ELSEVIER

European Journal of Pharmaceutical Sciences, 6 (1998) 131–139

EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES

Effect of elevated viscosity in the upper gastrointestinal tract on drug absorption in dogs

C. Reppas[a,*], G. Eleftheriou[a], P. Macheras[a], M. Symillides[a], J.B. Dressman[b]

[a]*Department of Pharmacy, Laboratory of Biopharmaceutics and Pharmacokinetics, University of Athens, Panepistimiopolis, 157 71 Athens, Greece*
[b]*Institut für Pharmazeutische Technologie, JW Goethe Universität, Frankfurt D-60439, Germany*

Received 24 February 1997; accepted 9 July 1997

Abstract

The objectives of these studies were, first, to determine the effect of elevated luminal viscosity on the gastrointestinal absorption of four model drugs and, second, to identify the key processes influencing drug absorption under elevated viscosity conditions. Studies were conducted in vitro and in healthy female mongrel dogs under fasting conditions. In the canine model, both the rate and extent of paracetamol and hydrochlorothiazide absorption were significantly decreased by the coadministration of 15 g guar gum dissolved in 500 ml normal saline. In the case of cimetidine, the rate but not extent of absorption was decreased. Owing to the high variability in the data, no statistically based conclusion could be drawn about the effects of coadministered guar gum on the oral absorption of the poorly soluble mefenamic acid. Based on the in vitro data, it appears that substantial reductions in the dissolution rate of paracetamol, hydrochlorothiazide and cimetidine account for the effects observed in vivo. It is concluded that the effect of an elevation in the intraluminal viscosity on drug absorption is greatest for highly soluble drugs, and results from a combination of a decrease in dissolution rate and gastric emptying rate. © 1998 Elsevier Science B.V.

Keywords: Gastrointestinal drug absorption; Canine model; Viscosity; Dissolution; Binding; Diffusion; Guar gum; Paracetamol; Mefenamic acid; Hydrochlorothiazide; Cimetidine

1. Introduction

The viscosity in the gastrointestinal (GI) tract can be elevated in several ways, including the administration of suspension dosage forms containing viscosity-inducing suspending agents, the ingestion of foodstuffs containing soluble polymers, and the administration of supplementary soluble polymers, usually with the intent to regulate bowel movements or glucose absorption.

Suspending agents are used to improve the homogeneity of suspensions and hence the dosage reproducibility, but in certain cases they alter the absorption of the drug via the associated increase in luminal viscosity. Oral administration of nitrofurantoin in suspensions prepared with 2 or 5% methylcellulose solutions was shown in clinical studies to decrease the rate (Soci and Parrott, 1980) or rate and extent (Seager, 1968) of nitrofurantoin absorption, respectively. In contrast, the absorption of riboflavin and thiamine from solution was not influenced by the presence of 2.5% methylcellulose (Hewitt and Levy, 1971).

Canine studies indicate that typical increases in luminal viscosity after eating ordinary meals are modest, on the order of 100 cP (Greenwood, 1994), and therefore unlikely to affect drug absorption. However, the consumption of water-soluble fibers can result in the elevation of GI viscosity by several orders of magnitude. The extent of the increase depends on the physicochemical properties of the fiber, its concentration in the vehicle, and the total amount administered (Blackburn and Johnson, 1981; Roberts et al., 1990; Reppas et al., 1991). The most frequently used soluble fiber is guar gum which is a naturally occurring polysaccharide (MW 220 000) not absorbed or metabolized in the upper GI tract (Seaman, 1980; The Merck Index, 1989). When administered at a dose of 15 g in a solution containing about 3%, it has been shown to be effective in reducing the postprandial elevation of blood glucose levels in humans (Pilch, 1987). Single-dose studies in healthy subjects have shown that, although guar gum coadministered as a 2.5% aqueous dispersion has no effect on the absorption of glipizide (Huuponen et al., 1985), it

*Corresponding author. Tel.: +30 1 7284367; fax: +30 1 7244191; e-mail: hreppas@atlas.uoa.gr

0928-0987/98/$19.00
PII S0928-0987(97)00077-8

decreases the rate of absorption of digoxin by approximately 16% and both the maximum plasma concentration, C_{max}, and the area under the plasma concentration versus time curve (from time zero to last quantifiable concentration), AUC_{0-t}, of potassium phenoxymethylpenicillin by 25 and 28%, respectively (Huuponen et al., 1984). It is not clear whether in those studies a suspension or a solution of guar gum was coadministered with the drugs. The low hydration rate of guar may lead to low intraluminal viscosity if it is administered as a suspension (Wolever et al., 1979). In further studies, in which the fiber and the drug were both dissolved in 400 ml orange juice, a 36% reduction of the maximum plasma concentration of paracetamol was observed when 4% guar gum and 2.5% pectin had been added in the solution (Holt et al., 1979). This decrease correlated well with the decrease in gastric emptying rate (Holt et al., 1979).

Suspending agents are usually administered in relatively small amounts and are likely to exert their primary effect through a decrease in the drug's dissolution rate. By contrast, the doses of water-soluble fibers are much higher, creating large changes in the bulk luminal viscosity and thereby reducing fluid convection in the gut lumen. For example, the reduction of glucose absorption (55% for C_{max} and 37% for AUC_{0-t}), after administration of 250 ml solution of diluted diabetic squash (50 g glucose) containing 5.8% guar gum, was shown to be mediated via both a damping of the influence of motility on fluid convection in the intestine and a reduction in the gastric emptying rate (Blackburn et al., 1984a,b).

It is apparent from the existing literature that the effect of viscosity on drug absorption varies with the drug, the type and amount of viscosity-inducing agent coadministered and whether the drug and viscosity-inducing agent are already dissolved or not. The objectives of the present studies were two-fold. The first was to compare the effect of increased luminal viscosity on the oral absorption of drugs with various solubility and permeability characteristics, namely paracetamol, mefenamic acid, hydrochlorothiazide, and cimetidine, in a canine model. The second was to determine which processes are important limiting factors to the rate and extent of drug absorption under elevated luminal viscosity conditions. The luminal viscosity was elevated with guar gum using amounts and concentrations similar to those frequently used for controlling carbohydrate and/or lipid metabolism (Pilch, 1987).

2. Experimental procedures

2.1. Materials

Guar gum and cimetidine were purchased from Sigma-Aldrich GmbH (Deisendorf, Germany). Paracetamol was donated by Uni-Pharma S.A. (Athens, Greece), hydrochlorothiazide by Adelco (Athens, Greece) and mefenamic acid from Wyeth (Athens, Greece).

2.2. Guar solutions

To prepare solutions of guar gum, the appropriate amount was slowly added to normal saline under rigorous agitation conditions at room temperature. The resulting suspension was sealed and allowed to fully hydrate over a 24-h period. Solutions so prepared were stored in the refrigerator for up to 1 week. Since guar is a naturally occurring gum, batch to batch variability in its rheological characteristics is to be expected (Seaman, 1980). Viscosity measurements were carried out at 37°C with a Contraves Rheomat 135-S rotational viscometer (Cincinnati, OH, USA) using the DIN 125 measuring system. Guar is known to exhibit pseudoplastic flow (Seaman, 1980); i.e., the viscosity decreases dramatically as the shear rate increases. Therefore, viscosity measurements were performed at three different shear rates (1, 100, and 1000 s^{-1}). The viscosity characteristics of the guar solutions used in the current study are presented in Table 1.

2.3. In vivo studies

Absorption of the four drugs was studied in four female mongrel dogs, ranging in weight from 20 to 27 kg and in age from 2 to 4 years. A randomized crossover study design was implemented. On each occasion, the appropriate dose was administered in the form of one or two soft gelatin capsules along with 500 ml saline containing guar (Test Solution) or not containing guar (Control Solution). In all cases, the solution was warmed to 37°C for 1 h in an incubator prior to administration. This period was sufficient for increasing the temperature of the administered solution up to physiological values without affecting its rheological properties. The four drug studies were separated by approximately 1 month, and within each drug

Table 1
Mean(SD) viscosities[a] (cP) of the isoosmotic (with 0.9% NaCl) guar gum solutions used in the present study

Concentration (%)	Shear rate (s^{-1})		
	1	100	1000
2 ($n=4$)	4.25×10^4 (0.82×10^4)	1.29×10^3 (0.13×10^3)	163 (26)
3 ($n=3$)	1.37×10^5 (0.23×10^5)	2.29×10^3 (0.90×10^3)	258 (78)

[a]At 37°C.

study the washout period between phases was at least 2 weeks for each dog.

2.3.1. Study protocol

Dogs were fasted for 16 h from food but not water before each phase. On the study morning the dog was transferred to the treatment room, placed in a harness and administered the drug and solution via an orogastric tube. Blood samples were drawn by means of an indwelling catheter positioned in a suitable foreleg vein. Twenty-four-hour samples were collected by individual venipuncture. After centrifugation, serum was stored at −40°C for not more than 3 days prior to sample analysis. Five hours after drug administration the dog was offered a standard meal (100 g pellets and 200 ml tap water), which was consumed in all cases. Twelve hours after dosing the catheter was removed and the dog returned to her cage, where she was allowed to eat and drink ad libitum. This protocol was approved by the Committee for Research of the University of Athens for all four drugs studied.

2.3.2. Paracetamol study

Two capsules, each containing 250 mg paracetamol were administered with 500 ml normal saline which contained either 3% guar (Test Solution A) or no guar (Control Solution). In each phase, 5-ml blood samples were drawn at 0.0, 0.50, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 h following paracetamol administration. Paracetamol assay in serum was performed with an HPLC method using 2-acetamidophenol (Sigma-Aldrich Chemie, Deisendorf, Germany) as internal standard (Ameer et al., 1981). The accuracy of this analytical procedure ranged from −7.4 to 5.0% and the precision was estimated to be ≤8.1% over the concentration range 0.50–10 μg/ml.

2.3.3. Mefenamic acid study

This study was conducted in three phases. In the first phase, one capsule containing 250 mg of mefenamic acid was administered with 500 ml normal saline (Control Solution). In the second phase, one capsule containing 250 mg of mefenamic acid was administered with 500 ml normal saline in which 3% guar had been dissolved (Test Solution A). In the third phase, one commercially available Ponstan® capsule (Parke Davis, Cambridge, England, Lot≠4D407) containing 250 mg mefenamic acid was administered with 500 ml normal saline (Control Solution). In each phase, 5-ml blood samples were drawn at 0, 0.50, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10, 12 and 24 h following drug administration. Mefenamic acid assay in serum was performed with an HPLC method using flurbiprofen (Vianex S.A., Athens, Greece) as internal standard (Imai et al., 1991). The accuracy of this analytical procedure ranged from −2.5 to 4.5% and the precision was estimated to be ≤7.9% over the concentration range 0.40–3.6 μg/ml.

2.3.4. Hydrochlorothiazide study

In one phase of this study, one capsule containing 50 mg of hydrochlorothiazide was administered with Test Solution A, while in the other phase it was administered with the Control Solution. Five-ml blood samples were withdrawn at 0, 0.50, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 12 and 24 h following drug administration. Hydrochlorothiazide assay in serum consisted of a modification of the HPLC method of Barbahaiya et al. (1981), using chlorothiazide (Adelco S.A., Athens, Greece) as internal standard. The accuracy of this analytical procedure ranged from −9.2 to 5.2% and the precision was estimated to be ≤9.3% over the concentration range 0.04–0.50 μg/ml.

2.3.5. Cimetidine study

This study was conducted in three phases: one capsule containing 300 mg cimetidine was administered with Test Solution A (3% guar in 500 ml normal saline), Test Solution B (2% guar in 500 ml normal saline) or Control Solution. Five-ml blood samples were drawn at 0, 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0 and 12.0 h following drug administration. Cimetidine assay in serum was performed with an HPLC assay (Mummaneni et al., 1995) using codeine phosphate (Elvipy S.A., Athens, Greece) as internal standard. The accuracy of this analytical procedure ranged from −4.0 to 1.0% and the precision was estimated to be ≤9.7% over the concentration range 0.25–6.5 μg/ml.

2.3.6. Data analysis

The maximum serum concentration, C_{max}, and the time that this occurred, T_{max}, were directly obtained from the concentration versus time plots. The area under the concentration versus time plots up to the last quantifiable concentration, AUC_{0-t}, was calculated with the linear trapezoidal rule. Values of the elimination rate constants, k_{el}, were calculated by linearization of the elimination phase of the control studies using the last two to five quantifiable concentrations. For mefenamic acid, estimations of k_{el} were made from the post-absorptive concentration data obtained after the administration of the Ponstan® capsules. Differences in C_{max} and AUC_{0-t} values among phases were statistically assessed at the 0.05 level by two-factor analysis of variance, with dogs and dosing conditions as the factors (SuperAnova®, Abacus Concepts, Inc., Berkeley, CA, USA). T_{max} values were compared with the Friedman test (Statview® Abacus Concepts, Berkeley, CA, USA).

2.4. In vitro studies

2.4.1. Particle size measurements

The particle size of the four drug powders used in the in vivo studies was analyzed with a Coulter® counter (Model D Industrial, Luton, England), fitted with a 140-μm

aperture tube. Stock suspensions contained 1 mg drug/ml medium, using 4% sodium chloride as a saturated medium in the case of paracetamol and cimetidine and 0.1 N hydrochloric acid as the saturated medium in the case of hydrochlorothiazide and mefenamic acid.

2.4.2. Diffusion studies

The effect of guar on the diffusivity of the four drugs was evaluated with the Franz cell (Franz, 1975). The two compartments were separated with a dialysis membrane (Visking, dialysis tubing, Serva Feinbiochemica, exclusion limit 8000–15 000 Da). The donor compartment solution consisted of drug and normal saline containing 3% guar or no guar, while the receptor compartment solution was composed of normal saline. The initial concentration of drug in the donor compartment was 1.00 mg/ml (paracetamol), 100 μg/ml (hydrochlorothiazide) and 600 μg/ml (cimetidine). These concentrations correspond to the 'dose:normal saline volume' ratios used in the in vivo studies. The receiving compartment was held at 37°C and stirred magnetically to ensure homogeneity. The concentration of drug in the receptor compartment was followed by UV spectroscopy in the case of paracetamol (λ_{max}=250 nm) and by HPLC for hydrochlorothiazide (Barbahaiya et al., 1981) and cimetidine (Mummaneni et al., 1995). Due to its low aqueous solubility (4.60 μg/ml in normal saline at 20°C, n=3), the preparation of a mefenamic acid solution in normal saline corresponding to the dose:normal saline volume ratio used in the in vivo studies was not possible. Instead, solutions containing 3.00 μg/ml mefenamic acid were used for the diffusion studies. The concentration of mefenamic acid in the receptor compartment was followed by HPLC (Imai et al., 1991).

For each drug, 200- or 400-μl samples were drawn from the receptor compartment with a microsyringe after 0, 0.25, 0.50, 1.0, 1.5 and 2.0 h. An equivalent volume of saline was added to the receptor compartment after each sampling time to restore the compartment volume of 15 ml. At the end of the experiment, corrections for the dilution of the receptor solution resulting from the successive samplings were made (Aronson, 1993). Experiments were run in triplicate. The initial diffusion rates were estimated from the slopes of the plots of concentration in the receptor compartment versus time, using only data obtained under sink (<20% equilibrium concentration) conditions. Confirmation that the three repetitions resulted in regression lines with consistent slope and intercept was made with one-factor analysis of covariance (ANCOVA) at the 0.05 level (SuperAnova®, Abacus Concepts, Berkeley, CA, USA). All data from the three repetitions were then pooled to estimate the initial diffusion rate under a given experimental condition. Initial diffusion rates were estimated with the slope of the regression line ($0.97 \leq r \leq 0.993$) of concentration versus time data, $(\text{slope})_{diff}$. The apparent first-order diffusion rate constant, k_{diff}, was estimated using the following equation:

$$(\text{slope})_{diff} = k_{diff} C_{eq}$$

where C_{eq} is the drug concentration at equilibrium. Comparisons of the diffusion rate constants were made with *t*-test (Glantz, 1981).

2.4.3. Binding studies

The ability of guar gum to interact with the drugs was assessed with a Dianorm® equilibrium dialyser with Teflon dialysis cells (type macro 2, Diachema AG Rushlikon, Zurich, Switzerland). The dialysis membranes (Diachema, type 10–14) had a declared molecular weight cutoff of 5000 Da. In each case, 3.5 ml drug solution in normal saline were dialyzed against 3.5 ml of 3% guar solution (Test Solution A) containing equivalent drug concentration. The initial concentrations (μg/ml) in both compartments ranged between 200 and 1.00×10^3 for paracetamol, 0.600 and 3.00 for mefenamic acid, 20.0 and 100 for hydrochlorothiazide, and 120 and 600 for cimetidine. Experiments were carried out in triplicate at 37°C. Concentrations in both compartments were measured after equilibration using the procedures described for the diffusion studies.

2.4.4. Dissolution studies

Dissolution rates were measured in rotating disk apparatus (Levich, 1962). The dissolution media were normal saline (Control Solution) and 2% guar in normal saline (Test Solution B). A 2% solution (instead of 3%) was used because earlier studies using a porcine model (Roberts et al., 1990) had shown that a 2% guar solution in normal saline has a viscosity approximately similar to a viscosity of 3% guar solution after its passage through the upper gastrointestinal tract. The rotating disk apparatus consisted of a water-jacketed beaker maintained at 37°C with a circulating water bath (Edmund Bühler, Tübingen, Germany) and a stainless-steel Wood's die supported by a stainless steel holder with a shaft attached to an overhead synchronous motor with continuously variable rotational speed (Hanson Res. Corp., Chatsworth, CA, USA). One-cm diameter disks of pure drug were compressed in a Perkin-Elmer press at 2000 psi for 1 min. The stainless steel die supporting the drug disk was immersed in 200 ml of dissolution medium prewarmed in the jacketed beaker. Sample collection and analysis was performed using the same procedure as for the diffusion experiments. In cases where guar was present in the medium, it was precipitated prior to analysis using the method described by Sirois et al. (1990). Each drug was studied at rotational speeds of 50, 100 and 150 rpm (n=2 per rotational speed), over the period in which the concentration in the medium stayed below 10% of the solubility. In all cases, the plots of concentration in the dissolution medium versus time were linear, with nonsignificant intercepts ($p>0.08$) and significant slopes ($p<0.0005$). The initial dissolution rates were estimated from the slopes of the plots, and their concurr-

ence for each drug/rpm/medium combination checked with a *t*-test (Glantz, 1981). All data from each set were subsequently pooled to estimate the initial dissolution rate under a given experimental condition. Initial dissolution rates were estimated with the slope of the regression line ($0.97 \leq r \leq 0.9996$) of concentration versus time data, $(\text{slope})_{\text{diss}}$. For each rotational speed, the apparent first-order dissolution rate constant, k_{diss}, was estimated using the following equation:

$$(\text{slope})_{\text{diss}} = k_{\text{diss}} C_s$$

where C_s is the saturation solubility. Comparisons of the dissolution rate constants were made with *t*-test at the 0.05 level (Glantz, 1981).

3. Results

3.1. In vivo studies

The average serum concentration versus time profiles for each drug are shown in Fig. 1, and the corresponding pharmacokinetic parameters are presented in Table 2.

3.1.1. Paracetamol study

The estimated average elimination rate constant was $1.12 \pm 0.18\ h^{-1}$, in accordance with previously published canine data ($1.2\ h^{-1}$, Souchay et al., 1976). Coadministration of 3% guar in 500 ml normal saline with the paracetamol dose resulted in a 65% reduction in the $C_{\max}$ and a 28% reduction in the AUC_{0-t}, but had no significant effect on the $T_{\max}$.

3.1.2. Mefenamic acid study

Following administration of the commercial capsule, the serum concentrations decreased continuously after $T_{\max}$ in only two of four dogs, in the other two the concentration lingered around 0.8 μg/ml. Thus, only two elimination rate constants could be calculated (0.12 and $0.09\ h^{-1}$). These values are lower than the value ($0.15\ h^{-1}$) calculated from previously reported data in dogs (Imai et al., 1991). $C_{\max}$ and AUC_{0-t} values in the mefenamic acid study exhibited large coefficient of variations and although average $C_{\max}$ and AUC_{0-t} values were lower when the prototype capsules were coadministered with the guar than with the Control Solution, significance at the 0.05 level was not achieved. No trends were observed in the $T_{\max}$ values. The prototype capsules appeared to have similar bioavailability characteristics as the commercially available product in terms of $C_{\max}$ and AUC_{0-t}, although $T_{\max}$ values varied considerably.

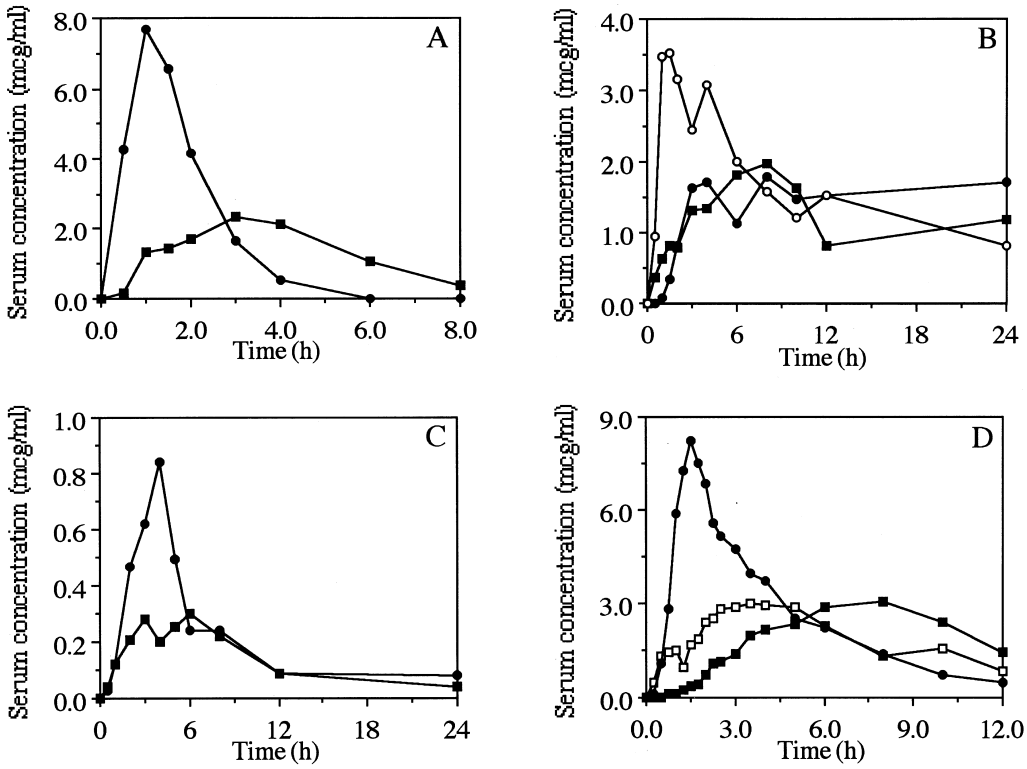

Fig. 1. Average serum concentration versus time plots following the administration of (A) 500 mg paracetamol, (B) 250 mg mefenamic acid, (C) 50 mg hydrochlorothiazide, and (D) 300 mg cimetidine, to four dogs. Key: (●) prototype capsule(s) with Control Solution; (○) commercially available formulation with Control Solution; (■) prototype capsule(s) with Test Solution A; (□) prototype capsule with Test Solution B.

Table 2
Pharmacokinetic parameters for paracetamol, mefenamic acid, hydrochlorothiazide, and cimetidine following single-dose administration of prototype hard gelatin capsule(s) with 500 ml normal saline (containing or not containing guar gum) to four dogs[a]

Drug/guar gum concentration	AUC_{0-t} (μg/ml/h)	C_{max} (μg/ml)	T_{max} (h)
Paracetamol			
No guar	15.1 (7.4)	8.1 (2.6)	1.2 [1.0–1.5]
3%	10.8 (5.8)*	2.8 (1.8)*	2.2 [1.0–6.0]
Mefenamic acid			
No guar	35 (15)	3.5 (0.71)	6.0 [3.0–10]
No guar[b]	39 (24)	4.4 (2.5)	1.2 [1.0–2.0]
3%	28.6 (6.5)	2.86 (0.62)	8.0 [3.0–24]
Hydrochlorothiazide			
No guar	4.84 (0.74)	0.90 (0.11)	4.0 [4.0–5.0]
3%	3.14 (0.92)*	0.37 (0.11)*	4.0 [2.0–8.0]
Cimetidine			
No guar	30.9 (5.1)	9.9 (2.8)	1.4 [1.0–2.2]
2%	22.6 (1.9)	3.8 (1.0)*	3.2 [0.7–5.0]
3%	23.5 (2.3)	3.8 (1.3)*	7.0 [4.0–8.0]

[a]Values are mean(SD) for AUC_{0-t} and C_{max} and median[range] for T_{max}. Asterisks denote significant differences from normal saline at the 0.05 level.
[b]Ponstan® capsules were administered in this phase.

3.1.3. Hydrochlorothiazide study

The elimination rate constant was estimated at 0.058 ± 0.032 h^{-1}. No bibliographic data were found for the elimination constant of this compound in dogs. Coadministration of a 3% guar solution in 500 ml normal saline reduced the C_{max} by 59% and AUC_{0-t} by 35% in comparison with coadministration of the control solution. Differences in T_{max} values did not, however, reach significance.

3.1.4. Cimetidine study

The elimination rate constant of cimetidine in the four dogs averaged 0.26 ± 0.06 h^{-1}, somewhat lower than the value (0.39 ± 0.06 h^{-1}) observed in male dogs by Mummaneni et al. (1995). Although coadministration of 2 or 3% guar decreased the C_{max} value by 62%, differences in AUC_{0-t} and T_{max} did not reach significance at the 0.05 level.

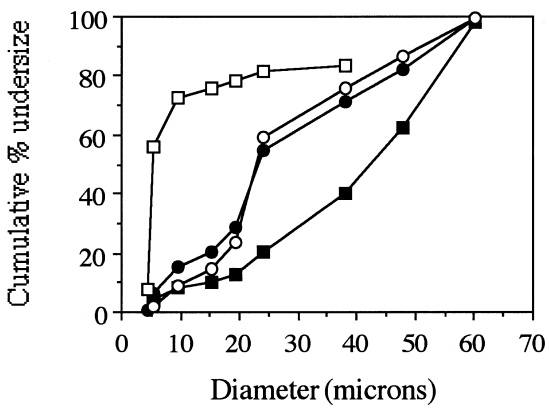

Fig. 2. The cumulative percent undersize distribution for paracetamol powder (○), mefenamic acid powder (□), hydrochlorothiazide powder (■), and cimetidine powder (●), in the prototype capsule(s) used for the in vivo experiments.

3.2. In vitro studies

3.2.1. Particle size measurements

Fig. 2 shows the cumulative percent undersize distribution of the four drug powders used to prepare the dosage forms for the canine studies. The average particle diameter lay below 100 μm for all samples, and in the case of mefenamic acid the powder was essentially micronized, with an average particle diameter of less than 10 μm.

3.2.2. Diffusion studies

The apparent diffusion rate constant of the four drugs in the absence and presence of guar are presented in Table 3. The presence of guar resulted in a reduction of the diffusion rate constant by 35% for paracetamol, 44% for mefenamic acid and 33% for cimetidine, whereas no significant reduction in the diffusion rate constant was observed for hydrochlorothiazide.

3.2.3. Binding studies

The binding data indicated that none of the drugs interact to an appreciable extent with guar. For every drug at all concentrations tested, the concentration of free drug remained within assay error of the original concentration.

Table 3
Apparent first-order diffusion rate constant (h^{-1}) for paracetamol, mefenamic acid, hydrochlorothiazide, and cimetidine determined with the Franz cell in the absence and in the presence of guar gum in the donor compartment[a]

	Solution of the donor compartment	
	Normal saline	3% guar gum in normal saline
Paracetamol	0.188 (0.027)	0.1212 (0.0051)*
Mefenamic acid	0.250 (0.016)	0.140 (0.010)*
Hydrochlorothiazide	0.153 (0.018)	0.120 (0.015)
Cimetidine	0.1265 (0.0070)	0.0852 (0.0060)*

[a]Standard error of estimation in the parentheses. Asterisks denote statistically significant differences from the control at the 0.05 level.

Table 4
Apparent first-order dissolution rate constants (h^{-1}) for paracetamol, mefenamic acid hydrochlorothiazide, and cimetidine determined with the rotating disk apparatus (37°C, at 150 rpm) in normal saline which contained or did not contain guar gum[a]

	Dissolution medium	
	Normal saline	2% guar gum in normal saline
Paracetamol	0.02494 (0.00039)	0.00316 (0.00008)*
Mefenamic acid	0.01482 (0.00057)	0.00711 (0.00020)*
Hydrochlorothiazide	0.0341 (0.0030)	0.01083 (0.00093)*
Cimetidine	0.02253 (0.00020)	0.00621 (0.00012)*

[a]Standard error of estimation in the parentheses. Asterisks denote statistically significant differences from the control at the 0.05 level.

3.2.4. Dissolution studies

For all dissolutions in the Control Solution the Levich plot (initial dissolution rate as a function of the square root of the rotational speed) was linear ($0.98<r<0.9997$) with a slope significantly different from zero ($p<0.04$) but an intercept not significantly different from zero ($p>0.08$). This analysis indicated that dissolution in Control Solution occurs by convective diffusion (Levich, 1962). The Levich model could not be applied to the data obtained in viscous solution owing to the low Reynold's number (<1) (Levich, 1962; Grijseels et al., 1981). The apparent first-order dissolution rate constants at 150 rpm in absence and presence of guar are presented in Table 4. The reduction in dissolution rate constant resulting from the addition of guar to the medium was more than seven-fold for paracetamol, more than three-fold for hydrochlorothiazide and cimetidine, and about two-fold for mefenamic acid. Similar reductions were observed at lower rotational speeds (data not presented). The decreases in the dissolution rate observed with guar are in accordance with previous studies of drug dissolution in viscous media (Braun and Parrott, 1972; Sarisuta and Parrott, 1982).

4. Discussion

The four drugs chosen for study do not encounter significant stability problems in the upper GI environment, and were chosen on the basis of their wide range of solubilities under gastrointestinal conditions and permeability through the intestinal wall. According to the recently proposed Biopharmaceutics Drug Classification (Amidon et al., 1995), paracetamol would be classified as a Case I drug due to its high solubility and favorable permeability characteristics (Sietsema, 1989; Etman and Naggar, 1990). Mefenamic acid is a poorly soluble compound (TenHoor et al., 1991) with a lipophilicity that is commensurate with facile flux across the lipid bilayer, thus fitting Case II requirements. Hydrochlorothiazide and cimetidine can both be classified as Case III drugs since, even though both have good aqueous solubility, they are absorbed only to an extent of 60–80% (Sietsema, 1989). One difference between hydrochlorothiazide and cimetidine is that cimetidine (Taylor et al., 1978; Brunton, 1990) but not hydrochlorothiazide (Welling, 1986) undergoes first-pass metabolism; these characteristics suggest that the permeability of hydrochlorothiazide is somewhat lower than the permeability of cimetidine.

For the three high-solubility drugs, the C_{max} was reduced by the coadministration of guar. These drugs all exhibited a reduction in dissolution rate of more than three-fold in the in vitro experiments. The slower rate of dissolution would naturally lead to lower concentrations in solution at the absorptive sites and consequently a reduction in the absorption rate of the drug. In the case of paracetamol and hydrochlorothiazide, the extent of absorption was also reduced in presence of guar. These results suggest that the principal sites of absorption for these two drugs are found in the proximal part of the intestine. An alternative hypothesis, namely, that the drugs became bound to the guar and were therefore not available for absorption, could be ruled out on the basis of the in vitro binding data. In contrast, the extent of absorption of cimetidine was not affected. Previous studies (Kaneniwa et al., 1986; Mummaneni and Dressman, 1994) in rats have shown that cimetidine is almost equally permeable in the ileum as in the duodenum, with the jejunum exhibiting a somewhat lower permeability to this drug.

In contrast to the results obtained with the highly soluble drugs, the coadministration of guar did not result in significant reductions in the C_{max} or AUC_{0-t} values for mefenamic acid. There are several factors that may combine to explain these results. First, the reduction in dissolution rate was not as dramatic for mefenamic acid as for the more soluble compounds, even though the reduction in the molecular diffusivity was greater. Second, there was great interdog variability in the serum profiles. With such high coefficients of variation (more than 50% in some parameters), studies in only four dogs have insufficient statistical power to detect all but the coarsest effects.

In the case of paracetamol and cimetidine, the times to peak tended to be longer when guar was coadministered, although these effects did not reach statistical significance. The rate of absorption of both drugs has been shown to be greatly influenced by gastric emptying (Clements et al., 1978; Oberle and Amidon, 1987). Increasing the intragastric viscosity has a profound effect on the gastric emptying rate in fasted dogs (Russell and Bass, 1985; Reppas et al.,

1991). Thus, it is not surprising that the coadministration of a viscous solution would prolong the gastric emptying time and, therefore, the time to peak. Hydrochlorothiazide, with its long time to peak even in the absence of guar, would be less susceptible to gastric emptying-related effects on absorption. In the case of mefenamic acid the data is so variable even in the absence of guar (compare times to peak for prototype and commercially available product in Table 2) that any effects on T_{max} would be completely masked. Moreover, the absorption rate of mefenamic acid is more likely to be affected by changes in its dissolution rate than by changes in gastric emptying rate.

The results of the present study indicate that the absorption rate of highly soluble drugs, stable during upper GI residence, may be reduced by the coadministration of guar solutions, and potentially by other water-soluble fibers. In certain cases, the extent of absorption also appears to be compromised. Extrapolation of these results to humans should be made only in light of the quantitative differences in GI physiology between the two species. For example, the decrease in gastric emptying rate that can be induced by administration of water-soluble fibers in humans (Dressman et al., unpublished data) appears to be not as pronounced as that observed in dogs (Reppas et al., 1992). Holt et al. (1979) studied paracetamol absorption in humans after administration in orange juice 400 ml with or without guar and pectin. A reduction in the rate, but not extent of absorption was observed. A potential explanation for the modest differences in their results compared to the large reduction in rate plus reduction in AUC_{0-t} in our study may lay in the caloric content of the vehicle. Due to feedback inhibition, calorie-containing fluids are emptied from the stomach at much lower rates than calorie-free liquids (Hunt and Stubbs, 1975). Thus, in the presence of calorie-containing fluids, viscosity-inducing agents can exert little further effect on the gastric emptying rate (Reppas et al., 1992). Other quantitative differences between the two species include the shorter small intestine transit time in dogs (especially important for slow dissolving drugs) and permeability of the mucosa to various drugs (Dressman and Yamada, 1991).

In conclusion, studies with four model drugs indicated that an elevation of the viscosity of the contents in the upper gastrointestinal tract can reduce drug absorption. The effect appears to be greater for highly soluble drugs, and results from a combination of a decrease in dissolution rate and gastric emptying rate.

Acknowledgements

Partial support of this research by the Greek State Scholarships Foundation, Athens, Greece, and the Dow Chemical Co., Midland, USA, is greatly appreciated.

References

Ameer, B., Greenblatt, D.J., Divol, M.R., Abernethy, D.R., Shargel, L., 1981. High performance liquid chromatography determination of acetaminophen in plasma: single dose pharmacokinetic studies. J. Chromatogr. 226, 224–230.

Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res. 12, 413–420.

Aronson, H., 1993. Correction factor for dissolution profile calculations. J. Pharm. Sci. (Letter) 82, 1190.

Barbahaiya, R.H., Phillips, T.A., Welling, P.G., 1981. High performance liquid chromatographic determination of chlorothiazide and hydrochlorothiazide in plasma and urine: preliminary results of clinical studies. J. Pharm. Sci. 70, 291–295.

Blackburn, N.A., Johnson, I.T., 1981. The effect of guar gum on the viscosity of the gastrointestinal contents and on glucose uptake from the perfused jejunum in the rat. Br. J. Nutr. 46, 239–246.

Blackburn, N.A., Redfern, J.S., Jarjis, H., Holgate, A.M., Hanning, I., Scarpello, J.H.B., Johnson, I.T., Read, N.W., 1984. The mechanism of action of guar gum in improving glucose tolerance in man. Clin. Sci. 66, 329–336.

Blackburn, N.A., Holgate, A.M., Read, N.W., 1984. Does guar gum improve post-prandial hyperglycemia in humans by reducing small intestinal contact area?. Br. J. Nutr. 52, 197–204.

Braun, R.J., Parrott, E.L., 1972. Influence of viscosity and solubilization on dissolution rate. J. Pharm. Sci. 61, 175–178.

Brunton, L.L., 1990. Agents for control of gastric acidity and treatment of peptic ulcers. In: Gilman, A.G., Rall, T.W., Nies, A.S., Taylor, P. (Eds.), Goodman and Gilman's, The Pharmacological Basis of Therapeutics, Ch. 37. Pergamon Press, Inc., New York.

Clements, J.A., Heading, R.C., Nimmo, W.S., Prescott, L.F., 1978. Kinetics of acetaminophen absorption and gastric emptying in man. Clin. Pharmacol. Ther. 24, 420–431.

Dressman, J.B., Yamada, K., 1991. Animal models for oral drug absorption. In: Welling, P.G., Tse F.L.S., Dighe, S. (Eds.), Pharmaceutical Bioequivalence. Marcel Dekker, Inc., New York.

Etman, M.A., Naggar, V.F., 1990. Thermodynamics of paracetamol solubility in sugar-water cosolvent systems. Int. J. Pharm. 58, 177–184.

Franz, T.J., 1975. Percutaneous absorption. On the relevance of in vitro data. J. Invest. Dermatol. 64, 190–195.

Glantz, S.A., 1981. Primer of Biostatistics. McGraw-Hill Book Company, NY.

Greenwood, D.E., 1994. Small Intestinal pH and Buffer Capacity: Implications for Dissolution of Ionizable Compounds. Ph.D. Thesis, The University of Michigan, College of Pharmacy, Ann Arbor, Michigan.

Grijseels, H., Crommelin, D.J.A., de Blaey, C.J., 1981. Hydrodynamic approach to dissolution rate. Pharm. Weekbl. (Sci. Ed.) 3, 1005–1020.

Hewitt, R.R., Levy, G., 1971. Effect of viscosity on thiamine and riboflavin absorption in man. J. Pharm. Sci. 60, 784–786.

Holt, S., Heading, R.C., Carter, D.C., Prescott, L.F., Tothill, P., 1979. Effect of gel fibre on gastric emptying and absorption of glucose and paracetamol. Lancet 24 March, 636–639.

Hunt, J.N., Stubbs, D.F., 1975. The volume and energy content of meals as determinants of gastric emptying. J. Physiol. 245, 209–225.

Huuponen, R., Seppala, P., Iisalo, E., 1984. Effect of guar gum, a fibre preparation on digoxin and penicillin absorption in man. Eur. J. Clin. Pharmacol. 26, 279–281.

Huuponen, R., Karhuvaara, S., Seppala, P., 1985. Effect of guar gum on glipizide absorption in man. Eur J. Clin. Pharmacol. 28, 717–719.

Imai, T., Nohdomi, K., Acarturk, F., Otagiri, M., 1991. Enhancement of dissolution and absorption of mefenamic acid by egg albumin. J. Pharm. Sci. 80, 484–487.

Kaneniwa, N., Funaki, T., Furuta, S., Watari, N., 1986. Study of the absorption site of cimetidine. J. Pharmacobio-Dyn. 9, 321–326.

Levich, V.G., 1962. Physicochemical Hydrodynamics. Prentice Hall, Englewood Cliffs, NJ, pp. 60–72.

Mummaneni, V., Dressman, J.B., 1994. Intestinal uptake of cimetidine and ranitidine in rats. Pharm. Res. 11, 1599–1604.

Mummaneni, V., Amidon, G.L., Dressman, J.B., 1995. Gastric pH influences the appearance of double peaks in the plasma concentration-time profiles of cimetidine after oral administration in dogs. Pharm. Res. 12, 780–786.

Oberle, R.L., Amidon, G.L., 1987. Influence of variable gastric emptying and intestinal transit rates on the plasma level curve of cimetidine; an explanation of the double peak phenomenon. J. Pharmacokinet. Biopharm. 15, 529–544.

Pilch, S.M. (Ed.), 1987. Physiological effects and health consequences of dietary fiber. Life Sciences Research Office, FASEB, Bethesda, MD, USA.

Reppas, C., Meyer, J.H., Sirois, P., Dressman, J.B., 1991. Effect of hydroxypropylmethylcellulose on gastrointestinal transit and luminal viscosity in dogs. Gastroenterology 100, 1217–1223.

Reppas, C., Greenwood, D.E., Dermentzoglou, L.C., Meyer, T.H., Dressman, J.B., 1992. Effect of hydroxypropylmethylcellulose on hydrodynamics of nutrient solutions in the canine gastrointestinal tract (1st European Gastroenterology Week Athens, Greece). Hellen. J. Gastroenterol. 5, S–296.

Roberts, F.G., Smith, H.A., Low, A.G., Ellis, P.R., Morris, E.R., Sambrook, I.E., 1990. Influence of guar gum flour of different molecular weights on viscosity of jejunal digesta in the pig. Proc. Nutr. Soc. 49, 53A.

Russell, J., Bass, P., 1985. Canine gastric emptying of fiber meals: Influence of meal viscosity and antroduodenal motility. Am. J. Physiol. 249, G662–G667.

Sarisuta, N., Parrott, E.L., 1982. Relationship of dissolution rate to viscosity of polymeric solutions. J. Pharm. Sci. 71, 1375–1380.

Seager, H., 1968. The effect of methylcellulose on the absorption of nitrofurantoin from the gastrointestinal tract. J. Pharm. Pharmacol. 20, 968–969.

Seaman, J.K., 1980. Guar Gum. In: Davidson, R.L. (Editor-in-Chief), Handbook of Water-Soluble Gums and Resins, Ch. 6. McGraw-Hill Book Co., NY, USA.

Sietsema, W.K., 1989. The absolute oral bioavailability of selected drugs. Int. J. Clin. Pharm. Ther. Toxicol. 27, 179–211.

Sirois, P.J., Amidon, G.L., Meyer, J.H., Doty, J., Dressman, J.B., 1990. Gastric emptying of nondigestible solids in dogs: A hydrodynamic correlation. Am. J. Physiol. 258, G65–G72.

Soci, M.M., Parrott, E.L., 1980. Influence of viscosity on absorption from nitrofurantoin suspensions. J. Pharm. Sci. 69, 403–406.

Souchay, S., Worner, A., Kampffmeyer, H.G., Selbmann, H.K., 1976. Comparison of the pharmacokinetics of phenacetin in beagles after oral and intravenous administration. Eur. J. Drug Metab. Pharm. 1, 21–24.

Taylor, D.C., Cresswell, P.R., Bartlett, D.C., 1978. The metabolism and elimination of cimetidine, a histamine H_2-receptor antagonist, in the rat, dog, and man. Drug. Metab. Dispos. 6, 21–30.

TenHoor, C.N., Bakatselou, V., Dressman, J., 1991. Solubility of mefenamic acid under simulated fed- and fasted state conditions. Pharm. Res. 8, 1203–1205.

The Merck Index, 1989. Monograph #4486, 11th ed. Merck & Co., Inc., Rahway, NJ, USA.

Welling, P.G., 1986. Pharmacokinetics of the thiazide diuretics. Biopharm. Drug Dispos. 7, 501–535.

Wolever, T.M.S., Jenkins, D.J.A., Nineham, R., Alberti, K.G.M.M., 1979. Guar gum and reduction of postprandial glycemia: Effect of incorporation into solid food, liquid food, and both. Br J. Nutr. 41, 505–510.