Novel Gastroretentive Dosage Forms: Evaluation of Gastroretentivity and Its Effect on Riboflavin Absorption in Dogs

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Purpose. The purpose of this study was to design novel gastroretentive dosage forms (GRDFs) based on unfolding multilayer polymeric films, to investigate the mechanism of their gastroretentivity in dogs, and to assess the effect of compounding a narrow absorption window drug in a GRDF on the drug's absorption properties.

Methods. Dosage forms (DFs) with different dimensions and mechanical properties were administered to beagle dogs with acidic buffer (pH = 1.5), whose gastric retention time (GRT) was then determined by X-ray pictures. Concurrent administration of radiopaque markers was used to assess the effect of the GRDF and/or acidic buffer on GRT. The absorption of riboflavin from a prototype GRDF was compared with a nongastroretentive controlled-release DF and to an oral solution of the drug.

Results. Large DFs (≥2.5 × 2.5 cm) containing rigid frame had prolonged GRT (>4 h). Administration of 400 mL of acidic buffer (or water) prolonged GRT whereas the GRDF did not cause additional prolongation. The extended absorption phase (>48 h) of riboflavin administered in a GRDF led to 4-fold increased bioavailability.

Conclusion. The combination of large dimensions with rigidity produce gastroretentivity that can be used to improve absorption properties of a model of narrow absorption window drugs in the gastrointestinal tract.

KEY WORDS: drug delivery; controlled release; gastroretentive; dogs; riboflavin; intestinal absorption.

INTRODUCTION

A gastroretentive dosage form (GRDF) that releases drugs in a controlled manner is needed to increase absorption and improve the therapy of drugs characterized by a limited and narrow absorption window at the upper part of the gastrointestinal tract, as well as in drugs intended to treat local ailments in the stomach or the duodenum (1).

For the past few decades the development of a GRDF has been a major pharmaceutical challenge (2,3), and recently the interest has been heightened and increased by the discovery of an association between *Helicobacter pylori* and ulcer (4,5).

Thus far, a number of ways to retain GRDFs in the stomach have been designed, including 1) a low-density form that causes buoyancy above the gastric fluid (6); 2) high density that retains the dosage form (DF) in the body of the stomach, which is anatomically lower than the pyloric sphincter; 3) concomitant administration of drugs or excipients, which slows the motility of the gastrointestinal tract (7); 4) bioadhesion to the gastric mucosa (8); 5) swelling to a large size, which delays emptying of the DF through the pyloric sphincter (9,10).

The current study assessed the correlation between gastric retention times (GRTs), mechanical properties, and size of novel GRDFs, which combine extended dimensions (attained after unfolding of the DF in the stomach) with substantial mechanical properties as a mechanism to extend retentivity in the stomach of dogs.

Riboflavin (vitamin B_2), a model of narrow absorption window drugs (11,12), was used to demonstrate the impact of controlled drug release from the prototype GRDF on it pharmacokinetics. This model drug is advantageous because it lacks adverse effects and has no pharmacological effect on gastric motility (13).

MATERIALS AND METHODS

Materials

Enzymatically hydrolyzed gelatin with a molecular weight (Mw) of 10,000–12,000 (Byco E®) was obtained from Croda Colloids Ltd. (Plymouth Devon, UK). L-polylactic acid with a Mw = 427,000 (Resomer L 207®) was purchased from Boehringer Ingelheim Pharma KG (Ingelheim am Rhein, Germany). Ethylcellulose (N = 100), USP/NF methacrylic acid copolymer type B (Eudragit S 100®), and barium-impregnated polyethylene spheres (BIPS®) were generous gifts from Teva Pharmaceutical Industries (Kfar Sava, Israel), Rohm GmbH (Darmstadt, Germany), and Chemstock Animal Health Ltd (Christchurch, New Zealand), respectively. Shellac and microcrystalline cellulose (avicel PH102®) were gifts from Taro Pharmaceutical Industries (Haifa Bay, Israel). Riboflavin-5-phosphate (also known as flavin mononucleotide), as sodium salt, was obtained from Sigma (St. Louis, MO, USA). All reagents were of analytical or high-pressure liquid chromatography (HPLC) grade purity. X-ray contrast threads were obtained from surgical gauze pads.

Preparation, Structure, and Physical Characteristics of the Tested DFs

The DFs were constructed as multilayer films (sandwiches) as seen in Fig. 1 (14). The prototype DF was composed of an inner layer, covered on both sides by outer (shielding) layers with a thin anti-adhering layer spread over their exterior side. The inner layer was composed of polymer-drug matrix (shellac-riboflavin 7:3, unless stated otherwise) framed with rigid polymeric strips. All films used to construct this multilayer GRDF were prepared by dissolving the polymers in suitable solvents with subsequent casting and solvent evaporation. The layers were attached to each other using minute amounts of organic solvents (methylene chloride or ethyl alcohol). The corners of the DFs were rounded.

DF #1 (Prototype)

The scheme of this prototype and the constitution of each layer are shown in Fig. 1A. Its exterior dimensions were

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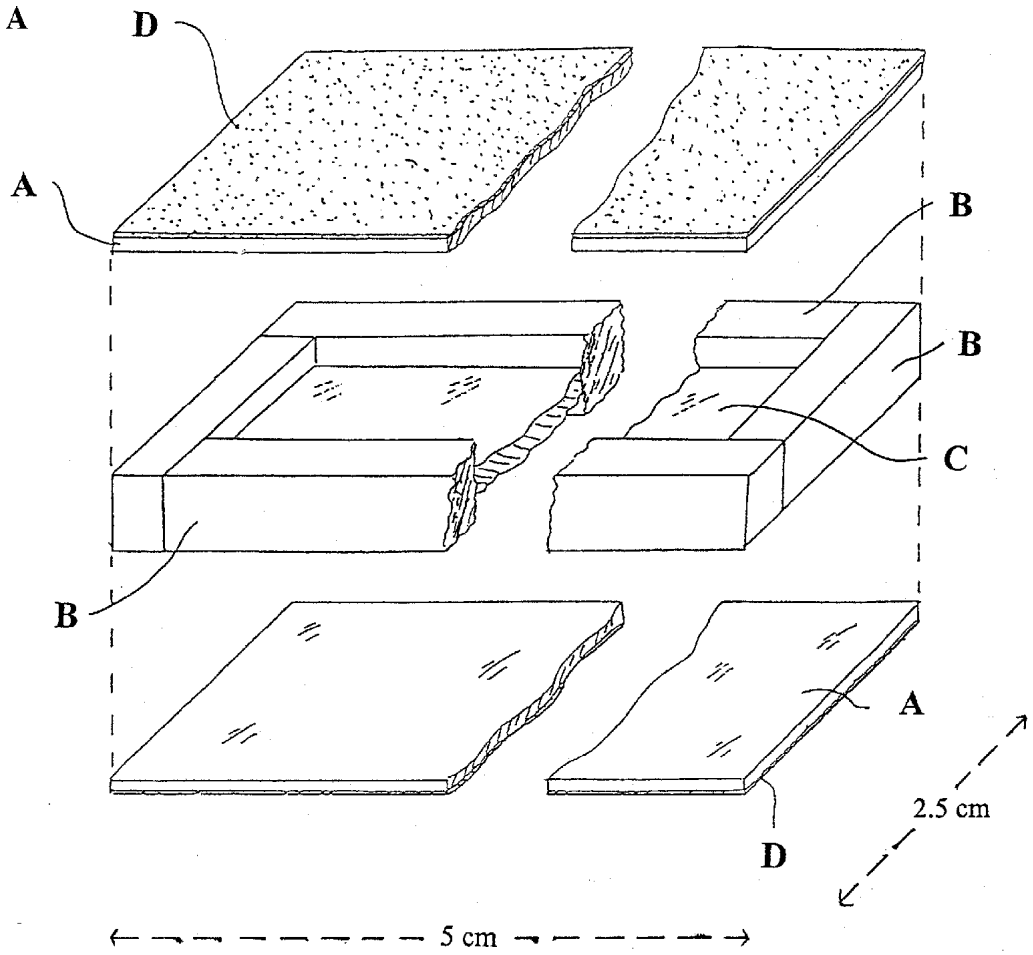

A - Shielding (outer) layers (48% hydrolyzed gelatin, 30% Eudragit S®, 20% glycerine, 2% glutaraldehyde)
B - Rigid (frame) strips (L-polylactic acid-ethylcellulose, 9:1)
C - Polymer-drug matrix (shellac-riboflavin, 7:3)
D - Anti-adhering layers (microcrystalline cellulose)

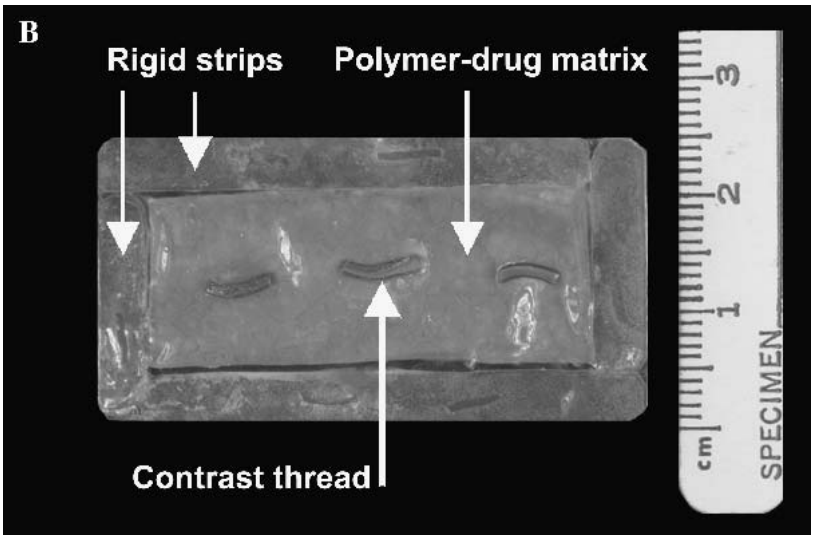

Fig. 1. (A and B). A, Scheme presenting the different polymeric layers of the prototype gastroretentive dosage form (GRDF); B, picture of the prototype GRDF (lacking the anti-adhering layer for clarity) from above. The multilayer (sandwich) GRDF has an inner polymer-drug matrix that is framed by four rigid strips. The upper shielding layer is transparent in the picture.

5 cm × 2.5 cm, whereas the inner matrix layer was 4 cm × 1.5 cm. The matrix layer was framed by four rigid strips consisting of a L-polylactic acid-ethylcellulose mixture (9:1). The length of each of the two strips was 4.5 cm and 2 cm, for the long and short dimensions of the DF, respectively. Their width and thickness were 0.5 cm and 0.65 mm, respectively. The thickness of the shielding layers was 0.13 mm.

For DFs #2–#4 and #7, only deviations from the prototype structure (DF #1) are mentioned. In all cases, the size of the shielding layers was equal to the size of the DF.

DF #2

Two and four equally sized (0.5 cm × 1 cm) rigid strips were placed on each side of the short and long dimensions of the frame, respectively. There was a distinct gap of 2 mm between each of the 12 rigid strips.

DF #3

The thickness of the rigid strips in the frame of the inner layer was 0.2 mm.

DF #4

The rigid strips in the frame of the DF were constituted from ethylcellulose-triethylcitrate (97:3).

DF #5

The size of the DF was 2.5 cm × 2.5 cm, the polymer-drug matrix was 1.5 cm × 1.5 cm, and each of the four rigid strips was 2 cm × 0.5 cm.

DF #6

The size of the DF was 1 cm × 1 cm and each of the two rigid strips was 1 cm × 0.5 cm.

DF #7 (Control)

There was no rigid frame, and the polymer-drug matrix was 5 cm × 2.5 cm.

DF #8

Matrix tablets (0.8 cm diameter, 0.35 cm thickness).

In the DFs used for the pharmacokinetic experiment, the inner polymer-drug matrix layer was a combination of shellac-riboflavin-5-phosphate (55:45) containing 100 mg of the later (equivalent to 73 mg riboflavin). The thicknesses of all films deviated by not more than 10% of the mentioned values.

In Vivo Assessment of Gastroretentivity

The dog experiments were approved by the Ethics Committee for Animal Experimentation of the Faculty of Agriculture, Food & Environmental Quality Sciences, The Hebrew University of Jerusalem.

Beagle dogs (14.2 ± 0.7 kg, n = 6) were deprived of food (with *ad libitum* access to water) 18 h before the experiment and during the experiment. Before the administration of the tested DF, the dogs were given 400 mL of acidic buffer (pH = 1.5, HCl-KCl) via an oral-gastric tube. All experiments started at 17:00. All DFs except #8 were folded (6-mm long folds in the long dimension, each consecutive fold in the opposite direction to the former) and inserted into gelatin capsules (000) before administration. The same experimental conditions were kept in subsequent *in vivo* experiments unless stated otherwise.

Evaluation of food effect was conducted by feeding each dog with 375 g of Tuffy's liver canned food after a 24-h fasting period. Immediately after eating each dog received DF #1.

Radiology was used for imaging. Three pieces of 0.5-cm long X-ray opaque thread were incorporated in one of the shielding layers and one or two pieces in each of the short or long, respectively, rigid strips during their fabrication. X-ray pictures were taken at times 1, 2, 4, 6, 8, and 13 h from two perpendicular recumbencies (ventral-dorsal and right-lateral). This enabled the following: 1) determination of the anatomic location of the DF in the gastrointestinal tract; 2) evaluation of the DF size *in vivo*; and 3) estimation of whether the DFs disintegrate *in vivo*.

Mechanical Characterization

Mechanical properties of films that constitute the DFs and sandwiches of each of the inner films enveloped by two identical shielding films were evaluated using an Instron tester applying stress-strain test with 10 KN tension load cell. Cross head speed was 25 mm·min^{-1}. Young's modulus of elasticity and yield strength (at 0.5% offset) of ten samples (7 cm × 1 cm) were measured.

Estimation of DF Size *in Vivo*

Percent Exposed Size Parameter (ESP), an indirect metric measurement of real size *in vivo*, was determined from X-ray pictures at each time point. Percent ESP was calculated according to Eq. (1)

$$\%ESP = 100(Ls \times Ll)/S$$

where *Ls* and *Ll* are the average lengths between parallel contrast threads of frame strips in the shorter and longer dimensions, respectively, and *S* is the respective area of the DF before folding. The *Ls* and *Ll* were determined from two X-ray pictures taken at each time point (from different recumbencies) and choosing from each time point the larger of the two measured values.

Effect of Gastric Acidification and DF Administration on GRT of Radiopaque Markers

The effect of acidic buffer administration on gastric pH was assessed in beagle dogs (17.1 ± 0.7 kg, n = 10) that received 400 mL of acidic buffer (pH = 1.5, HCl-KCl). Samples of gastric fluid were collected (via a gastric tube) 1 h before and 1, 2, 4, and 13 h after acidification.

Beagle dogs (14.8 ± 0.8 kg, n = 8) received radiopaque markers of BIPS® in the following modes of administration: Mode #1: without addition of fluids or DFs; Mode #2: insertion of the gastric tube (2 min) without addition of fluids; Mode #3: with 400 mL of water; Mode #4: with 400 mL of acidic buffer (pH = 1.5, HCl-KCl); Mode #5: with 400 mL of acidic buffer and prototype DF; Mode #6: with 400 mL of acidic buffer and control DF.

Each administration contained 30 small (1.5 mm) mark-

ers and 10 large (5 mm) markers. GRTs of the radiopaque markers and the DFs were assessed using radiology.

Evaluation of Riboflavin-5-Phosphate Containing GRDF

The *in vitro* release rate of 100 mg riboflavin-5-phosphate from the GRDF and the control DF into acidic buffer (pH = 2.2, HCl-phthalate) was conducted using USP apparatus 2 at 37°C (Caleva ST7, Dorset, UK). The drug concentration was determined by an UV spectrophotometric method at absorption wavelength of 444 nm.

Beagle dogs (13.7 ± 1.2 kg, n = 6) received 100 mg of riboflavin-5-phosphate in four different modes of administration in a crossover design: 1) prototype GRDF (#1); 2) control DF (#7); 3) drug dissolved in acidic buffer; or 4) intravenous bolus injection (5 mL). X-ray pictures were taken at times 1, 2, 4, 6, 8, 13, 24, and 48 h. Blood samples were obtained periodically and assayed for riboflavin by an HPLC method with spectrofluorometric detection (15,16).

The absorption properties of riboflavin were estimated by numerical deconvolution of the concentration-versus-time data after the extravascular modes of administration in comparison to intravenous administration (17). An unconstrained algorithm was applied using PCDCON software (18).

Statistical Analysis

The ANOVA test, followed by a Tukey-Kramer Multiple Comparisons Test, where appropriate, was used to assess the statistical significance of the differences between the results. A p value of less than 0.05 was termed significant. Data is presented as mean ± SEM.

RESULTS

In Vivo Assessment of Gastroretentivity

The GRTs obtained for various DFs are presented in Table I. It was found that for certain DFs at 4 h postadministration, the DF was retained in the stomach of half or even fewer of the tested dogs. These DFs had either small size (DF #6), or no rigid frame (DF #7) or were the matrix tablets (DF #8). In contrast, all the DFs having both rigid strips and substantial size (DF #1–#5) were retained in the stomach for longer periods than DFs #7 and #8 ($p < 0.05$) and were therefore defined as gastroretentive.

All the riboflavin-5-phosphate containing GRDFs were retained in the stomach for at least 48 h whereas the control DFs were retained for 2–4 h. Assessing GRTs after food intake showed that all the prototype DFs (#1) were in the stomach at least for 13 h. It was verified using endoscopy that the unfolding process of the prototype DF occurs within 5–10 min. In all cases the DFs were evacuated spontaneously from the stomach.

Table I. Number of DFs (of 6) Retained in Stomach at Different Time Points after Administration of #1–#8 to Dogs

DF number	1 h	2 h	4 h	6 h	8 h	13 h
#1 (prototype)*	6	6	6	6	6	6
#2*	6	6	5	4	4	4
#3*	6	6	6	5	5	5
#4*	6	6	6	5	4	3
#5*	6	6	6	5	5	5
#6	6	5	3	3	3	2
#7 (control)	6	3	2	1	0	0
#8 (tablet)	6	5	2	1	0	0

* Statistically significant from DFs #7 and #8.
DFs with rigid strips and extended dimensions (#1–#5) retained in the stomach more than control DFs (#7 and #8). GRT of small but rigid DF (#6) is inconsistent.
DF = dosage form; GRT = gastric retention time.

Mechanical Characterization

The mechanical properties of the polymeric films and film sandwiches are summarized in Table II (a and b, respectively). It was found that by adding rigid strips the mechanical properties of the multilayer systems were elevated by about one order of magnitude.

Size of DF *in Vivo*

The percent ESP of GRDFs #1–#4 was very close; therefore, their mean data is shown in Fig. 2, which presents the relationship between percent ESP of DFs #1–#4, #5, and #7 versus time in the stomach. After 1 h (first sampling point), all the DFs had unfolded in the stomach at a size similar to their size before folding. It is seen that DFs with a certain rigidity (GRDFs #1–#4, #5) did not undergo significant changes in percent ESP during their stay in the stomach. DF #7 reached a similar size to GRDFs #1–#4 1 h after intake but a significant percent ESP reduction took place over time.

Effect of Gastric Acidification and DF Administration on GRT of Radiopaque Markers

The gastric pH measurements showed that the mean pH values at 1 h before and 1, 2, 4, and 13 h after acidic buffer administration were 6.4 ± 0.7, 1.9 ± 0.2, 1.8 ± 0.1, 3.0 ± 0.7, and 6.6 ± 0.9, respectively.

After concomitant administration of acidic buffer and radiopaque markers, the prototype GRDFs were retained in the stomach for over 10 h whereas the less rigid control DFs were retained for 3.4 ± 0.7 h. In all modes of administration, similar GRTs were obtained for the small (1.5 mm) and the large (5 mm) markers.

The effect of administration of 400 mL of acidic buffer (or equal volume of water) on GRT of small radiopaque markers is presented in Fig. 3. It is seen that the stress induced by inserting a gastric tube for 2 min did not cause GRT prolongation whereas the addition of the same volume of either

Table IIa. Mechanical Properties of Polymeric Films

Sample	Young's Modulus (Mpa)	Yield Strength (Mpa)
Outer (shielding) layer	20.6 ± 0.8	0.41 ± 0.02
Polymer–drug matrix	40.4 ± 1.3	0.92 ± 0.02
Strips (L-polylactic acid-ethylcellulose)	589 ± 34*	10.9 ± 0.4*
Strips (ethylcellulose-triethylcitrate)	1685 ± 20*	16.2 ± 2.1*

* Statistically significant from all other groups.

Table IIb. Mechanical Properties of Sandwiches of Samples within Two Identical Outer (Shielding) Layers

Sample	Young's Modulus (Mpa)	Yield Strength (Mpa)
Polymer–drug matrix	30.6 ± 1.3	0.72 ± 0.03
Strips (L-polylactic acid-ethylcellulose)	255 ± 10*	5.11 ± 0.15*
Strips (ethylcellulose-triethylcitrate)	542 ± 6*	9.41 ± 0.06*

* Statistically significant from all other groups.
Note. Strips in the frame are substantially more rigid than other constituents of the dosage forms. The difference is apparent in the sandwich systems as well.

water or acidic buffer had a similar delaying effect on the emptying time of radiopaque markers from the stomach.

The effect of DFs on GRT of small radiopaque markers is presented in Fig. 4. It can be seen that gastric emptying of the markers was not significantly delayed by GRDF administration and was enhanced by administration of the control DF.

Figure 5 (A and B) shows radiographs of a dog, which received prototype GRDF with concurrent administration of radiopaque markers after 4 and 6 h, respectively. The markers left the stomach while the GRDF was retained for more than 10 h.

Evaluation of Riboflavin-5-Phosphate Containing GRDF

The results of the *in vitro* drug release test show that after an initial fast (burst) release of 20% of drug content, the release of riboflavin-5-phosphate from the GRDF and the control DF were constant (1.51 $mg \cdot h^{-1}$) and followed a zero-order kinetics throughout the release process.

The effect of the extravascular modes of riboflavin-5-phosphate administration on mean riboflavin plasma concentrations and absorption profile in dogs is presented in Fig. 6 (A and B, respectively). As can be seen, GRDF produced elevated riboflavin plasma concentrations for at least 48 h after drug administration (significantly higher than the baseline riboflavin levels of 7.8 ± 2.6 $mg \cdot mL^{-1}$). This outcome is considerably different from the short-lasting elevation of riboflavin concentrations produced by the other two oral modes of administration.

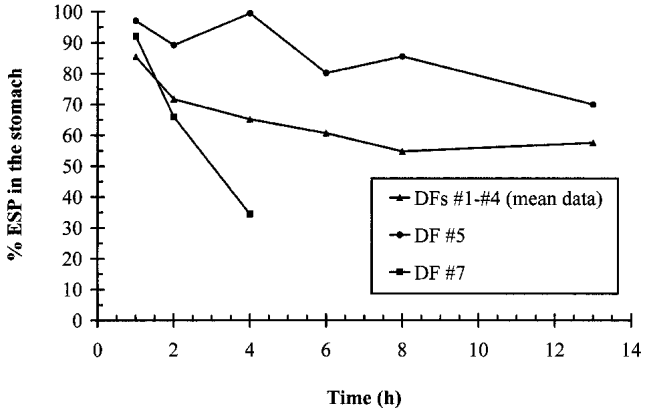

Fig. 2. Percent exposed surface area of dosage forms (DFs) in the stomach of dogs (n = 6) versus time in the stomach. The graph shows DFs of size 5 cm × 2.5 cm with rigid frame (#1–#4, mean data), DF of size 2.5 cm × 2.5 cm with rigid frame (#5), and control DF lacking rigid frame (#7).

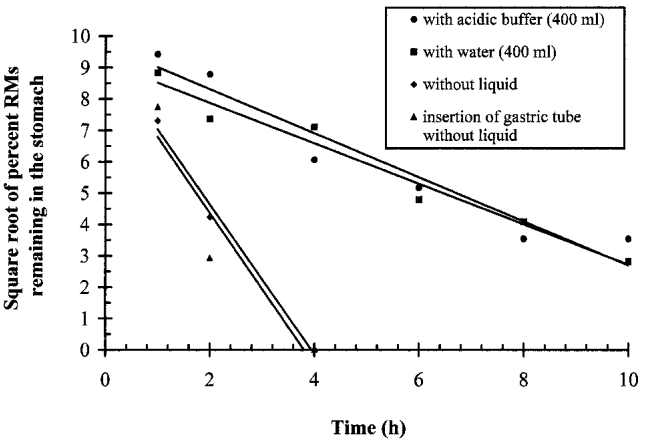

Fig. 3. Effect of administration of 400 mL of acidic buffer on mean gastric emptying time of small (1.5 mm) radiopaque markers in dogs (n = 8).

The rates of absorption for control DF and GRDF were very close during the first 5 h (0.37 $mg \cdot h^{-1}$ and 0.45 $mg \cdot h^{-1}$, respectively) and were much slower than the absorption rate obtained after administration of the drug as an oral solution (1.54 $mg \cdot h^{-1}$), which lasted for less than 3 h. Absolute bioavailabilities (percentage) were 17.1 ± 3.5, 3.9 ± 0.4, and 3.9 ± 1 for the GRDF, control DF, and oral solution, respectively.

DISCUSSION

The outcome of this investigation highlights the importance of two factors, geometrical dimension and DF rigidity, in determining the gastroretentive properties of the tested unfolding multilayer polymeric DF in dogs, and in particular, the additive properties of their combination. The importance of size is reflected by the prolonged GRT of DFs with sizes 2.5 cm × 2.5 cm or larger (e.g., #1, #5), whereas the smaller DF (1 cm × 1 cm) was not consistently retained in the stomach.

The importance of the mechanical properties provided by the rigid polymeric strips is evident by the fact that a large DF without the additional rigidity (i.e., #7) was considerably less retentive than the equivalent size rigid DF (#1). The ad-

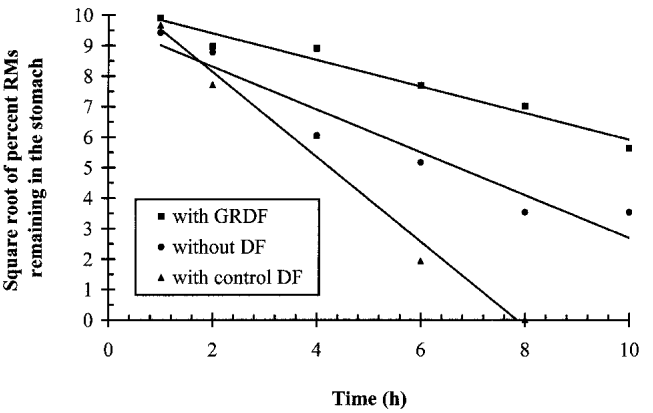

Fig. 4. Effect of dosage forms on mean gastric emptying time of small (1.5 mm) radiopaque markers in dogs (n = 8).

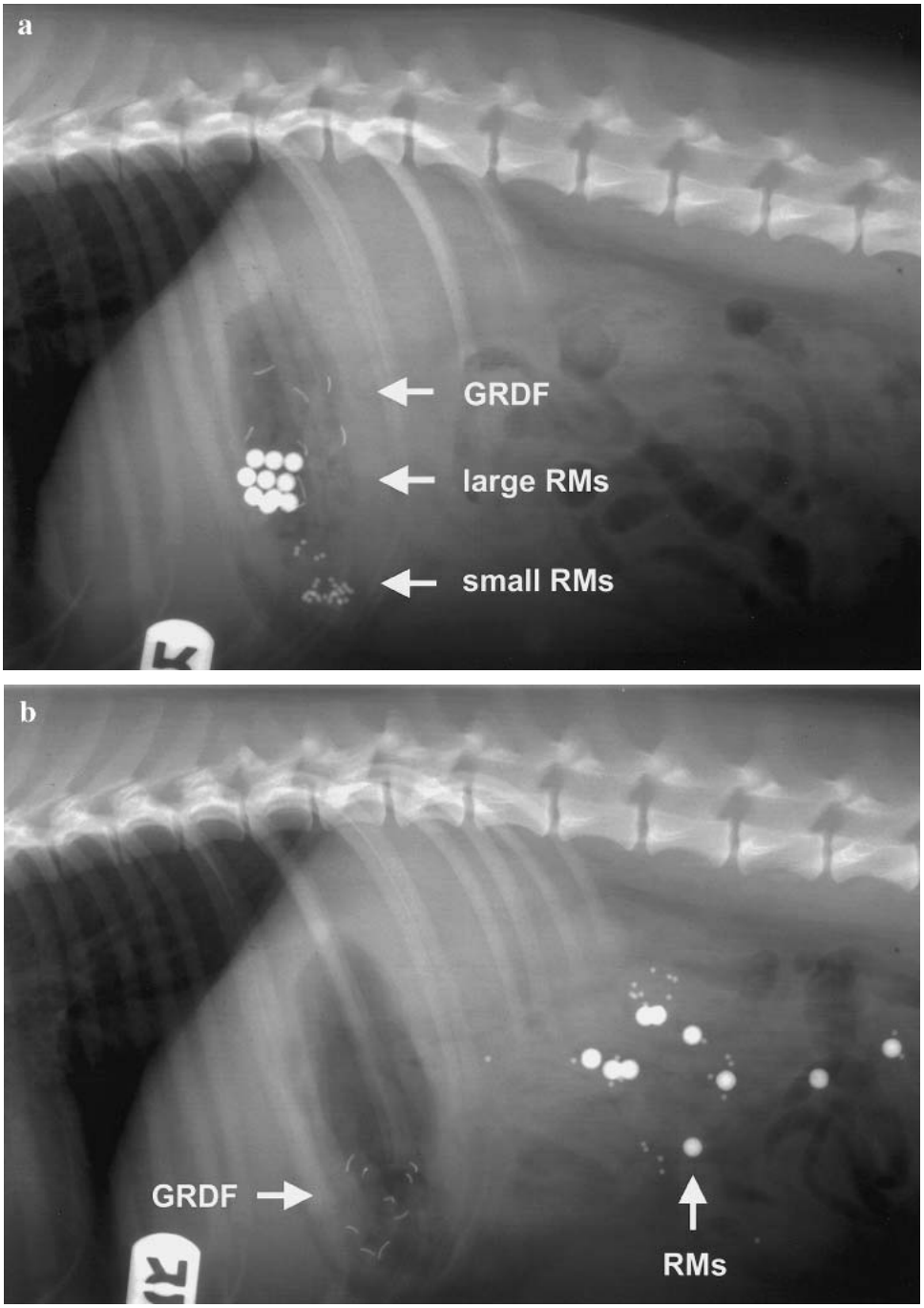

Fig. 5. Dog radiographs showing, at 4 (A) and 6 h (B), postconcomitant administration of prototype gastroretentive dosage form and radiopaque markers. Note that the radiopaque markers evacuate from the stomach in the presence of the gastroretentive dosage form, which remains.

dition of a rigid polymeric frame reduces the tendency of the stomach muscle contractions to reduce or fold the DF into smaller dimensions as exemplified by percent ESP versus time measurement (see Fig. 2). Rigidity alone tends to be an important factor in prolonging the GRT of the DF. However, when it is not combined with extended dimensions of the DF, the gastroretentivity is less consistent, as seen in DF #6 (Table I).

It was interesting to find that DFs that have significantly thinner strips in the frame than the prototype, or DFs with enhanced probability to bend or fold by using short rigid strips of 1-cm length with 2-mm gaps between them (GRDFs #3, #5, and #2, respectively), produced similar gastroretentivity.

The advantage of the rectangular shape of the unfolding GRDF, used in this study, in comparison to rounded shapes of such DFs, is that when entrapped in the same size gelatin capsule, the rectangle form provides a larger size and also can be loaded with larger amounts of drug that would be required for prolonged release.

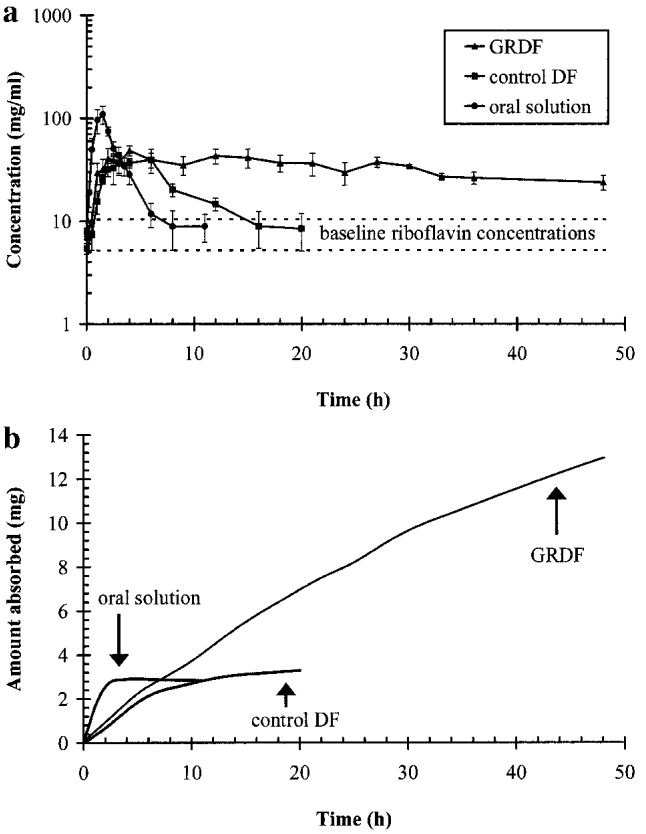

Fig. 6. Effect of mode of administration of 100 mg of riboflavin-5-phosphate on mean riboflavin plasma concentrations (A) and cumulative amount of riboflavin absorbed (B) in dogs (n = 6).

The findings obtained by the X-ray detection lead to the following conclusions: 1) For the most part, the DFs do not disintegrate in the stomach. It was evidenced by the fact that the contrast threads, embedded in different components of the DFs, were located very close to each other within the stomach; 2) The DFs do not adhere to the gastric mucosa. In consecutive radiographs taken at different recumbencies of only a few seconds apart, the DF was located in different parts of the stomach; 3) Incorporation of the contrast threads in a specific succession enabled a noninvasive method (in comparison to endoscopy) to determine the size of the DF in the stomach.

In this work, we used for the first time radiopaque markers (BIPS®) as biopharmaceutical indices. BIPS® are inert spheres having a density similar to food (19) that provide quantitative information about the process of solids emptying from the stomach of small animals. The small radiopaque markers mimic the passage of food (when administered concomitantly with food; 20,21) whereas the larger markers are usually used to diagnose physical obstruction (22).

The fact that the large radiopaque markers, when taken concurrently with GRDF, left the stomach, excludes the possibility that the gastroretentivity of the GRDF was associated with pyloric obstruction induced by the GRDF. Furthermore, as shown in Fig. 5, complete emptying of the radiopaque spheres can take place while the GRDF is retained in the stomach.

The lowering in mechanical properties of the polymer-drug matrix or frame strips that are enveloped into a sandwich of shielding layers, as seen by comparing the data shown in Table IIa to that in Table IIb, is expected according to the "rule of mixtures." This rule was initially developed for copolymers but was further extended to blends of polymers and sandwiches of polymers (23). According to this rule, the value of the property of the sample is the sum of the values of the property of its constituents according to the constituents' fraction (24).

It can also be seen from Table II that using polymers with close mechanical properties e.g., L-polylactic acid-ethylcellulose and ethylcellulose-triethylcitrate (incorporated into GRDFs #1 and #4, respectively), yields similar gastroretentive properties. This means that the existence of a rigid frame in the DF is more important than the specific polymer used. Thus, it is expected that gastroretentivity may also be obtained with many other polymers that produce mechanical properties close to those used in this research.

The dog was used as a preclinical screening model before human studies. To improve this experimental model, the GRDF was administered together with 400 mL of acidic buffer to the dogs for two reasons: 1) To ensure that the stomach was not shrunken or collapsed, thus enabling the unfolding process of the DF and 2) the gastric pH of dogs varies significantly and in general tends to be close to neutral, as reported here and by others (25,26). In contrast, gastric pH in humans, the target species for this research, is mostly acidic (27). Thus, the exogenous administration of acidic buffer ensured acidification for at least 4 h, enabling the difference in basal acidity (which may affect dissolution and disintegration properties of the GRDFs) between the dog model and human to be overcome.

The mechanical distension, caused by the relatively large volume of liquid administered in comparison to the holding capacity of the stomach of beagle dogs (400–500 mL; 28), induced a certain delay in gastric emptying. This effect was previously shown to be mediated via the autonomic nervous system (29) and did not interfere with the differentiation between GRDFs and nongastroretentive DFs, but it may explain the late cut-off time of 4 h (discussed above and presented in Table I).

The slow and continuous drug release obtained after administration of the GRDF enabled significant prolongation of the time period in which the drug levels were above baseline concentrations. This result conforms to a previous study, which assessed riboflavin-5-phosphate containing enzyme-digestible hydrogel type GRDF (30).

The deconvolution analysis indicates that the *in vivo* absorption rate from GRDF and the control DF is initially similar but begins to differ 5 h after administration because of the shorter gastric retention time of the control DFs in the stomach. When the control DF leaves the stomach, it releases the drug in nonabsorbing distal segments of the gastrointestinal tract and thereby yields less absorbed drug as reflected by the smaller bioavailability. This phenomenon stresses the importance of GRDF as an optimal delivery system for drugs with a narrow absorption window that could benefit from a prolonged absorption phase.

In conclusion, the current study presents novel GRDFs. The promising outcomes in the preclinical assessment of these GRDFs are an important step towards the goal of using these GRDFs in the clinical setting. It is expected that in addition to narrow absorption window drugs that are already on the mar-

ket, this approach may be used for potentially important active agents in which pharmaceutical development is currently blocked resulting from the lack of appropriate GRDF technologies.

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