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Report

Controlled Gastric Emptying. 1. Effects of Physical Properties on Gastric Residence Times of Nondisintegrating Geometric Shapes in Beagle Dogs

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The importance of three physical parameters (size, shape, and flexibility) on gastric retention in fasting dogs was examined to assess the feasibility of designing a dosage form to achieve a consistent and predictable residence in the stomach. Test shapes were molded from Silastic elastomer or made from extruded polyethylene or polyethylene blends and included 15% barium sulfate for X-ray visualization. Beagle dogs were dosed with test shapes administered in gelatin capsules. Gastric retention was monitored by X ray over a 24-hr period. Six shapes (ring, tetrahedron, cloverleaf, disk, string, and pellet) were screened *in vivo* for their gastric retention potential. The tetrahedrons (each leg 2 cm in length) exhibited 91–100% retention at 24 hr. The rings (3.6-cm diameter) provided 100% retention at 24 hr. Rings and tetrahedrons of varying flexural moduli were prepared by blending low-density polyethylene and ethylene:vinyl acetate copolymer. A positive correlation existed between flexural modulus and gastric retention. The results indicate that it is feasible to design a platform for a dosage form that can be administered to beagle dogs in capsule form and be retained for 24 hr.

KEY WORDS: controlled gastric emptying; nondisintegrating geometric shapes; physical parameters; dogs.

INTRODUCTION

The success of sustained- or controlled-release oral formulations can be dependent on the location of the dosage form in the gastrointestinal (GI) tract (1). Variations in acidity, enzyme content, bile salts, and mucosal absorptive surface occur along the length of the GI tract and may influence release characteristics of a dosage form, drug stability, or absorption. The ability to control the GI transit of a sustained-release dosage form might be expected to provide significant therapeutic advantages in terms of optimizing drug absorption to achieve a desired drug plasma profile.

An important initial determinant of GI transit is the residence time in the stomach. Since the transit time for solid particles through the small intestine is relatively constant (2), the length of time a dosage form resides in the stomach appears to be the single most variable factor in the overall GI transit time.

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A number of investigators have attempted to increase the gastric residence time of dosage forms by employing a variety of concepts such as flotation (3,4), swelling (5,6), inflation (7), and adhesion (8,9). While each of these reports has claimed delayed gastric emptying, none has demonstrated reliable retention of more than a few hours beyond the appropriate controls.

It is clear from the literature that the residence time of particles in the stomach is strongly dependent on the particle size (10–12) and feeding state (13,14). Ideally, the retention of a controlled-release dosage form in the stomach should not be influenced by the presence or absence of food. In the present study attempts have been made to determine the importance of physical parameters, such as size, shape, and flexibility on gastric retention in dogs. From such data, the feasibility of designing a dosage form for achieving consistent and predictable GI retention might become more clear.

MATERIALS AND METHODS

Device Manufacture

Cloverleaf, disk, string, and pellet shapes were molded from Silastic 382 medical-grade elastomer (Dow Corning). For X-ray visualization the Silastic 382 was loaded with 20% barium sulfate ($BaSO_4$). Silastic 382 at room temperature cures in about 1 hr, but the curing time was accelerated by placing the Silastic in a warm (40–50°C) oven for a period of 10 minutes.

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Table I. Material Composition of Shapes Examined in the Size/Shape Study

Shape	Size	Material composition[a]
Ring	2.5-cm diameter	Polyethylene (low density)[b]
	3.6-cm diameter	
Tetrahedron	1.5 × 1.5 × 1.5 × 1.5 cm	Polyethylene (low density)
	2 × 2 × 2 × 2 cm	
Cloverleaf	2.2-cm diameter	Silastic 382[c]
	2.7-cm diameter	
	3.2-cm diameter	
Disk	2.5-cm diameter	Silastic 382
String	12 cm × 2 mm × 2 mm	Silastic 382
	24 cm × 2 mm × 2 mm	
Pellet	4 mm	Silastic 382

[a] Materials examined were fabricated incorporating 15–20% $BaSO_4$ for X-ray visualization.
[b] Density, 0.92 g/ml.
[c] Specific gravity, 1.13.

The tetrahedron and rigid-ring shapes were fabricated from extruded rods (1.5 mm in diameter). Polyethylene and polyethylene/ethylene:vinyl acetate blends were extruded using a benchtop CSI Max-Mixing extruder. All extruded materials included 15% $BaSO_4$ for X-ray visualization. Polyethylene (low density) and ethylene:vinyl acetate copolymers were obtained from Aldrich. Extruder header and rotor zone temperatures ranged from 75 to 210°C, depending on the blend being processed. Extrusion temperatures increased with increasing polyethylene content.

Flexural Modulus Test

To assess polymer rigidity, flexural tests were performed utilizing a three-point bend system according to ASTM D790 (15). The 1.5-mm-diameter extruded specimens were cut into pieces 5.0 cm in length. The specimens were bent in a three-point transverse testing device which was fitted to a mechanical testing machine (Instron Tester 1130), with a distance of 2.5 cm between supports. The bend tests were carried out at room temperature with a crosshead speed of 0.5 cm/min. The testing machine was calibrated with a 5000-g load cell. Stress/strain diagrams were recorded and flexural moduli were calculated as kilograms per square inch (KSI).

In Vivo Dog Model

Male and female beagle dogs (11–15 kg) were used to study the feasibility of gastric retention of a platform for a drug delivery device. The parameters investigated were size, shape, and polymer flexibility. Standard X-ray techniques (CRG compact X-ray unit No. 726B951G) were employed to screen the test device. Each test device was loaded with 15–20% barium sulfate (depending on the material) for X-ray visualization. Food was withheld for a 54-hr period commencing at 18 hr before dosing. Water was available ad libitum. The device was loaded in a No. 000 or smaller gelatin capsule, and after dosing each dog was administered 15–50 ml of water. An X-ray examination was performed immediately after administration to assure that the device was in the stomach. Gastric retention of the device was monitored by X-ray at seven or eight time intervals over a 24-hr period. If the device was retained for longer than a 1-week period, it was removed using an endoscope.

Six shapes (ring, tetrahedron, cloverleaf, disk, string, and pellet) were screened in these *in vivo* studies for their gastric retention potential. The specific shapes and compositions examined in a size/shape study are shown in Table I. Materials examined in the flexibility study and their flexural moduli appear in Table II.

RESULTS AND DISCUSSION

In Vivo Size/Shape Study

The six shapes examined in the size/shape study are shown in Fig. 1. The overall size of the shapes was limited to what could easily be contained in a No. 000 gelatin capsule. The devices were fabricated from flexible materials so that, once deployed in the stomach (released from the gelatin capsule), the devices would quickly regain their original shapes. The shapes were assembled into capsules immediately prior to dosing.

Table III summarizes the mean percentage retention

Table II. Physical Properties of a Series of Polyethylene/Ethylene:Vinyl Acetate Blends

Geometry	Dimensions (cm)	Composition			Flexural modulus (KSI)
		% PE[a]	% EVA	% $BaSO_4$	
Ring	3.6	85		15	48
Ring	3.6	25	60[b]	15	22
Ring	3.6	5	80[b]	15	14
Ring	3.6		85[c]	15	2.5
Tetrahedron	2.0	85		15	48
Tetrahedron	2.0	80	5[b]	15	37
Tetrahedron	2.0	25	60[b]	15	22
Tetrahedron	2.0	5	80[b]	15	14
Tetrahedron	2.0		85[c]	15	2.5

[a] Polyethylene (low density).
[b] Ethylene:vinyl acetate copolymer (14% vinyl acetate, 86% ethylene).
[c] Ethylene:vinyl acetate copolymer (25% vinyl acetate, 75% ethylene).

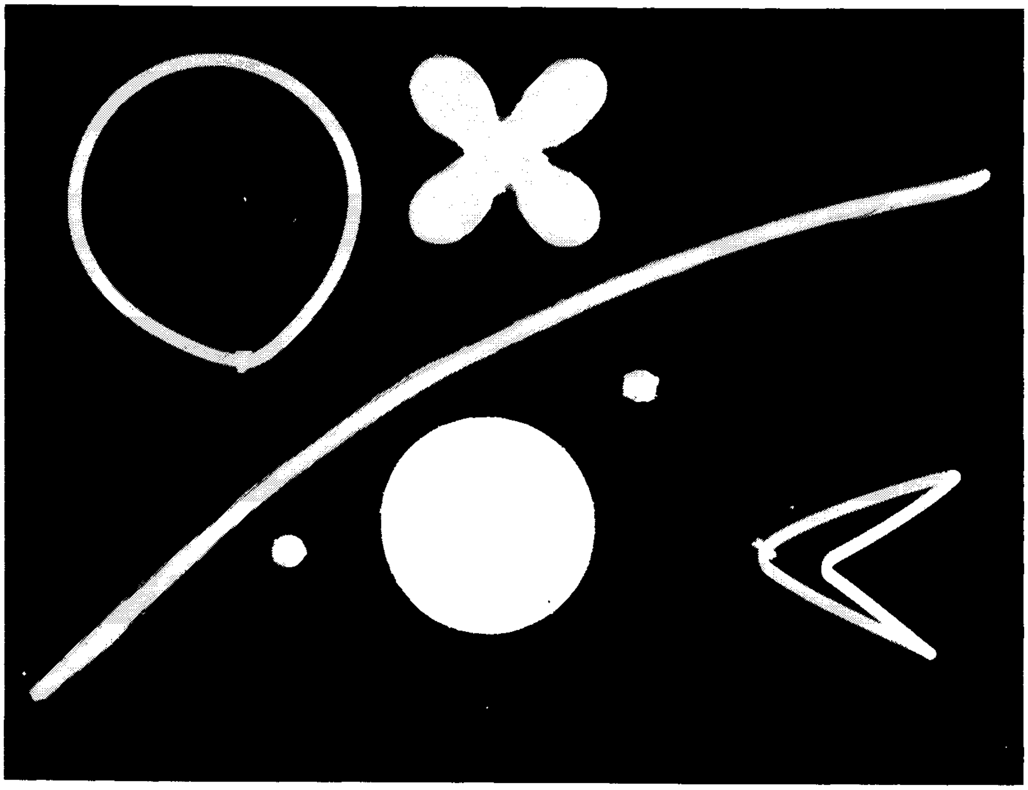

Fig. 1. Shapes examined in the *in vivo* size/shape study.

times of the six shapes at 24 hr. The tetrahedron made with extruded low-density polyethylene resided in the stomach for longer periods (91–100% retention at 24 hr) than other devices of a similar size. Although extended gastric retention was observed with the rigid rings, a significant size dependency for adequate retention was noted. While the rigid rings with a diameter of 3.6 cm demonstrated 100% retention at 24 hr, only 33% retention was observed when rigid rings with a diameter of 2.5 cm were used.

The cloverleaf and the flexible disk, both made with medical-grade Silastic 382, were solid planar devices, filling the entire space of a No. 000 gelatin capsule. The percentage retained in the stomach for 24 hr ranged from 40 to 67% (Table I). Because of the poor retention at 24 hr and the overall bulkiness of these disk and cloverleaf shapes, they were not further investigated as potential gastric retention devices.

Strings (12 cm × 2 mm) and pellets (2 × 4 mm) of Silastic 382 were also found to be inadequately retained. The strings were consistently eliminated from the stomach in less than 24 hr (Table I). The pellets were also rapidly discharged from the stomach. Similar results for normal gastric emptying of particles of similar dimensions were seen by Meyer *et al.* (16) with liver particles and Itoh *et al.* (10) with polyethylene pellets.

Based on this preliminary examination of the gastric re-

Table III. Gastric Retention at 24 hr of Various Geometrical Shapes

Shape	Size	% devices retained at 24 hr
Ring	2.5-cm diameter	33 (N = 3)
Ring	3.6-cm diameter	100 (N = 5)
Tetrahedron	1.5 × 1.5 × 1.5 × 1.5 cm	100 (N =3)
Tetrahedron	2 × 2 × 2 × 2 cm	91 (N = 11)
Cloverleaf	2.2-cm diameter	40 (N = 10)
Cloverleaf	2.7-cm diameter	55 (N = 11)
Cloverleaf	3.2-cm diameter	67 (N = 3)
Disk	2.5-cm diameter	67 (N = 3)
String	12 cm × 2 mm × 2 mm	0 (N = 6)
	24 cm × 2 mm × 2 mm	0 (N = 6)
Pellet	4 mm	0 (N = 40 × 12)[a]

[a] Twelve pellets were administered together on 40 separate occasions.

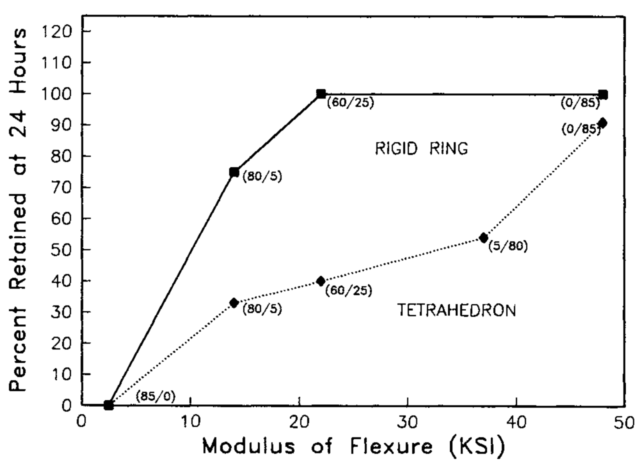

Fig. 2. Gastric retention of the rigid ring and the tetrahedron made from polymer blends of varying flexural moduli.

tention of various shapes and sizes, the tetrahedron and rigid ring were selected as the preferred shapes for further investigation.

Flexural Modulus (Stiffness) of Devices

When food is present, the contractile activity of the stomach subdivides the food into small particles (<1–2 mm) which pass through the pylorus into the intestine for subsequent digestion. Larger particles (>2 mm), however, are retained in the stomach during this digestive period (17). The purpose of this antral sieving is to empty preferentially particles <2 mm into the duodenum during the fed state.

During the fasting state, indigestible solids are emptied from the stomach by strong muscular contractions known as the interdigestive migrating myoelectric complex (IMMC) (18). Preliminary investigation suggested that for a device (tetrahedron or ring) to stay deployed while the stomach was undergoing the strong contractions of the fasting state, the "stiffness" of the device became a crucial factor. For this reason, rings and tetrahedrons of varying flexural moduli (stiffness) were prepared. Variations in flexural moduli were achieved by preparing blends of low-density polyethylene and ethylene:vinyl acetate copolymer. The physical properties of the various devices are shown in Table II. The greater the flexural modulus, the greater the flexural strength or stiffness of the material. As shown in Table II, polyethylene (low density) has a flexural modulus of 48 KSI. For comparison purposes, an extruded rod of polyurethane (1.5 mm in diameter) has a flexural modulus of 318 KSI.

In Vivo Performance of Rings and Tetrahedrons of Varying Flexural Moduli

The data for percentage retention at 24 hr of the rigid ring and the tetrahedron made from a series of polymer blends with increasing flexural moduli are shown in Fig. 2.

The ring (3.6-cm diameter) achieved 100% retention at 24 hr with a material which had a flexural modulus of 22.5 KSI. Because of its large size, the ring had to be collapsed and folded once for proper inclusion in a No. 000 gelatin capsule. The ring was assembled 1–2 hr before dosing [which allowed the device to regain its original shape quickly (1 hr) once released].

The 1.5- and 2.0-cm tetrahedrons achieved greater than 90% retention at 24 hr with a material which had a flexural modulus of 48 KSI. The cross-sectional area of the tetrahedral shape is considerably smaller than that of the ring, and because of the tetrahedral geometry the shape is not altered for capsule inclusion. Since adequate retention was achieved with a smaller device, the tetrahedron would be the device of choice to study further.

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