/PE, 65:35; (c) POE/PE, 75:25; (d) POE/PE, 85:15; and (e) POE/PE, 90:10.

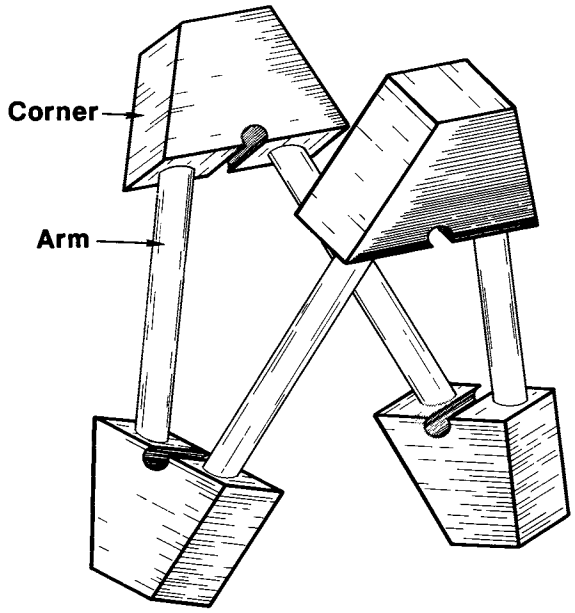

Fig. 1. Gastric drug platform. Tetrahedron-shaped devices formed by assembling two components, silastic corners and polymeric arms.

RESULTS AND DISCUSSION

In Vitro Dissolution Study

A number of polymers were tested for their dissolution properties (Table I). The target for these initial studies was to identify polymers with erosion characteristics compatible with a 24-hr gastric residence device. Of the single-component polymers examined, poly(ϵ-caprolactone), poly(3-hydroxybutyrate), poly(propylene-co-acrylic acid), poly(acrylic acid), and poly(vinyl alcohol) were not pursued beyond the initial observations because their dissolution rates were too slow (0% erosion at 12 hr). In contrast, the dissolution rates of poly(vinyl pyrrolidone), *n*-vinyl pyrrolidone/vinyl acetate copolymer, and the vinyl alcohol/vinyl butyral copolymer were too fast (100% erosion at 12 hr) to be suitable materials for a 24-hr device. Blending these fast-eroding polymers with nonerodible thermoplastics, such as polyethylene (PE), it was not possible to decrease the erosion rate due to the wide differences in the melting temperatures of the various polymers.

Poly(ortho ester) (POE) is a hydrophobic polymer with a wide range of erosion rates which can be controlled by the incorporation of acid anhydride catalysts (5,6). The erosion is a chemical hydrolysis of the polymer backbone, producing water-soluble by-products. POE rods alone eroded 26% in 12 hr in pH 1.5 simulated gastric juice. Prior to attempts to increase the erosion rate by incorporating acid anhydride, the physical properties of the POE rods were modified to decrease rigidity and increase flexibility, thereby allowing satisfactory tetrahedron assembly for *in vivo* testing. Poly-

Table I. Preliminary *in Vitro* Dissolution Study

Material	Fabrication method	% dissolution at 12 hr		
		pH 1.5	pH 4.0	pH 7.0
1. Poly(ϵ-caprolactone)	Extrusion	0	0	0
2. Poly(3-hydroxybutyrate)	Tableting	0	0	0
3. Poly(vinylpyrrolidone)	Tableting	100	—	0
4. Poly(propylene-co-acrylic acid)	Extrusion	0	0	0
5. Poly(acrylic acid)	Tableting	0	0	0
6. Poly(vinyl alcohol)	Extrusion	0	0	0
7. Poly(ortho ester)	Extrusion	26	0	—
8. Klucel HF	Extrusion	100	—	—
9. Vinylpyrrolidone/vinyl acetate copolymer	Tableting	100	—	100
10. Vinyl alcohol/vinyl butyral copolymer	Tableting	100	—	100
11. HPMCP[a] 15% diethylphthalate	Extrusion	0	0	0
Polymer Blends				
Poly(ortho ester)/polyethylene, 50/50	Extrusion	45	0	0

[a] Hydroxypropyl methylcellulose phthalate.

ethylene (PE), a noneroding polymer, was blended with POE to provide devices of the desired flexibility and strength.

Figure 2 summarizes the *in vitro* dissolution data of the POE/PE blends in pH 1.5 simulated gastric fluid. By blending PE with POE, some degree of erosion rate control was achieved at pH 1.5. In Table I POE, a homogeneous polymer, exhibited 26% dissolution at 12 hr, and in Fig. 2 POE 50/50, a polymer blend, exhibited 45% dissolution at 12 hr. Electron microscopic cross sections of extruded rods of POE and POE/PE blends revealed distinct structural differences. The POE/PE blends were porous structures composed of a noneroding polyethylene matrix filled with erodible POE. The POE rods were homogeneous. Because of the structural dissimilarities between these two polymers, one might expect differences in dissolution rate. As the amount of polyethylene in the POE/PE rod increased, the POE erosion rate decreased. No erosion was observed at pH 4 and 7.

In order for the device to erode at any site in the GI tract, particularly if premature loss from the stomach occurs, pH-independent erosion is required. These previously tested

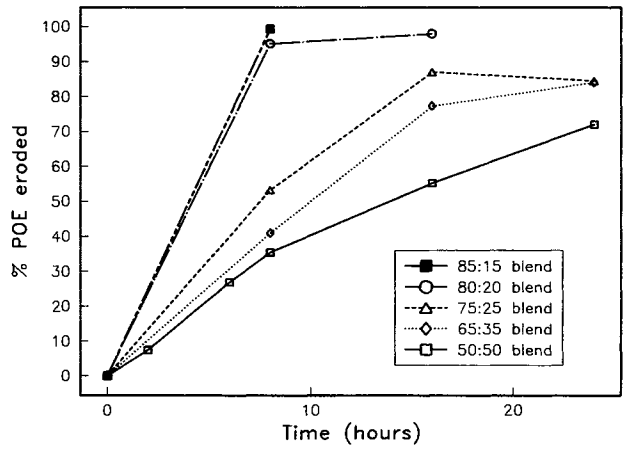

Fig. 2. Dissolution of POE:PE blends. Polymeric rods made from POE:PE blends were incubated at 37°C in simulated gastric juice (pH 1.5).

POE/PE blends were unacceptable since they exhibited a pH-dependent erosion (no erosion at pH 4 or greater). Therefore various amounts of phthalic anhydride were added to the 50/50 POE/PE blend in an attempt to provide pH-independent erosion (Figs. 3A–C). The 50/50 POE/PE blend was chosen for testing since its erosion rate of 72%/24 hr was slightly below the intended target of 100% erosion at 24 hr. The incorporation of 1% phthalic anhydride did not affect the erosion rate at pH 1.5, indicating that erosion was controlled primarily by the external acidic medium. At pH 4 and 7, the erosion rates with catalyst (4.4 and 4.9%/hr) were significantly increased over the blends with no phthalic anhydride (no erosion). With the 1% phthalic anhydride blend, lag times increased sixfold as the solution pH was increased from pH 1.5 to pH 7. The erosion rate and lag time of the blend containing 2% phthalic anhydride were pH independent. Since it was desired to have the devices erode at similar rates in all parts of the GI tract (pH range of 1 to 7), the POE/PE blend containing 2% phthalic anhydride was chosen for *in vivo* testing.

In Vivo Gastric Retention of Tetrahedral Devices in Beagle Dogs

Table II summarizes the *in vivo* gastric retention data of the POE/PE blends. Consistent with the *in vitro* dissolution data at pH 1.5, the fast-eroding POE/PE blends (i.e., 80/20 and 85/15 eroded at 11 and 12%/hr, respectively) were rapidly emptied from the stomach *in vivo* (none retained at 24 hr). The *in vitro* dissolution rate of the POE/PE 75/25 blend was significantly slower, at 6%/hr, and devices fabricated from this blend exhibited 100% retention at 24 hr ($N = 5$). Although the *in vivo* data exhibited greater variation than the *in vitro* dissolution data, a definite trend existed for increased gastric retention of devices made from the more slowly eroding blends.

Additional *in vivo* studies were conducted to test the gastric retention of devices fabricated from a 50/50 POE/PE blend with varying percentages of phthalic anhydride. The gastric retention data indicate a strong correlation ($r = 0.9774$) between the percentage retained at 24 hr and the

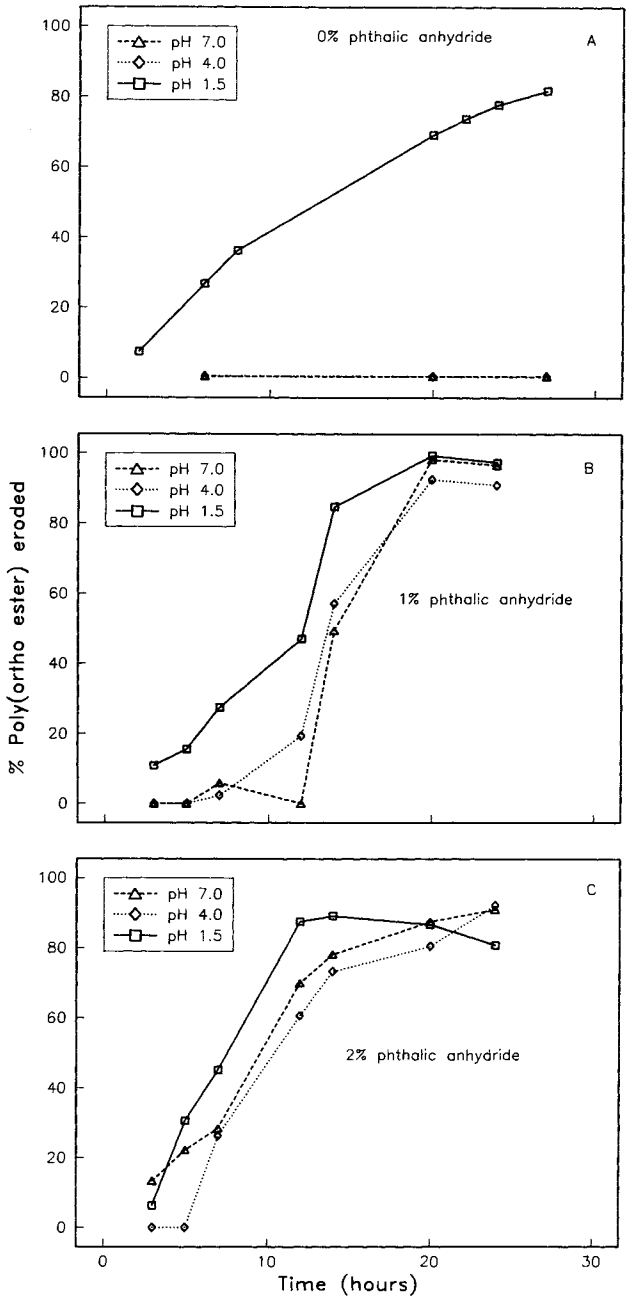

Fig. 3. Dissolution of POE:PE blends with phthalic anhydride. Polymeric rods made from POE:PE blends with phthalic anhydride were incubated at 37°C in simulated gastric juice (pH 1.5).

Table II. *In Vivo* Gastric Retention of Poly(Ortho Ester)/ Polyethylene Tetrahedral Devices

Polymer blend (ratio of POE/PE)	% retained in stomach at 24 hr	*N*
50/50	80	5
65/35	80	5
72/25	100	5
80/20	0	4
85/15	25	4
90/10	0	5

phthalic anhydride content between 0 and 1.5% catalyst. The gastric retention data were as follows: 0% phthalic anhydride, 80% retention; 0.5% phthalic anhydride, 66.7% retention; 1.0% phthalic anhydride, 20% retention; 1.5% phthalic anhydride, 0% retention; and 2% phthalic anhydride, 50% retention. It is not clear why devices with 2% phthalic anhydride afforded 50% retention at 24 hr when the devices should erode faster than those containing 1.5% catalyst (0% retention at 24 hr).

Because of additional variables which occur *in vivo* (fluctuations in stomach pH, contractile forces of the stomach, and the possibility of food being present even in the fasted dog) which are not factors in *in vitro* dissolution studies, *in vivo* data would not be expected to be as consistent as *in vitro* data.

These studies have, however, still shown that the blending of erodible and nonerodible polymers is a valid approach for obtaining materials that will provide the necessary structural properties to achieve gastric retention yet lose integrity within a desired time.

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