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Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms

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Abstract

Controlled release gastroretentive dosage forms (CR-GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. CR-GRDF provide a means to utilize all the pharmacokinetic (PK) and pharmacodynamic (PD) advantages of controlled release dosage forms for such drugs. Thus, CR-GRDF may improve therapy with clinically used medications, as well as enable oral administration of drugs, or drug candidates, that hitherto had to be infused parenterally. This manuscript discusses the complexity of the PK and PD factors that influence the treatment benefits of CR-GRDF and summarizes the results of our recent in vivo investigations in animal models (rats and dogs) and in human subjects. We found that a CR-GRDF formulation was superior to the other modes of administration for levodopa and riboflavin, but not for metformin. The PK and PD rationales of GRDFs for the studied drugs are presented and discussed. We conclude that due to the complexity of the PK and PD factors for a certain drug, the rationale for continuous administration obtained by CR-GRDF should be assessed and established in vivo.
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1. Introduction

Oral administration is the most convenient mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake. However, oral administration has only limited use for important drugs, from various pharmacological categories, that have poor oral bioavailability due to incomplete absorption and/or degradation in the gastrointestinal (GI) tract. Some of these drugs are characterized by a narrow absorption window (NAW) at the upper part of the gastrointestinal tract. This is because the proximal part of the small intestine exhibits extended absorption properties (including larger gaps between the tight junctions, and dense active transporters). Despite the extensive absorption

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properties of the duodenum and jejunum, the extent of absorption at these sites is limited because the passage through this region is rapid. Enhancing the gastric residence time (GRT) of a NAW drug may significantly improve the net extent of its absorption. This issue was demonstrated in a seminal experiment by Levy (1976) that compared the bioavailability of riboflavin when taken with Coca Cola, light cola, or water. The GRT of riboflavin attained by the glucose together with phosphoric acid in the Coca Cola was considerably larger than that produced by phosphoric acid alone in the light cola, while the GRT following intake with water was the shortest. There was a direct correlation between the prolonged GRT and enhanced bioavailability.

To further increase the GRT of drugs, a gastroretentive dosage form (GRDF) can be developed. It is quite complex to achieve extensive retention of the GRDF since the natural activity of the stomach is to evacuate its contents into the intestine. The development of the GRDF has generated enormous interest and the pharmaceutical aspects of these developments are reviewed elsewhere (Deshpande et al., 1996; Hwang et al., 1998). The main approaches that have been examined thus far are: low density of the GRDF that causes buoyancy above gastric fluid; high density which retains the dosage form (DF) in the body of the stomach that is anatomically lower than the pyloric sphincter; concomitant administration of drugs or excipients which slow the motility of the gastrointestinal tract; bioadhesion to gastric mucosa; swelling to a large size which prevents emptying of the DF through the pyloric sphincter.

Controlled release (CR) dosage forms have been extensively used to improve therapy of many important medications. However, in the case of NAW drugs this pharmaceutical approach cannot be utilized since it requires sufficient colonic absorption of the drug (which is, by definition, not the case for NAW agents). On the other hand, incorporation of the drug in a controlled release gastroretentive dosage forms (CR-GRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic (PK) and pharmacodynamic (PD) factors. The aim of this review is to delineate these aspects in order to suggest rational selection of drugs for which CR-GRDF would be a beneficial strategy.

1.1. Pharmacokinetic aspects

1.1.1. Absorption window—validation that the drug is within the category of NAW agents

Currently various experimental techniques are available that permit us to verify the absorption properties of the tested molecule, to determine the mechanism of intestinal absorption and to elucidate the permeability at different regions of the GI tract. In general, appropriate candidates for CR-GRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GI tract. In the case of absorption by active transporters that are capacity limited, the efficacy of the transport activity may increase following sustained presentation of the drug to the transporting enzymes in comparison to non-CR mode of administration.

1.1.2. Enhanced bioavailability

Once it has been ascertained that the compound in question is defined as NAW, the possibility of improving bioavailability by continuous administration of the compound to the specific site should be tested. For example, we have found that certain bisphosphonates, including alendronate, are absorbed directly from the stomach. However, the magnitude of this pathway remains modest even in the case where the prolonged gastric retention of the bisphosphonate in rats is produced by experimental/surgical means (Ezra et al., 2000). On the other hand, as shown in the next chapters of this manuscript, the bioavailability of riboflavin and levodopa CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations (Klausner et al., 2002, 2003). It may be concluded that several different processes, related to absorption and transit of the drug in the gastrointestinal tract, act concomitantly and influence the magnitude of drug absorption. Therefore, in vivo studies are necessary to determine the release profile of the drug from the dosage form that will provide enhanced bioavailability.

1.1.3. Enhanced first pass biotransformation

In a similar fashion to increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented

to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input.

1.1.4. Improved bioavailability due to reduced P-glycoprotein (P-gp) activity in the duodenum

In apparent contrast to the higher density of CYP3A4 at the upper part of the intestine, P-gp mRNA levels increase longitudinally along the intestine such that the highest levels are located in the colon. Therefore, for drugs that are P-gp substrate and do not undergo oxidative metabolism, such as digoxin, CR-GRDF may elevate absorption compared to the immediate and CR dosage forms.

1.1.5. Reduced frequency of dosing

For drugs with relatively short biological half-life, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

1.1.6. Targeted therapy for local ailments in the upper GI tract

The prolonged and sustained administration of the drug from the GRDF to the stomach may be advantageous for local therapy in the stomach and the small intestine. By this mode of administration, therapeutic drug concentrations may be attained locally while the systemic concentrations, following drug absorption and distribution, are minimal.

1.2. Pharmacodynamic aspects (Hoffman, 1998; Hoffman and Stepensky, 1999)

1.2.1. Reduced fluctuations of drug concentration

Continuous input of the drug following CR-GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.

1.2.2. Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

1.2.3. Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

1.2.4. Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as beta-lactam antibiotics, the clinical response is not associated with peak concentration, but rather, with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

1.2.5. Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to development of microorganism's resistance.

In most cases, due complexity of pharmacokinetic and pharmacodynamic parameters, in vivo studies are required to establish the optimal dosage form for a specific drug. For a certain drug, interplay of its pharmacokinetic and pharmacodynamic parameters will determine the effectiveness and benefits of the CR-GRDF compared to the other dosage forms. In the next chapters we discuss the development and evaluation of CR-GRDF for several drugs that were performed in our laboratory.

2. Methods

2.1. Assessment of pharmacokinetic and pharmacodynamic (PK–PD) rationale for CR-GRDF formulations in a rat model: metformin as a model drug (Stepensky et al., 2001)

Two controlled release matrix based tablet formulations with different rates of metformin release in vitro were used: CR tablets I (matrix tablets) and CR tablets II (matrix tablets with ethylcellulose coating). The in vitro rate of drug release was assessed according to method stated in the USP Pharmacopoeia.

To enable simultaneous PK and PD assessment in vivo, streptozotocin-diabetic rats (Sabra, male, 200–250 g, $n = 5$–6) received different modes of metformin administration in a crossover design. The studied modes were CR tablets I or II at a dosage corresponding to 450 mg kg^{-1} metformin, or the same dose of the drug administered as a bolus oral solution or a constant rate intraduodenal infusion (duration of the infusion was 4 h). Serial blood samples were collected from the tail artery and assayed for glucose and metformin. The gastric retention of the tablets was assessed radiographically in a separate study applying radiopaque markers added to the tablet formulation.

2.2. Evaluation of novel CR-GRDF formulation of levodopa in dogs (Klausner et al., 2003)

The CR-GRDFs were comprised of an inner layer composed of a polymer–drug matrix framed with rigid polymeric strips covered on both sides by two outer (shielding) layers (Klausner et al., 2002; Friedman et al., 2001). The CR-GRDFs were folded before insertion into gelatin capsules (000). The dimensions, prior to folding, of the CR-GRDF (and of the shielding layers) were 5 cm × 2.5 cm. Several types of the CR-GRDFs were prepared with different thickness and amount of levodopa compounded (CR-GRDF A–C).

The in vitro release rate of levodopa from the DFs into simulated gastric fluid was conducted according to the method described in the USP Pharmacopoeia, and the drug concentrations were determined applying UV detection.

The absorption of levodopa following intragastric administration of the GRDFs was studied in Beagle dogs in a crossover design in comparison to the CR dosage form and drug solution. Serial blood samples were collected, plasma was obtained and assayed for levodopa. The anatomical location of the CR-GRDFs in the gastrointestinal tract was accomplished radiographically by incorporating the radiopaque threads in the dosage form. The unfolding of the GRDFs was studied applying gastroscopic equipment.

2.3. Evaluation of novel CR-GRDF formulation of riboflavin in dogs (Klausner et al., 2002)

The dosage forms contained 100 mg riboflavin-5-phosphate (a prodrug of riboflavin), and the composition of the prepared dosage forms is shortly described in Table 4 (see reference Klausner et al., 2002 for more complete description). In general, the preparation of the dosage forms was similar to that of levodopa and the dosage forms were characterized both by extended dimensions and rigid structure. The CR-GRDFs were folded before insertion into gelatin capsules (000).

Radiology was used for determination of the anatomical location of the DF in the gastrointestinal tract and evaluation of the DF size in vivo. The CR-CRDF with X-ray opaque thread were prepared and given to the dogs, and series of radiograms were taken. To evaluate if CR-GRDF affects the emptying time of the gastic contents, Beagle dogs received BIPS® radiopaque markers alone or together with the prototype CR-GRDF (DF #1) and the GRTs of the radiopaque markers and the DFs were assessed radiologically.

The in vitro release of riboflavin-5-phosphate from the GRDF and the control DF was conducted using USP apparatus 2 and acidic buffer (pH 2.2, HCl–phthalate), and the drug concentrations were determined applying UV detection.

In vivo pharmacokinetic investigation was performed in a crossover design in Beagle dogs applying four different modes of administration: (a) prototype GRDF (#1); (b) control DF (#7); (c) drug dissolved in acidic buffer; (d) intravenous bolus injection (5 ml). X-ray pictures were taken at several time points. Blood samples were obtained periodically and assayed for riboflavin by an HPLC method with spectrofluorometric detection.

3. Results and discussion

3.1. Assessment of pharmacokinetic and pharmacodynamic (PK–PD) rationale for CR-GRDF formulations in a rat model: metformin as a model drug (Stepensky et al., 2001)

Metformin is glucose-lowering agent that is widely used for management of type 2 diabetes. Metformin is absorbed mainly in the upper parts of the gastrointestinal tract (Marathe et al., 1999; Vidon et al., 1988) and, due to the fact that metformin molecule is ionized at physiologic pH, has tendency to adsorb to the intestinal epithelium thus affecting the drug absorption pattern and increasing the incidence of gastrointestinal adverse effects. In addition to these unique pharmacokinetic properties, the pharmacodynamics of metformin is rather complex and does not follow a direct relationship between plasma drug concentration and magnitude of effect (Marchetti et al., 1987; Stepensky et al., 2002).

Metformin was suggested recently as a suitable drug for CR-GRDF (Gusler et al., 2001). However, the PK–PD rationale for such formulation was not assessed in a systematic manner. Previous studies at our laboratory confirmed that the colonic absorption of metformin is poor and produced poor and inconsistent glucose-lowering effects. On the other hand, it was determined that most of the metformin absorption occurs in the upper parts of the gastrointestinal tract. This fact, together with the findings that major sites of metformin action are located in the gastrointestinal tract and the liver, provides a clear rationale for a sustained and prolonged release of this drug from a CR-GRDF into the stomach and duodenum, since absorption from these sites would result in continuous input of metformin to the sites of action.

The preclinical model of the diabetic rat used in this work enabled simultaneous assessment of the PK and PD outcomes following administration of different dosage forms of metformin, and determination of the possible advantages of GRDF for this drug. The metformin blood concentrations versus time (PK data) and the glucose lowering effects (PD data) obtained for various modes of drug administration are presented in Figs. 1 and 2. No significant differences in the bioavailability and the extent of the glucose-lowering effect were found following administration of the GRDF, bolus oral administration, or slow infusion of metformin to the duodenum.

The underlying reason for these PK and PD outcomes for the GRDF of metformin is apparently the high affinity of the drug to the negatively charged intestinal wall. Due to the basic properties of the biguanide molecule (positive charge), it adsorbs to the intestinal wall, producing a ‘natural’ sustained

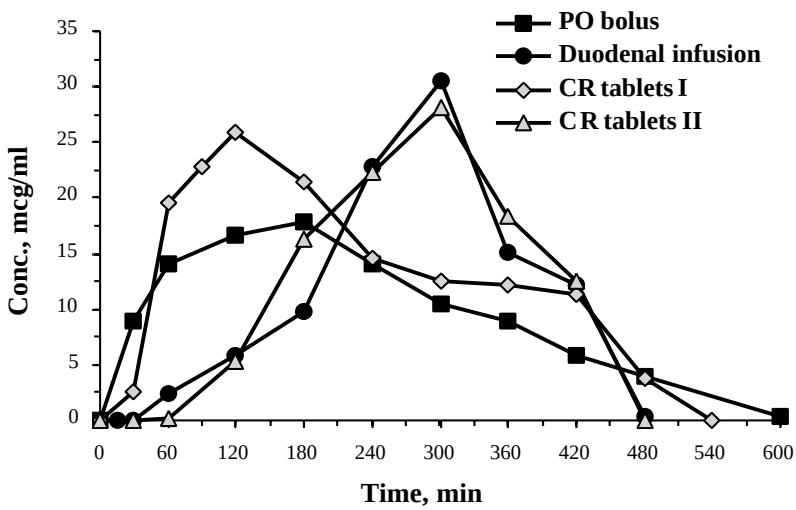

Fig. 1. Plasma metformin concentrations following administration of metformin (450 mg kg^{-1}) as PO bolus, duodenal infusion, and gastroretentive CR tablets (CR I or CR II) to the streptozotocin-diabetic rats (taken from reference Stepensky et al., 2001).

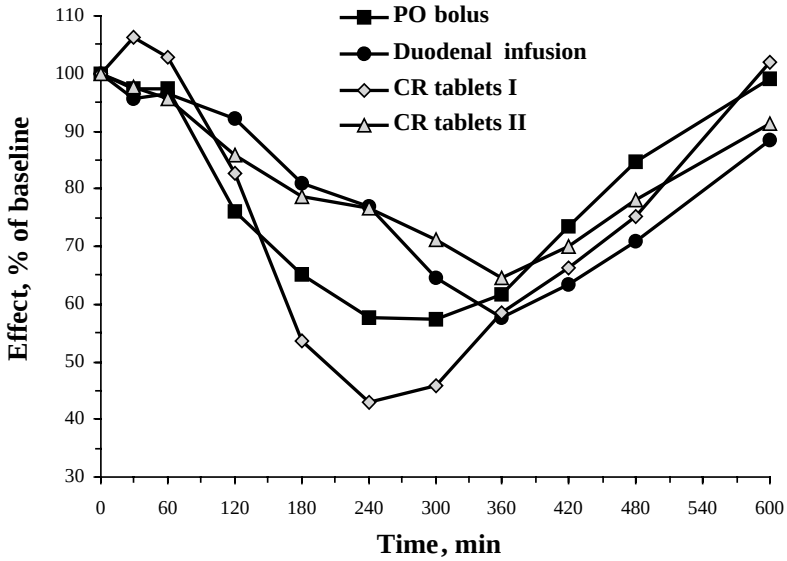

Fig. 2. Glucose-lowering effects following administration of metformin (450 mg kg^{-1}) as PO bolus, duodenal infusion, and gastroretentive CR tablets (CR I or CR II) to the streptozotocin-diabetic rats (taken from reference Stepensky et al., 2001).

release system. The adsorbed metformin is released from the intestinal wall in a sustained manner, producing a drug absorption profile similar to that of the CR formulation. As a result, the pharmaceutical manipulations that modify the release rate do not seem to improve the extent of metformin absorption and the magnitude of glucose-lowering effect. Thus, due to this "natural" sustained release property, CR-GRDF of metformin does not seem to offer PK or PD advantages over immediate release formulations. This work demonstrates the need for a combined PK and PD assessment in vivo to determine whether a certain drug is a proper candidate for GRDF.

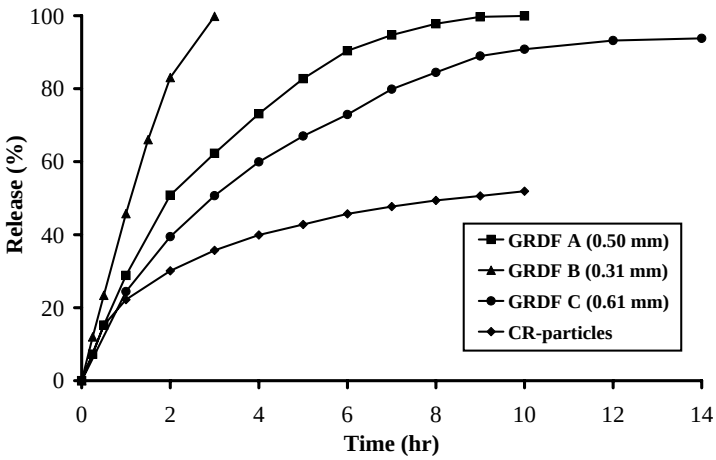

Fig. 3. In vitro release of levodopa from the CR dosage form and CR-GRDFs (taken from reference Klausner et al., 2003). The dissolution was conducted using USP 23 apparatus 2 (37 °C, 100 rpm) and USP 23 simulated gastric fluid without pepsin (pH 1.2, HCl–KCl).

3.2. Evaluation of novel CR-GRDF formulation of levodopa in dogs (Klausner et al., 2003)

Levodopa, a NAW drug that is absorbed solely via a specific transporter in the small intestine (Deleu et al., 1991), is used for the treatment of Parkinson's disease. Sustained levodopa blood concentrations following continuous levodopa administration (Nilsson et al., 1998) or administration of CR dosage forms (Wolters and Tesselaar, 1996) provide a clear clinical advantage compared to conventional oral dosage forms in terms of improved pharmacological efficacy and reduced "wearing off" effect at the end of dose interval (Harder et al., 1995).

Based on the pharmacokinetic and pharmacodynamic properties of levodopa it is expected that a CR-GRDF would optimize the therapy for this drug. After oral administration, such a CR-GRDF would be retained in the stomach and would release the drug there in a controlled and sustained manner, providing continuous supply of the drug to its absorption sites in the small intestine, and yielding a sustained and prolonged levodopa input to the systemic blood circulation (Hoffman, 1998; Hoffman and Stepensky, 1999).

A buoyant levodopa dosage form was previously developed (Erni and Held, 1987), and had shown some therapeutic advantage (Pacchetti et al., 1990), but it was not established whether this dosage form was

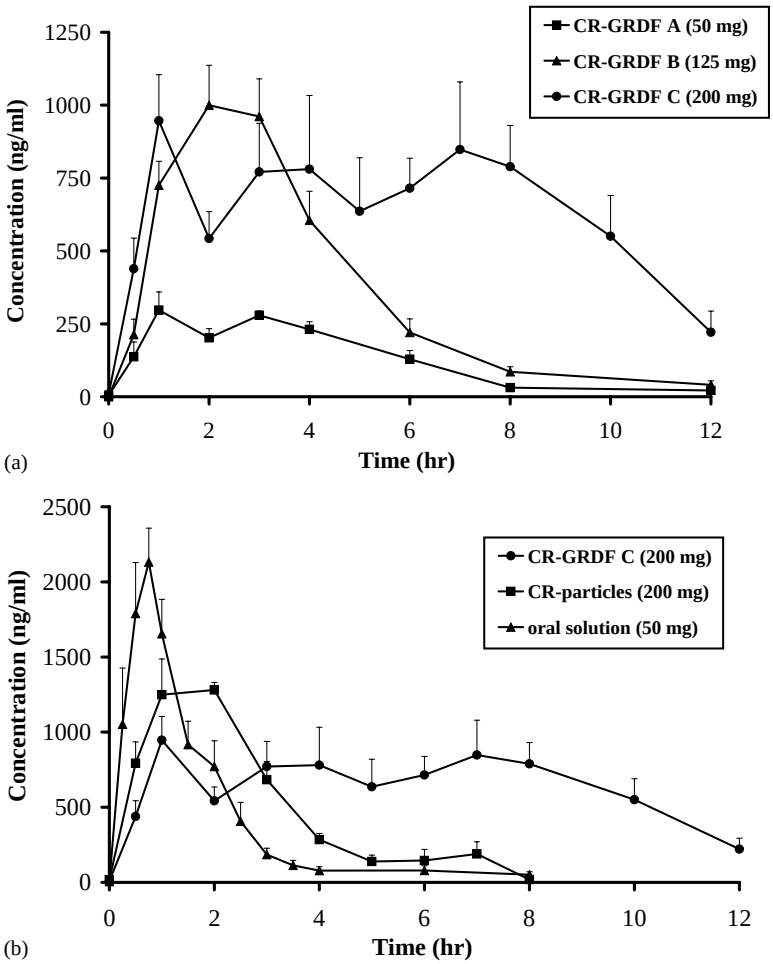

Fig. 4. (a and b) Mean plasma levodopa concentrations following administration of levodopa CR-GRDFs, CR-DF, or as drug solution to the Beagle dogs ($n = 6$) (taken from reference Klausner et al., 2003).

characterized by increased gastric retention. In our study, novel unfolding CR-GRDFs of levodopa that were characterized by extended geometrical dimensions with enhanced rigidity (Klausner et al., 2003) were developed, the levodopa release from these GRDFs was studied in vitro, and the pharmacokinetics following administration to dogs was assessed.

The results of the in vitro drug release test showed that the CR-GRDFs released levodopa in a controlled manner. Levodopa release rate showed an inverse correlation to the ethylcellulose–levodopa membrane thickness, and different types of the GRDFs were characterized by different release rates (see Fig. 3). The gastroscopy experiment showed that the GRDF had already unfolded to its extended dimensions 15 min after its administration and maintained its opened shape for at least 2 h. Consecutive X-rays showed that all of the CR-GRDFs were retained in the dogs' stomach for at least 24 h. We conclude that the gastric retention was due to the combination of large dimensions and rigidity of the dosage form. Rapid unfolding in the stomach, as found for the current GRDF, is a prerequisite to ensure the success of such systems, as otherwise they could be evacuated from the stomach by the normal gastric emptying processes.

Levodopa plasma concentrations following administration of the CR-GRDFs and the control modes of administration are presented in Fig. 4 and the pharmacokinetic parameters are presented in Table 1. The mean cumulative amount of levodopa absorbed in dogs following administration of the drug by the studied modes was calculated by numerical deconvolution and is presented in Fig. 5. Extended gradual absorption and sustained blood levels of levodopa were achieved applying the CR-GRDF compared to the CR dosage form and oral solution. Therefore, it is expected that CR-GRDF has potential to improve therapy with levodopa.

Results of this investigation confirm that a combination of extended physical dimensions with compounding rigid constituents enhances the gastroretentivity of DFs in vivo. Multilayer polymeric GRDFs with size = 5 cm × 2.1 cm that were characterized by high rigidity retained in the human stomach for more than 5 h. On the other hand, the formulation with extended dimensions but lacking high rigidity did not retain in the stomach like the equivalent size GRDFs.

The in vitro–in vivo correlations obtained in this study for CR-GRDF with different in vitro release properties reflect the complexity of the factors related to levodopa absorption in the intestine. Since levodopa undergoes degradation in the intestine, the resulting pharmacokinetic curve depends both on the release profile of the drug from the formulation and on the metabolic activity of the enterocytes. Sustained mode of drug input to the intestinal epithelial cells following administration of CR-GRDFs may reduce the bioavailability of drugs with a substantial degree of first pass

Table 1
Levodopa pharmacokinetic parameters following administration as bolus intravenous injection, CR-GRDFs, CR-DF, and oral solution in Beagle dogs ($n = 6$)

Pharmacokinetic parameter	Intravenous bolus	CR-GRDF A	CR-GRDF B	CR-GRDF C	CR-particles	Oral solution
Dose (mg)	50	50	125	200	200	50
AUC (ng h ml^{-1})	4468 ± 908	1684 ± 163	4560 ± 420	9901 ± 1446[a]	4494 ± 647	3294 ± 474
C_{max} (ng ml^{-1})	5866 ± 1153	317 ± 46[a]	1124 ± 118	1240 ± 122	1334 ± 103	1907 ± 302
t_{max} (h)		1.67 ± 0.67	2.00 ± 0.26	5.00 ± 1.58[a]	1.67 ± 0.33	0.71 ± 0.10
MRT (h)	0.85 ± 0.09	4.88 ± 0.85	4.06 ± 0.29	7.49 ± 0.43[a]	3.79 ± 0.87	1.63 ± 0.14[a]
MAT (h)		3.98 ± 0.85	3.20 ± 0.29	6.55 ± 0.44[a]	2.80 ± 0.89	0.74 ± 0.15[a]
HVD (h)		3.83 ± 0.89[b]	2.42 ± 0.87	6.50 ± 0.95[a]	1.67 ± 0.17	1.12 ± 0.24
C_{apical} (ng ml^{-1})		286 ± 39[a]	1083 ± 129	1155 ± 156	1260 ± 106	1683 ± 270
t_{apical} (h)		2.4 ± 0.2[b]	2.4 ± 0.2[b]	6.5 ± 0.9[a]	1.5 ± 0.3	0.8 ± 0.1

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; MAT: mean absorption time; HVD: half value duration; 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}.

[a] Significantly different from all other groups.

[b] Significantly different from oral solution.

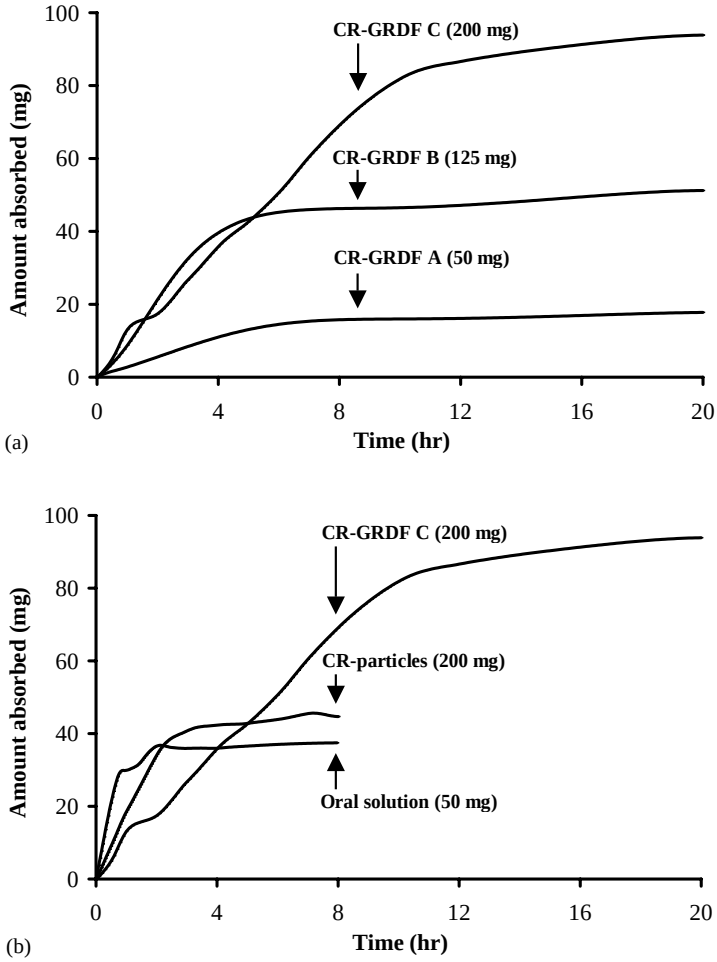

Fig. 5. (a and b) Mean cumulative amount absorbed following administration of levodopa CR-GRDFs, CR-DF, or as drug solution to the Beagle dogs ($n = 6$) (taken from reference Klausner et al., 2003).

metabolism (Antila et al., 1999), such as levodopa. On the other hand, rapid delivery of the drug to the metabolic enzymes may cause temporal saturation that leads to enhanced bioavailability (Crevoisier et al., 1987). This rate of administration-dependent efficacy of the metabolic enzymes may explain the lowered levodopa bioavailability following CR-GRDFs administration in comparison to the oral solution (see Table 1).

Additional consideration is related to the mechanism of levodopa absorption through the intestinal wall by means of active carrier transport (Deleu et al., 1991). Saturation of these carriers in case of immediate release formulations might limit the overall absorption of the drug. On the other hand, lower levodopa concentrations are obtained following its release from the DFs and may result in higher efficiency of the transporters.

Results of studies in dogs demonstrate that, due to the interplay of pharmacokinetic factors, prolonged absorption and sustained blood levels of levodopa were achieved by a novel CR-GRDF. We further evaluated the performance of levodopa CR-GRDF and compared the gastric retention and the pharmacokinetics of the CR-GRDF in comparison to the non-gastroretentive controlled release DF (Sinemet CR®) in healthy volunteers (paper submitted). We have found that the levodopa CR-GRDF yielded extended absorption phase in human subjects in

Table 2
Number of riboflavin DFs (out of six) retained in stomach at different time points following administration of DF #1 to DF #8 to Beagle dogs ($n = 6$)

DF number	DF composition[a]	1 h	2 h	4 h	6 h	8 h	13 h
1 (prototype)	Folded into gelatin capsule 000; rigid strips composed of 90% L-poly(lactic acid) and 10% ethylcellulose; size 5 cm × 2.5 cm	6	6	6	6	6	6
2	Different number and alignment of rigid strips	6	6	5	4	4	4
3	Different thickness of rigid strips	6	6	6	5	5	5
4	The rigid strips were composed of 97% ethylcellulose and 3% triethylcitrate	6	6	6	5	4	3
5	The size of the DF was 2.5 cm × 2.5 cm, different size of rigid strips	6	6	6	5	5	5
6	The size of the DF was 1 cm × 1 cm, different size of rigid strips	6	5	3	3	3	2
7 (control)	There was no rigid frame, and the polymer–drug matrix was 5 cm × 2.5 cm	6	3	2	1	0	0
8 (tablet)	Matrix tablets (0.8 cm diameter, 0.35 cm thickness)	6	5	2	1	0	0

[a] For DF #2 to DF #7 only major deviations from the prototype structure (DF #1) are stated. For more complete description see Klausner et al., 2002.

comparison to Sinemet CR®. Since Sinemet CR® in clinical studies showed superior pharmacokinetic performance compared to immediate release levodopa preparation (Wolters and Tesselaar, 1996), it is expected that CR-GRDF will further improve the drug therapeutic activity (Kurlan et al., 1988).

3.3. Evaluation of novel CR-GRDF formulation of riboflavin in dogs (Klausner et al., 2002)

Riboflavin (Vitamin B_2) is characterized by a narrow absorption window in the upper part of the small intestine (Jusko and Levy, 1975; Christensen, 1973), it lacks adverse effects and has no pharmacological effect on gastric motility (Marcus and Coulston, 2001). For these reasons, we applied riboflavin as a model drug to assess the pharmacokinetic aspects of CR-GRDF in human subjects. The outcomes of this investigation further confirm that a combination of geometrical dimensions and DF rigidity is crucial for the gastroretentive properties of the dosage form and each of these factors alone do not lead to consistent prolongation of the GRT (see Table 2).

The release of riboflavin-5-phosphate from the CR-GRDF and the control DF in vitro showed an initial fast (burst) release of 20% of drug content, that was followed by a constant zero order release at a rate of 1.51 mg h^{-1}. The pharmacokinetic curves

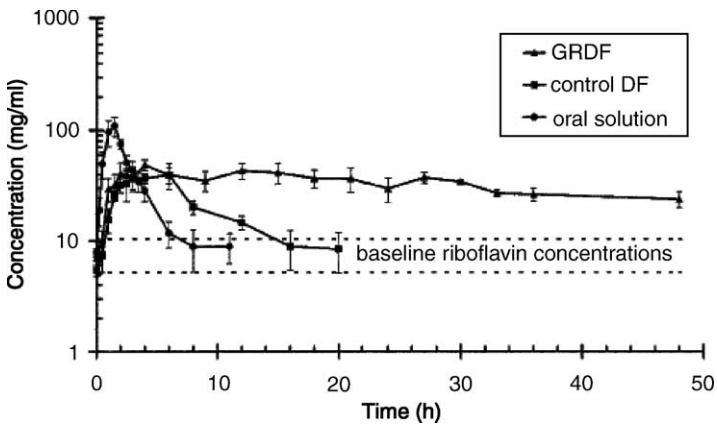

Fig. 6. Mean plasma riboflavin concentrations following administration of 100 mg riboflavin-5-phosphate as the CR-GRDF, CR-DF, or as drug solution to the Beagle dogs ($n = 6$) (taken from reference Klausner et al., 2002).

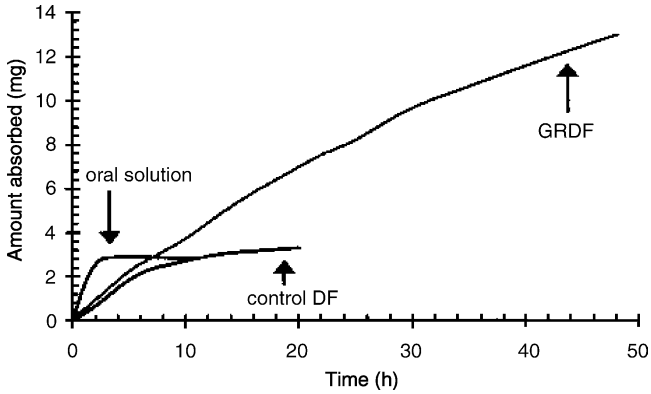

Fig. 7. Mean cumulative amount of riboflavin absorbed following administration of 100 mg riboflavin-5-phosphate as the CR-GRDF, CR-DF, or as drug solution to the Beagle dogs ($n = 6$) (taken from reference Klausner et al., 2002).

following administration of riboflavin by different modes to the Beagle dogs are presented in Fig. 6. As can be seen, CR-GRDF produced elevated riboflavin plasma concentrations for at least 48 h after drug administration, and only short-lasting elevation of riboflavin concentrations was produced by other modes of administration. The absolute bioavailability values were $17.1 \pm 3.5\%$, $3.9 \pm 0.4\%$, and $3.9 \pm 1\%$ for the CR-GRDF, control DF and oral solution, respectively.

The physiology of gastric emptying in presence and absence of CR-GRDF was studied applying small radiopaque markers (BIPS®) that are inert spheres having a density similar to food (Allan et al., 1996). We found that CR-GRDF did not lead to pylorus obstruction and had no major effect on gastric emptying and GRT of the radiopaque markers.

The deconvolution analysis indicated that in vivo absorption from CR-GRDF and the control DF was similar during the first 5 h after the administration (see Fig. 7). Later decrease in riboflavin absorption from the control DF was observed, apparently because of the shorter gastric retention time of the control DF in the stomach. When the control DF leaves the stomach it releases the drug in non-absorbing distal segments of the gastrointestinal tract, and thus less drug is absorbed as reflected by the lower bioavailability. This outcome stresses the importance of CR-GRDF as an optimal delivery system for drugs with a narrow absorption window that could benefit from a prolonged absorption phase.

4. Conclusions

Drugs that possess a narrow absorption window in the upper parts of the gastrointestinal tract are candidates for a GRDF that may provide multiple pharmacokinetic and pharmacodynamic advantages over immediate and controlled release dosage forms. This manuscript summarizes the results of our recent work on in vivo testing of GRDFs in animal models (in rats and in dogs) and in human subjects. The results demonstrate that the pharmacokinetic and pharmacodynamic rationale of GRDFs may be assessed in the rat model where gastric retention is achieved by compounding the drug into tablets of sufficient size to extend their gastric retention. In dogs and humans, prolonged absorption and sustained blood levels of narrow absorption window drugs, such as levodopa and riboflavin, could be achieved by the novel unfolding CR-GRDF that combines large dimensions with rigid structure.

Outcomes of this study demonstrate that due to the complexity of a drug's PK and PD properties, the rationale of the continuous drug administration obtained by CR-GRDF should be assessed and established in vivo. It is expected that an in vivo approach that was applied in our studies to assess the CR-GRDF for metformin, levodopa, and riboflavin could be successfully applied to determine the benefits of CR-GRDFs for other drugs. Relatively large amount of NAW drugs that are currently used clinically may possibly benefit from GRDF, and for some

drugs the treatment schedules could be significantly improved by replacing the parenteral administration with a more convenient oral GRDF. Furthermore, it is expected that in addition to the already marketed drugs, this CR-GRDF approach may be used in the developmental stage for novel drugs characterized by NAW in the upper parts of the gastrointestinal tract.

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