Novel Gastroretentive Dosage Forms: Evaluation of Gastroretentivity and Its Effect on Levodopa Absorption in Humans

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Purpose. To design novel expandable gastroretentive dosage forms (GRDFs) and evaluate their gastroretentive properties. Then, to assess the pharmacokinetics of levodopa compounded in such a GRDF in healthy volunteers.

Methods. Thin (<0.07 cm), large-dimensioned (≥ 5 × 2.1 cm), multilayer dosage forms (DFs) with different rigid polymeric matrices and mechanical properties were folded into gelatin capsules and were administered to healthy volunteers with a light breakfast. GRDF unfolding and physical integrity were evaluated *in vitro* and *in vivo* (by gastroscopy and radiology). The pharmacokinetics of levodopa-GRDF were compared to Sinemet CR® in a crossover design.

Results. The combination of rigidity and large dimension of the GRDFs was a decisive parameter to ensure prolonged gastroretentivity (≥ 5 h). Large-dimension DFs lacking rigidity had similar gastroretentivity as a nondisintegrating tablet (10 mm). The GRDFs rapidly unfolded and maintained their mechanical integrity. The absorption phase of levodopa was significantly prolonged following GRDF administration in comparison to Sinemet CR®.

Conclusions. The combination of size and rigidity of the novel GRDF enables a significant extension of the absorption phase of a narrow absorption window drug such as levodopa. This approach is an important step toward the implementation of such GRDFs in the clinical setting.

KEY WORDS: drug delivery; controlled release; gastroretentive; healthy volunteers; levodopa.

INTRODUCTION

A gastroretentive dosage form (GRDF) that releases medications in a controlled manner is needed to extend the absorption phase of drugs characterized by a limited and narrow absorption window at the upper part of the gastrointestinal tract or drugs intended to treat local ailments in the gastroduodenum. This mode of administration may prolong the time period in which the blood drug concentrations are within the "therapeutic levels" and improve therapy. Therefore, development of GRDFs has been a major pharmaceutical challenge during the past few decades (1).

Various GRDFs have been proposed previously, most of them designed according to the following approaches: (a) bioadhesion to the stomach mucosa; (b) buoyancy of low-density dosage form (DF) above gastric fluid (2); (c) expansion by swelling to a large size, which should prevent rapid emptying through the pyloric sphincter (3,4). Usually these GRDFs have been evaluated both under *in vitro* conditions that mimic the gastric milieu (5) and *in vivo* using a dog model (6,7). However, it should be noted that the majority of previous reports on GRDFs have not examined the gastric retention time (GRT) directly in controlled human studies (8,9). In some studies the gastroretentivity was assessed indirectly by using a bioequivalence pharmacokinetic study as a proof of concept (10).

Levodopa, the most commonly prescribed antiparkinsonian agent, has a short half-life and is absorbed almost solely from the duodenum and small intestine (11). There is a clear clinical advantage in having sustained levodopa blood concentrations (12), and pharmacokinetic-pharmacodynamic studies in parkinsonian patients have shown that a relatively small decline in blood concentrations might lead to loss of antiparkinsonian effect presented as the "wearing off" phenomenon at the end of dose interval (13). Accordingly, a controlled-release DF (Sinemet CR®) was developed (14), which reduced the incidence of "wearing off" episodes, decreased frequency of administration, and improved therapy (15). However, a further reduction of administration frequency, which in some cases reaches four times daily, is clinically desired (13).

In light of the pharmacokinetic and pharmacodynamic properties of levodopa, it was suggested that a GRDF would be the optimal delivery system for this drug (16). Previously, a levodopa-GRDF based on buoyancy, Madopar HBS® (hydrodynamically balanced system), was developed (17) and decreased adverse effects (18). However, its GRT was not proven to be prolonged (17), which may explain the similar pharmacokinetic behavior of Madopar HBS® and Sinemet CR® (19).

The novel GRDF approach tested here in humans was evaluated first in preclinical studies using beagle dogs. The key findings were that combining extended dimensions with rigidity of the DF prolongs gastroretentivity (20,21). The GRT of such DFs was more than 8 h. In addition, extended absorption phase and improved bioavailability were obtained for riboflavin (22) and levodopa (13) compounded into GRDFs, when compared to nongastroretentive controlled-release DFs.

The current study encompasses (a) direct assessment of the gastroretentive properties of novel unfolding GRDFs and evaluating the importance of the combination of large dimensions with rigidity, in humans. The study examines the gastroretentivity of the various GRDFs in relation to their dissolution, swelling, and stability in simulated gastric fluid as well as the *in vitro* and *in vivo* unfolding; (b) pharmacokinetic evaluation of levodopa-GRDF in comparison to Sinemet CR® in healthy volunteers.

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ABBREVIATIONS: DF, dosage form; GRDF, gastroretentive dosage form; GRT, gastric retention time; MRT, mean residence time.

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MATERIALS AND METHODS

Materials

Enzymatically hydrolyzed gelatin with MW 10,000–12,000 (Byco E®) was obtained from Croda Colloids Ltd. (Plymouth Devon, UK). L-Poly(lactic acid) with MW 427,000 (Resomer L 207®) was purchased from Boehringer Ingelheim Pharma KG (Ingelheim am Rhein, Germany). Glutaraldehyde 25% was obtained from Merck KGaA (Darmstadt, Germany). USP/NF methacrylic acid copolymer types A and B (Eudragit L 100® and Eudragit S 100®, respectively) and microcrystalline cellulose (avicel PH102®) were gifts from Rohm GmbH (Darmstadt, Germany) and Taro Pharmaceutical Industries (Haifa Bay, Israel), respectively. Levodopa, carbidopa, and ethylcellulose (N-100) were generous gifts from Teva Pharmaceutical Industries (Kfar Sava, Israel). All reagents were of analytic grade purity. X-ray contrast threads were obtained from surgical gauze pads.

Preparation, Structure, and Physical Characteristics of the Tested DFs

The prototype GRDF (#4), seen in Fig. 1a, was comprised of a noncontinuous inner layer, covered on both sides by outer (shielding) layers that had a thin antiadhering layer (of microcrystalline cellulose) spread over their exterior side. The outer layers (thickness 0.013 cm) were composed of enzymatically hydrolyzed gelatin, Eudragit S®, glycerine, and glutaraldehyde (48:30:20:2, respectively). The inner layer was composed of rigid polymeric strips (thickness 0.04 cm) in the center and the frame. All polymeric membranes (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 structure and composition of the DFs are specified in Table I.

The levodopa-GRDF was similar to GRDF #3 (see Table I) except for the inner layer, which contained only two long rigid strips in the frame with a polymeric membrane containing levodopa (200 mg) between them. The GRDF released levodopa over 3 h, and carbidopa was released immediately into USP 23 simulated gastric fluid without pepsin (pH 1.2, HCl–KCl). The thicknesses of all membranes deviated by not more than 10% of the mentioned values.

In Vivo Assessment of Gastroretentivity

The studies involving healthy volunteers followed the tenets of the Declaration of Helsinki promulgated in 1964 and were approved by the Ethics Committee of The National Medical Center, Budapest 1135, Hungary. The volunteers gave their informed consent to participate in the studies.

GRTs of the various DFs were evaluated in healthy volunteers (white, both genders, n = 11–15; age 39 ± 12 range 20–62; weight 67 ± 15 range 42–105 kg; mean ± SD). The DF was administered with 200 ml water and a 325-kcal sandwich at 8:00 following an overnight fast. Five hours postadministration, all volunteers ate the same type of sandwich. Otherwise, no food was allowed (with *ad libitum* access to water) during the 8 h of the experiment.

To detect the location in the gastrointestinal tract and to evaluate the mechanical integrity of the DFs *in vivo*, X-ray contrast threads were incorporated into the DFs, and radiographs of the abdominal area were taken at 3, 5, and 8 h postadministration. One (1.5 cm) and two (1 cm) pieces of contrast threads were embedded in each of the two outer layers during their fabrication. In addition, one or two pieces (0.5 cm) were appended in each of the short or long frame strips, respectively (see Fig. 1a). The egg albumin matrix tablet used for control contained two 0.5 cm contrast threads, perpendicular to each other, each in a different flat surface of the tablet, added during the tablet's compression.

Visual examination of the GRDF (prototype #4) in the stomach was conducted by gastroscopy. The GRDF was administered (following an overnight fast) at 8:00 to a healthy volunteer (age 31 years, weight 62 kg), with a glass of sugar-water (325 kcal). Immediately after intake, a 2.5 mg midazolam intravenous injection was administered, which was followed by a video recorded gastroscopy. All the DFs detailed in Table I, except #8, were administered after being folded into gelatin capsules. Each consecutive fold (0.6–0.7 cm long) was in the opposite direction to the former.

Mechanical Characterization

Mechanical properties of polymeric membranes were evaluated using an Instron tester applying a stress–strain test with 10 kN tension load cell. Cross head speed was 2.5 $cm \cdot min^{-1}$. Young's modulus of elasticity and yield strength (at 0.5% offset) of 10 samples (7 × 1 cm) were measured.

The measured samples were (a) combinations of Eudragit L® and ethylcellulose (70%) where ethylcellulose is in the range of 0–30%, with triacetin (30%); (b) combinations of enzymatically hydrolized gelatin and Eudragit S® (80%) where Eudragit S® is in the range of 0–40%, with glycerine (20%).

In Vitro Assessment of the GRDF Properties

The effect of the amount of cross-linking agent (glutaraldehyde) on *in vitro* dissolution rate of enzymatically hydrolyzed gelatin from polymeric membranes (having 50% enzymatically hydrolyzed gelatin and glutaraldehyde, 30% Eudragit S® and 20% glycerine) was studied by immersing the membranes in hydrochloric acid solution (pH 1.2) using USP 23 dissolution rate tester apparatus 2 at 37°C (n = 6, 100 rpm, Caleva ST7, Dorset, UK). Samples were collected in predetermined time points and amount of dissolved enzymatically hydrolyzed gelatin was measured against a suitable calibration curve using the Lowry method (23).

Polymeric membranes (n = 6) with 0, 15, and 30% Eudragit S®, 20% glycerine, and enzymatically hydrolyzed gelatin cross-linked with glutaraldehyde (in a ratio of 96:4), and GRDF #2 (n = 6), were immersed in simulated gastric fluid without pepsin. Five hours following immersion, GRDFs (n = 4) were transferred to USP 23 simulated intestinal fluid without pancreatin (pH 7.5, NaOH-phosphate). The experiments were conducted using the same dissolution rate tester and conditions described above. The membranes and GRDFs were inspected for their mechanical integrity and photographed at predetermined times.

GRDFs #2, #4, and #6, with or without folding and en-

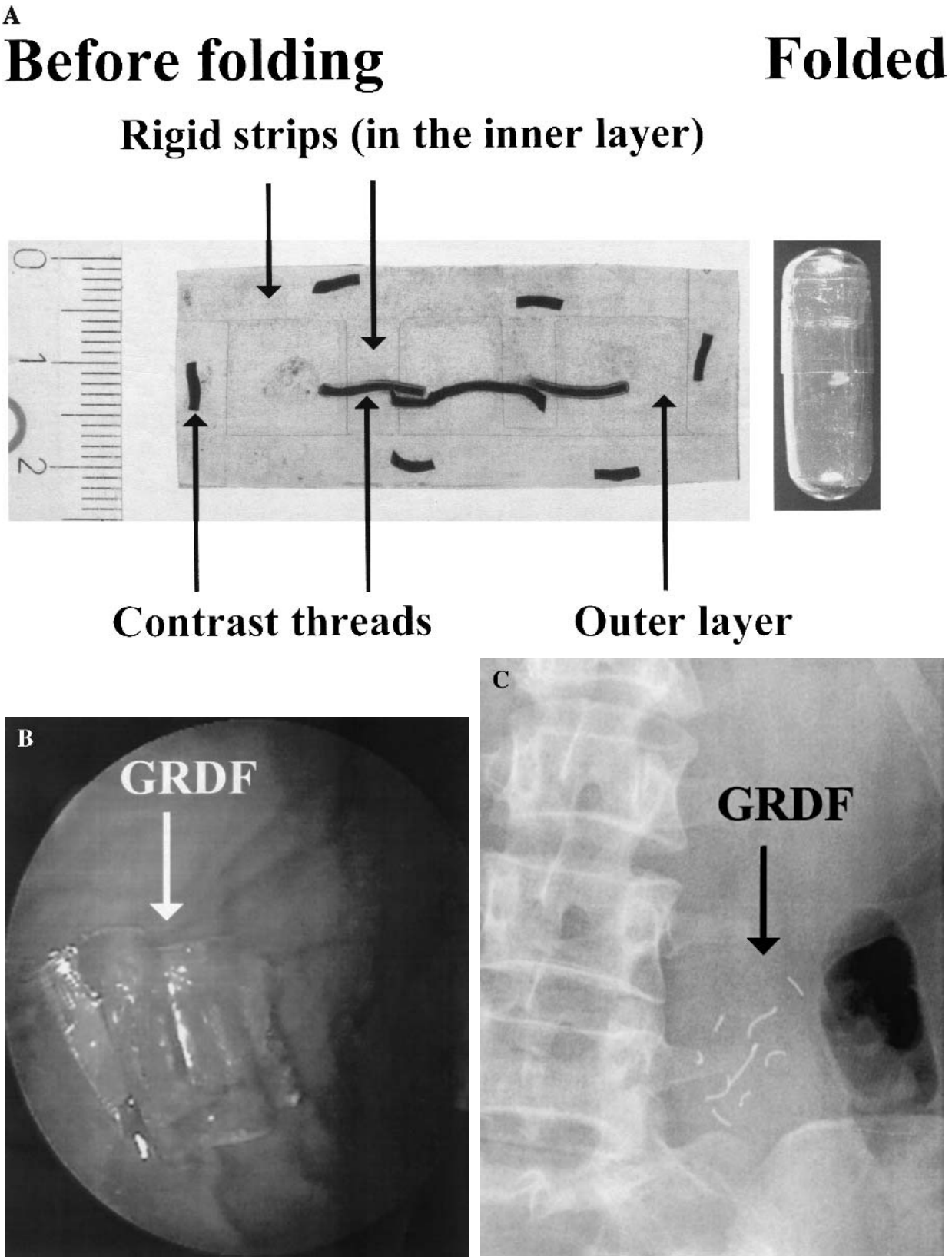

Fig. 1. The prototype gastroretentive dosage form (GRDF) is seen (a) prior to administration, before and after folding; (b) using gastroscopy, fully unfolded inside the stomach of a healthy volunteer 10 min postadministration; and (c) in a radiograph, 3 h postadministration. The contrast threads enabled evaluation of the anatomic location of the GRDF in the gastrointestinal tract as well as its mechanical completeness.

Table I. Structure and Composition of Various DFs

DF number	Main characteristics
#1	Folded into gelatin capsule 000; rigid strips composed of 90% L-poly(lactic acid) and 10% ethylcellulose; size 6.5 × 2.5 cm
#2	Capsule 00; rigid strips composition as DF #1; size 5 × 2.1 cm
#3	Capsule 000; rigid strips composed of 50% Eudragit L®, 30% triacetin, and 20% ethylcellulose; size as DF #1
#4 (prototype)	Capsule 00; rigid strips composition as DF #3; size 5.5 × 2.1 cm
#5	1.5% cross-linking agent (glutaraldehyde) in the outer layers (DF #4 had 2% glutaraldehyde); otherwise as DF #4
#6	Continuous rigid inner layer (instead of strips) composed of 70% Eudragit L® and 30% triacetin; otherwise as DF #4
#7 (control)	No rigid strips; otherwise as DF #4
#8	10-mm matrix tablets (from egg albumin)

DF, dosage form.

trapment in gelatin capsules, were immersed in simulated gastric fluid without pepsin (n = 6, 37°C, 50 rpm, Orbit shaker, Lab-Line Instruments, Inc.), and their dimensions were measured.

In Vivo Evaluation of Levodopa-Containing GRDF

Volunteers (male, white, n = 12, age 35 ± 8, weight 83 ± 16 kg, mean ± SD) whose good health was ascertained according to detailed medical history, SMAC biochemical and hematologic laboratory evaluation, and physical examination, were treated with 50 mg t.i.d. carbidopa during the day before the assessment of levodopa pharmacokinetics experiment. Levodopa/cabidopa (200/50 mg) was administered as a GRDF or a commercial controlled release DF (Sinemet CR®) in a crossover design.

Following an overnight fast, the volunteers received at 8:00 the levodopa with 200 ml water and a sandwich (325 kcal). The same type of sandwich, two cakes (480 kcal), and a standard meal were provided at 5, 8, and 12 h postadministration, respectively. An X-ray picture (these GRDFs had the contrast threads only in the rigid strips) was taken 5 h following administration. Blood samples were obtained at times 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 24 h postadministration, centrifuged immediately, and kept at –70°C pending analysis. The levodopa concentrations in plasma were determined by a high-pressure liquid chromatography (HPLC) method with electrochemical detection (24) using appropriate calibration curves in the range of 25 to 2500 ng·ml^{-1}. The limit of detection was 5 ng·ml^{-1}.

The pharmacokinetic parameters were determined from the experimental drug concentration–time data by the noncompartment method using Winnonlin® 1.1 software (Pharsight Corporation, Mountain View, CA). These parameters were total area under plasma drug concentration–time curve from time zero to infinity (AUC); maximal drug concentration (C_{max}); time to attain C_{max} (t_{max}); mean residence time (MRT, the average time the number of molecules introduced reside in the body); arithmetic mean of the concentrations within 25% of C_{max} (C_{apical}); arithmetic mean of the times associated with the concentrations within 25% of C_{max} (t_{apical}) (25).

Statistical Analysis

The ANOVA test, followed by Tukey-Kramer Multiple Comparisons Test, where appropriate, or the two-tailed *t* test were used to assess the statistical significance of the differences between the results. A *p* value of less than 0.05 was termed significant.

RESULTS

In Vivo Assessment of Gastroretentivity

The GRTs of DFs in the healthy volunteers are summarized in Table II. As seen in that table, GRDFs #1 through #6 were retained in the human stomach for longer periods of time than DFs #7 and #8 ($p < 0.01$). The majority of GRDFs #1 through #4 were retained for more than 8 h, and the slight decrease in retention observed for GRDFs #5 and #6 was not statistically significant. Control DF (#7), which had the same dimensions as the prototype DF (#4) but lacked a rigid frame, showed similar gastric retention as the matrix tablets.

The GRDFs sized 6.5 × 2.5 cm (#1, #3) entrapped in gelatin capsule type 000 were reduced to 5 × 2.1 cm and 5.5 × 2.1 cm (GRDFs #2 and #4, respectively) in order to enable folding them into 00 gelatin capsules without negative impact on their gastroretentivity.

Although GRDFs #1 and #2 contained rigid polymeric strips that do not degrade under the experimental conditions (namely during a few hours in the stomach), the nondegradable constituent of other GRDFs was substantially reduced to 20% ethylcellulose (in GRDFs #3 and #4) or to zero (GRDF #6, with a continuous inner layer platform) while exhibiting similar gastroretentivity. Reducing the percentage of the cross-linking agent (glutaraldehyde) yielded an enhanced *in vitro* dissolution rate of the enzymatically hydrolyzed gelatin (Fig. 2) from the outer layer of GRDF #5 in comparison to the outer layer of GRDF #4. However, this variation was not associated with any notable differences in the gastroretentivity of these GRDFs *in vivo*.

Gastroscopy ascertained that 10 min following adminis-

Table II. Percentage of DFs Retained in the Stomach at Different Time Points following Administration to Healthy Volunteers

DF number	Number of volunteers	3 h (%)	5 h (%)	8 h (%)
#1*	15	100	100	87
#2*	15	100	100	73
#3*	14	100	86	64
#4*	12	100	66	58
#5*	11	100	82	36
#6*	15	80	73	46
#7	12	75	8	8
#8	15	33	6	0

* Significantly different from DFs #7, #8
DF, dosage form.

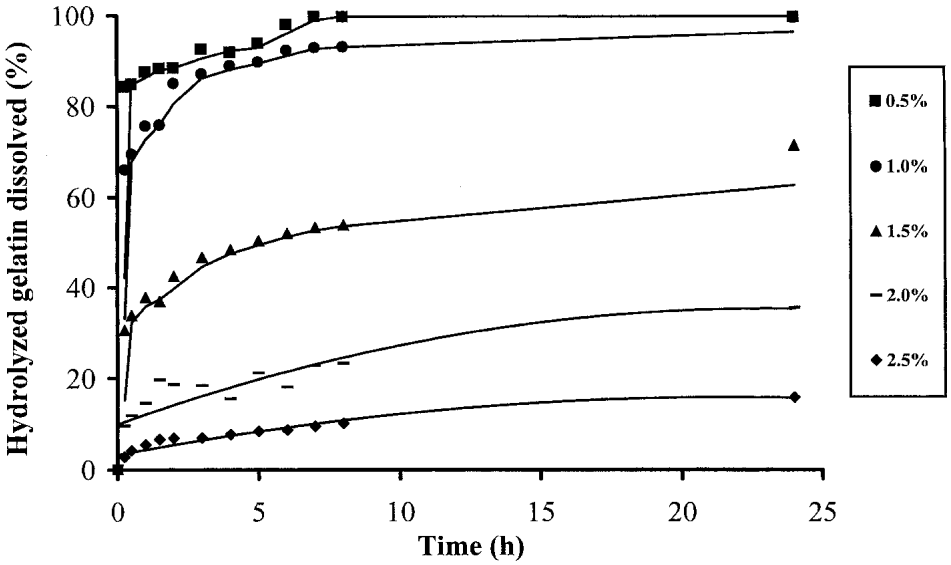

Fig. 2. Effect of percentage cross-linking agent (glutaraldehyde) on *in vitro* dissolution kinetics of enzymatically hydrolyzed gelatin, compounded in the outer layers of the gastroretentive dosage forms, into acidic solution (pH 1.2).

tration, the prototype GRDF was unfolded in the stomach (Fig. 1b). X-ray pictures showed that the GRDFs, as well as the control tablets, maintained their mechanical integrity in the stomach (Fig. 1c) and that in only 16% of the cases, one long contrast thread (from one of the shielding layers) left the GRDF in the stomach (with no difference between various types of GRDFs). No side effects were reported following administration of any of the GRDFs.

Mechanical Characterization of the Polymeric Membranes

The mechanical properties of polymeric membranes are summarized in Tables III and IV. It was found that addition of up to 20% ethylcellulose to Eudragit L®–triacetin (30%) combinations increased the mechanical properties; and addition of 30% or 40% Eudragit S® to enzymatically hydrolyzed gelatin–glycerine (20%) combinations increased the rigidity of the outer layers. As reported before (22) the Young's modulus and yield strength of: L-poly(lactic acid)–ethylcellulose strips were 589 ± 34 and 10.9 ± 0.4 Mpa, respectively; the outer layers were 20.6 ± 0.8 and 0.41 ± 0.02 Mpa, respectively. Components of the GRDFs with Young's modulus higher than 200 Mpa and with a yield strength higher than 4 Mpa were termed "rigid."

In Vitro Assessment of the GRDF Properties

An inverse correlation was noted between the percentage of cross-linking agent (glutaraldehyde) and dissolution rate of enzymatically hydrolyzed gelatin in the range of 1 to 2.5% (Fig. 2). As opposed to polymeric membranes with 30% Eudragit S® and GRDF #2, which maintained their mechanical integrity in simulated gastric fluid without pepsin for over 24 h, membranes with lower amounts of Eudragit S® were shown to disintegrate after 2.5 h; transfer of GRDF #2 after 5 h to simulated intestinal fluid without pancreatin resulted in rapid dissolution of the outer membrane, leading to fast (< 3 h) GRDF disintegration.

Table V shows that following immersion in simulated gastric fluid without pepsin, the GRDFs unfolded rapidly and reached extended dimensions, ≥ 3.6 ± 0.1 cm, within 15 min. As seen, whereas GRDFs #2 and #4 lost about 1 cm from their original length through the formation of folds, GRDF #6 (the only GRDF that swelled) showed a slight increase in length despite folding.

In Vivo Evaluation of Levodopa-Containing GRDF

In 67% of the cases the levodopa-GRDFs were retained in the stomach 5 h postadministration. Following GRDF ad-

Table III. Effect of Ethylcellulose Addition to Eudragit L®–Triacetin (30%) Combinations on the Mechanical Properties of Polymeric Matrices

Percent ethylcellulose	Young's modulus (Mpa)	Yield strength (Mpa)
0	207 ± 15	4.7 ± 0.3
10	357 ± 23*	9.1 ± 0.5*
20	456 ± 20**	10.7 ± 0.4**
30	521 ± 24**	11.6 ± 0.4**

* Significantly different from all other groups.
** Significantly different from 0% ethylcellulose, 10% ethylcellulose.

Table IV. Effect of Eudragist S® Addition to Enzymatically Hydrolyzed Gelatin–Glycerine (20%) Combinations on the Mechanical Properties of Polymeric Matrices

Percent Eudragit S®	Young's modulus (Mpa)	Yield strength (Mpa)
0	4.8 ± 0.4	0.01 ± 0.001
15	8.2 ± 0.6*	0.01 ± 0.002*
30	22.9 ± 1.7**	0.56 ± 0.053**
40	61.9 ± 3.8**	1.11 ± 0.059**

* Significantly different from 30% Eudragit S®, 40% Eudragit S®.
** Significantly different from all other groups.

Table V. Unfolding and Swelling Properties of GRDFs as Measured by Their Lengths when Immersed in Acidic Buffer (pH 1.2)

	Unfolding			Swelling		
GRDF number*	0.25 h	0.5 h	4 h	0.25 h	0.5 h	4 h
#2 (5 cm)	3.6 ± 0.1	3.8 ± 0.2	3.8 ± 0.2	4.9 ± 0.1	5 ± 0.1	5 ± 0.1
#4 (5.5 cm)	4.4 ± 0.4	4.7 ± 0.4	4.8 ± 0.3	5.7 ± 0.1	5.8 ± 0.1	5.8 ± 0.1
#6 (5.5 cm)	5.5 ± 0.6	5.6 ± 0.6	5.8 ± 0.6	6.2 ± 0.2	6.3 ± 0.1	6.3 ± 0.1

* Length before folding is shown in parentheses.
GRDF, gastroretentive dosage form.

ministration, the levodopa plasma concentration–time curve extended the absorption phase in comparison to Sinemet CR® (Fig. 3), which is illustrated by its prolongation of about 1 to 2 h in MRT, t_{max}, and t_{apical} (see Table VI). One volunteer suffered from nausea and vomiting after administration of a levodopa-GRDF.

DISCUSSION

This study highlights the validity of the approach of combining extended physical dimensions with compounding rigid constituents for prolonging gastroretentivity of DFs in healthy subjects. Multilayer polymeric GRDFs with size ≥ 5 × 2.1 cm and characterized by high rigidity (see Table III) were retained in the human stomach for more than 5 h. The importance of the rigidity is demonstrated by DF #7, which had extended dimensions but lacked high rigidity and was not retained in the stomach like the equivalent size GRDFs. Its short GRT may be attributed to the inability to withstand stomach contractions, as we have previously found that large but not rigid DFs had reduced dimensions in the dog's stomach a few hours after administration (22). The rapid unfolding process, validated both *in vitro* and *in vivo* is important to prevent emptying of the GRDF from the stomach by evacuation forces such as the interdigestive migrating myoelectric complex activity (26).

The soundness of this approach to improve gastroretentivity was exemplified by the finding that DFs having similar mechanical properties but composed of different polymeric blends, were retained in the stomach for equivalent time periods. It was also corroborated by the fact that these GRDFs were tested in a heterogeneous population composed of volunteers from both genders and having a wide range of ages and weights.

The suggested mechanism for the gastroretentivity of the current GRDFs is based on the retropulsive reflex of the stomach, which pushes, back from the pyloric-antrum toward the more proximal stomach body particles that are too large to be infused to the intestine (27). This suggested mechanism is in accord with the work of Shalaby *et al.* (28), who demonstrated, using ultrasound and fluoroscopic imaging, the validity of this mechanism in prolonging the GRT of swelling DFs in the dog stomach.

The positive outcomes of this investigation in humans are in agreement with the previous studies evaluating the same type of GRDFs in dogs (22). In fact, this is the first report that shows a positive correlation of GRDFs' performance between humans and beagle dogs. A previous study has found much

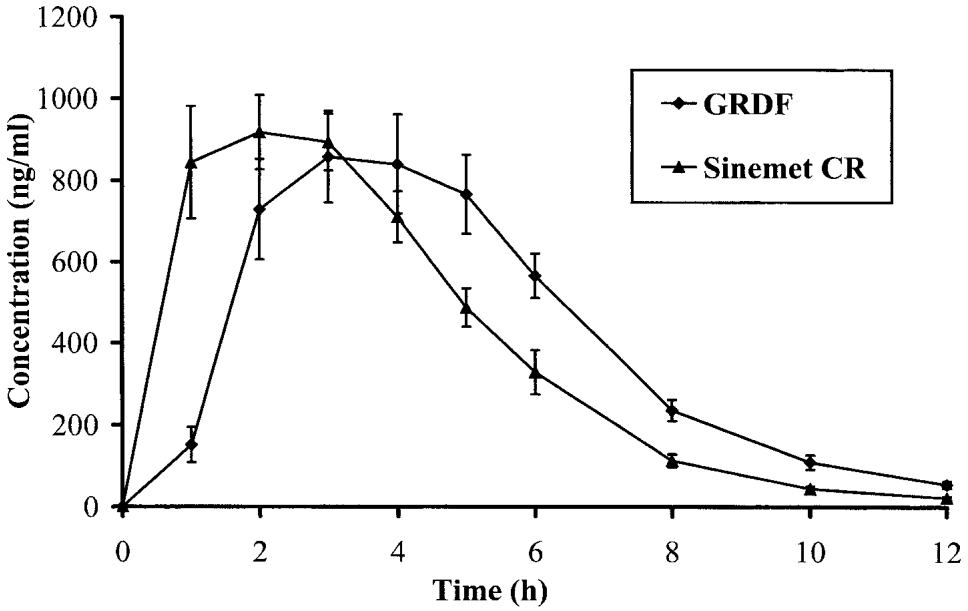

Fig. 3. Effect of levodopa administration (200/50 mg levodopa/carbidopa) as gastroretentive dosage form (GRDF) or Sinemet CR® on plasma concentrations in healthy volunteers (n = 12).

Table VI. Effect of Administration of Levodopa/Carbidopa (200/50 mg) as GRDF vs. Sinemet CR® on Levodopa Pharmacokinetic Parameters in Healthy Volunteers (n = 12)

Pharmacokinetic parameter	GRDF	Sinemet CR®
AUC ($ng \cdot h^{-1} \cdot ml^{-1}$)	5241 ± 339	4824 ± 292
C_{max} ($ng \cdot ml^{-1}$)	1142 ± 102	1117 ± 95
t_{max} (h)	3.8 ± 0.4*	2.1 ± 0.3
MRT (h)	5.5 ± 0.4*	4 ± 0.2
C_{apical} ($ng \cdot ml^{-1}$)	1087 ± 106	1043 ± 107
t_{apical} (h)	3.7 ± 0.4*	2.4 ± 0.2

AUC, area under plasma concentration–time curve; C_{max}, maximal drug concentration; t_{max}, time of occurrence for peak drug concentration; MRT, mean residence time; C_{apical}, arithmetic mean of the concentrations within 25% of C_{max}; t_{apical}, arithmetic mean of the times associated with the concentrations within 25% of C_{max};
* significantly different from the other group.
GRDF, gastroretentive dosage form.

shorter GRT of unfolding tetrahedral geometric shapes in humans [median 3 h in fasting state (9)] in comparison to beagle dogs [GRT of ≥ 24 h (29)]. In addition to the comparable GRTs (22) we were able to show similarities between the species in several properties including rapid unfolding *in vivo* (13), dependency on rigidity for gastroretentivity, ability to compound various polymeric matrices with comparable rigid mechanical properties to achieve similar gastroretentivity, maintenance of mechanical completeness, and lack of (apparent) side effects. Certain modifications in the dog model (i.e., administration of the GRDF together with 400 ml acidic buffer) may have contributed to this similarity (22).

The fact that enhancing the mechanical properties by increasing the amounts of enteric polymer to the outer GRDF layer (see Table IV) prevented *in vitro* disintegration only in acidic buffer, exemplifies the safety profile of these GRDFs, as they are expected to disintegrate in the intestine. In future improvements the enteric polymer that dissolves in pH 7 (e.g., Eudragit S®) used in the outer layer could be replaced with a similar polymer that dissolves in pH 5.5 (e.g., Eudragit L®). This may enhance intestinal dissolution of the outer layer, thus leading to GRDF disintegration.

Because there is already a controlled-release DF of levodopa (in combination with carbidopa) in clinical use that is pharmacokinetically better than the immediate-release preparation (30), we chose to examine the added value of the exploratory levodopa-GRDF in comparison to the nongastroretentive controlled-release DF (Sinemet CR®). We have found that the levodopa-GRDF yielded an extended absorption phase in comparison to Sinemet CR®. This was evident by the larger MRT (5.5 ± 0.4 vs. 4 ± 0.2 h for GRDF and Sinemet CR®, respectively), t_{max}, and t_{apical} values. Thus, the current study shows for the first time the ability of gastroretentive mode of administration to prolong the absorption phase in comparison to controlled-release administration in healthy volunteers. Previous reports have concentrated on demonstrating the possibility of GRDFs to extend the absorption phase in comparison to immediate-release DFs, where this phase is inherently brief (10,27).

As has been shown before by comparing the efficacy of controlled-release vs. immediate-release levodopa DFs in the case of levodopa bioavailability (AUC) alone is not a sufficient parameter for predicting the DF's impact on the clinical outcomes of levodopa. Despite the lower bioavailability of the two controlled-release DFs, Sinemet CR® and Madopar HBS®, in comparison to the respective immediate-release DFs Sinemet® (15) and Madopar® (18), extension of the input phase has yielded enhanced clinical efficacy.

The similarity in AUC values between the GRDF and Sinemet CR® indicates that the potential of the GRDF to enhance bioavailability by extending the absorption phase was not met in the tested exploratory GRDF. As evidenced from the drug plasma concentration–time plot, there was a certain lag time in the onset of drug release in the initial phase. The practical conclusion from these findings is that in order to further optimize this delivery system, the levodopa release rate from the GRDF has to be modified and should contain a certain rapid release component. Such modification, together with the extension of the absorption phase, would yield a clinically improved levodopa DF that in our view is expected to be superior to Sinemet CR®.

As discussed before, because C_{max} and t_{max} are single point parameters, they are not proper parameters to evaluate the pharmacokinetic properties of controlled-release DFs (25). Thus, we used C_{apical} and t_{apical}, which are pharmacokinetic parameters developed for controlled-release DFs to compare between the two levodopa DFs. These parameters take into account multiple concentration–time peaks, common for pharmacokinetic profiles of controlled-release DFs. They also have less dependence on sampling schedule (25). Because of their nature, the newer pharmacokinetic parameters are proposed as the state-of-the-art for pharmacokinetic studies of GRDFs.

In conclusion, achieving prolonged gastroretentivity of unfolding GRDFs, accompanied by extension of absorption phase in comparison to nongastroretentive levodopa controlled-release DF in humans, is an important step toward using levodopa-GRDFs in the clinical setting. Furthermore, because the current GRDF is a non-drug-specific platform and can be compounded with different medications (20,21), it may improve therapy of a variety of narrow absorption window drugs.

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