BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. **19**: 523–530 (1998)

The Effect of HPMC—a Cholesterol-Lowering Agent—on Oral Drug Absorption in Dogs

C. Reppas[a,*], G. Eleftheriou[a,1], P. Macheras[a], M. Symillides[a], D. Greenwood[b,2] and J.B. Dressman[c]
[a] *Laboratory of Biopharmaceutics and Pharmacokinetics, University of Athens, Athens, Greece*
[b] *College of Pharmacy, The University of Michigan, Ann Arbor, MI, USA*
[c] *Institut für Pharmazeutische Technologie, JW Goethe Universität, Frankfurt 60439, Germany*

ABSTRACT: The objective of this study was to evaluate the effects which hydroxypropylmethylcellulose (HPMC) may exert on oral drug absorption, in cases where this soluble fiber is administered to regulate blood lipid levels. Studies were conducted *in vitro* and in healthy female mongrel dogs using two different grades of HPMC, i.e. K8515 HPMC and ultra high molecular weight (UHMW) HPMC. The maximum plasma concentration, C_{max}, of paracetamol and both the C_{max} and the area under the concentration–time curve, AUC, of cimetidine were significantly decreased by the coadministration of 10 g of K8515 HPMC or 7.5 g of UHMW HPMC dissolved in 500 mL normal saline under fasting conditions. No statistically significant effects were observed on hydrochlorothiazide or mefenamic acid absorption. Based on *in vitro* data and previous studies it appears that reductions in gastric emptying and dissolution rate of paracetamol account for the effect observed *in vivo*. For cimetidine, a drug which can be absorbed from both the small and the large intestine, the indigestibility of HPMC in the colon in addition to the great reduction of dissolution rate led to reductions of both the C_{max} and AUC values. The long T_{max} values, even in the absence of HPMCs and the more modest reduction of the dissolution rate of hydrochlorothiazide by the HPMCs are thought to have precluded the observation of any significant alterations in the *in vivo* absorption profile. Owing to its erratic absorption, no statistically based conclusion could be drawn about the effects of coadministered HPMC on the oral absorption of the poorly soluble mefenamic acid. It is concluded that the effects of HPMCs on drug absorption in dogs are most pronounced for compounds with absorption profiles that are dependent on gastric emptying, i.e. compounds that are highly water soluble and that exhibit short T_{max} values. Compounds with long absorption profiles appear to be less susceptible to changes in absorption behavior due to coadministration of HPMCs. © 1998 John Wiley & Sons, Ltd.

Key words: hydroxypropylmethylcellulose; absorption; viscosity; dogs; cimetidine; hydrochlorothiazide; mefenamic acid; paracetamol

Introduction

Hydroxypropylmethylcellulose (HPMC) is a semisynthetic cellulosic ether available in a variety of molecular weights [1]. HPMCs are used in the pharmaceutical industry as tablet binders and suspending agents, in the food industry as thickeners, and in cosmetic products at concentrations up to 10% [1]. Medium- and long-term oral studies have indicated that these compounds are non-toxic when administered to laboratory animals, and no significant teratogenic or other adverse reproductive effects have been demonstrated [2]. The semisynthetic cellulosic ethers are similar to the so-called water-soluble fibers in that the polymeric backbone consists of a polysaccharide [3,4]. It has been shown that, when HPMCs are administered in doses much higher than those usually used in the pharmaceutical industry, they are capable of reducing postprandial blood glucose elevation in healthy dogs [5] and in humans with non-insulin dependent diabetes [6], and, also, they are effective in the clinical treatment of mild hypercholesterolemia [7]. These effects are most likely modulated via changes in the hydrodynamics in the gastrointestinal tract, since HPMCs are neither metabolized in nor absorbed from any part of the gastrointestinal tract [2,8]. Canine studies indicate that, as with other water-soluble fibers, HPMCs form viscous solutions whose viscosity is maintained intralumenally at values several orders of magnitude higher than viscosities usually observed after the consumption of regular meals [9,10].

* Correspondence to: Laboratory of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Athens, Panepistimiopolis, 157 71 Athens, Greece. Tel.: +30 1 7284367; fax: 30 1 7244191; e-mail: hreppas@atlas.uoa.gr
[1] Current address: Elpen S.A., Athens, Greece.
[2] Current address: Janssen Research and Technology Center, Ann Arbor, MI, USA.

CCC 0142–2782/98/080523–08$17.50

Received 18 September 1997
Accepted 30 March 1998

In a recent paper we have demonstrated that the increased intralumenal viscosity, required for the effect of a water-soluble fiber (guar gum) on carbohydrate and/or lipid metabolism, may affect drug absorption in dogs [11]. As a continuation of those studies we report here on the effect of HPMCs on the oral absorption of the same drugs, i.e. paracetamol, mefenamic acid, hydrochlorothiazide, and cimetidine. It was expected that due to differences in the doses required for the two polymers to exert their hypoglycemic and/or hypolipidemic effects, their different viscosity characteristics and the fact that, in contrast to HPMC, guar is metabolized in the large intestine [12], the effects that these two polymers exert on drug absorption may differ.

Methods

Materials and HPMC Solutions

All chemicals used in this study, apart from HPMCs, were obtained from the same manufacturers reported previously [11] and were of the same analytical grade.

Two types of HPMCs were tested. The first was a blend of 15% K15M Methocel® (number molecular weight, $M_n \approx 120000$ [13]) and 85% K100M Methocel® ($M_n \approx 250000$ [13]), namely K8515 HPMC, preblended by The Dow Chemical Company (Lot # MM920103). The second was a hydroxypropylmethylcellulose with ultra high molecular weight ($M_n \approx 450000-600000$, Lot # MM920131-1), namely UHMW HPMC (Dow Chem. Co.). To prepare solutions of HPMC (either K8515 or UHMW), the appropriate amount was slowly added to normal saline under rigorous agitation conditions at about 80°C. After dispersion of the solid particles in the liquid, the suspension was brought initially at room temperature and then at about 2–3°C under continuous stirring, so that a clear HPMC solution was formed. Solutions so prepared were stored in the refrigerator for up to 1 week.

In Vivo Viscosity Measurements

The viscosity characteristics of an isoosmotic (with NaCl) 2% K8515 HPMC solution and the ability of such solution to maintain its input value intralumenally has been studied previously using the fistulated canine model [14]. Similar measurements using identical methodology were performed in this study for the 1.5% UHMW HPMC solution. Intralumenal viscosities were measured in three medium sized (18–27 kg) female mongrel dogs fistulated at midgut. On three separate occasions each dog was administered 500 mL of 1.5% UHMW HPMC containing 0.9% NaCl and 0.8% PEG 4500 (as the nonabsorbable marker) under fasting conditions via an orogastric tube ($3 \times 3 = 9$ number of measurements). The chyme collected from midgut (recovery: 80–100% of the administered solution, based on PEG measurements) was pooled and its viscosity was measured. The use of this model had been approved by the University of Michigan Committee on Use and Care of Animals.

Both input viscosities and intralumenal viscosities were measured at 37°C with a Contraves Rheomat 135-S rotational Viscometer (Cincinnati, OH) using the DIN 125 measuring system. HPMC is known to exhibit pseudoplastic flow [13], i.e. the viscosity decreases dramatically as the shear rate increases. To obtain a global picture of the viscosity characteristics without the use of a model, viscosity measurements were performed at three different shear rates (1, 100, and 1000 s^{-1}).

Dissolution Studies

Dissolution rates were measured in a rotating disk apparatus [15]. The dissolution medium consisted of normal saline containing either 1.8% K8515 HPMC or 1.3% UHMW HPMC. 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, which was supported by a stainless steel holder and attached via a shaft to an overhead synchronous motor (Hanson Res. Corp., Chatsworth, CA, USA). One centimetre 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 which had been prewarmed in the jacketed beaker. For each drug, 200 or 400 μL samples were drawn from the dissolution medium at appropriate time intervals, with equivalent volume replacement with dissolution medium. For each drug, the procedures for the initial elimination of the HPMC and the subsequent drug analysis in the samples have been described previously [11,16]. 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. The initial dissolution rates were estimated from the slopes of the initial linear portions of the concentration–time plots, and their concurrence for each drug/rpm/medium combination checked with a *t*-test [17]. 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 ($0.92 \leq r \leq 1.000$) 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. Regardless of the presence of HPMC in the medium, for all drugs C_s values in water (37°C) were used for estimating the apparent dissolution rate constants. These values were taken from the literature [11,18–20]. Comparisons of the dissolution rate constants in the HPMC media with the dissolution rate constants estimated previously in a control medium, i.e. normal saline, under identical conditions [11], were made with *t*-test by normalizing the slopes and their associated standard error of estimate with the corresponding C_s value and applying the Bonferroni correction at the 0.05 level [17].

Diffusion Studies

The effect of K8515 HPMC and UHMW HPMC on the diffusivity of the four drugs was evaluated with the Franz cell [11,21]. The two compartments were separated with a dialysis membrane (Visking, dialysis tubing, Serva Feinbiochemica, exclusion limit 8000–15000 Da). The donor compartment solution consisted of drug and normal saline containing 2% K8515 HPMC or 1.5% UHMW HPMC, while the receptor compartment solution was composed of normal saline, which was held at 37°C and stirred magnetically to ensure homogeneity. The initial concentration of drug in the donor compartment was 1.00 mg mL^{-1} (paracetamol), 100 μg mL^{-1} (hydrochlorothiazide) and 600 μg mL^{-1} (cimetidine). These concentrations correspond to the 'dose/normal saline volume' ratios used in the *in vivo* studies. Due to its low aqueous solubility, 3.00 μg mL^{-1} solution of mefenamic acid was used. The methods of drug assay in the receptor compartment have been reported previously [11].

For each drug, 200 or 400 μL samples were drawn from the receptor compartment 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. 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, 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 ($0.93 \leq r \leq 0.998$) of concentration versus time data, $(\text{slope})_{\text{diff}}$. The apparent first-order diffusion rate constant, k_{diff}, was estimated using the following equation:

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

where C_{eq} is the drug concentration at equilibrium. Comparisons of the diffusion rate constants in the HPMC media with the diffusion rate constants estimated previously in a control medium (i.e. normal saline, under identical conditions [11]) were made with a *t*-test by normalizing the slopes and their associated standard error of estimate with the corresponding C_{eq} value and applying the Bonferroni correction at the 0.05 level [17].

Binding Studies

The ability of HPMCs 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 dialysed against 3.5 mL of 2% K8515 HPMC or 1.5% UHMW HPMC solution containing equivalent drug concentration. The initial concentrations (μg mL^{-1}) 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 previously described [11].

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. For each drug study the appropriate dose was administered under fasting conditions in the form of one or two soft gelatin capsules (filled in the laboratory and containing no excipients) along with 500 mL of normal saline containing either 2% K8515 HPMC or 1.5% UHMW HPMC. In all cases, the solution was warmed to 37°C for 1 h in an incubator prior to administration. This period was sufficient to increase the temperature of the administered solution to physiological values without affecting its rheological properties. The four drug studies were separated by approximately a month, and within each drug study the washout period between phases was at least 2 weeks for each dog. A protocol identical with that previously described was utilized [11]. The studies were approved by the Committee for Research of the University of Athens for all four drugs. Table 1 shows the administered dose and the

Table 1. The doses and the sampling schedules for each of the four pharmacokinetic studies performed in dogs

Type of study	Dose administered (mg)	Sampling times (h) after dose administration
Paracetamol study	500	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8
Mefenamic acid study	250	0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24
Hydrocholothiazide study	50	0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24
Cimetidine study	300	0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 3, 3.5, 4, 5, 6, 8, 10, 12

Table 2. Mean (S.D.) values (in centipoisse, cP) of the input viscosity and the average viscosity of chyme (based on PEG measurements) collected from the midgut of three fistulated dogs following the administration of 500 mL of 1.5% UHMW HPMC solution under fasting conditions[a]

	Shear rate (s^{-1})		
	1	100	1000
Pre-administered solution[b]	2.91×10^4 (0.22×10^4)	1.93×10^3 (0.02×10^3)	271 (5.5)
Chyme at midgut[c]	2.02×10^4 (0.57×10^4)	1.43×10^3 (0.15×10^3)	242 (35)

[a] All measurements were carried out at 37°C.
[b] $n = 9$.
[c] $n = 9$ (three dogs times three administrations per dog).

sampling schedule for each drug study. The analytical procedures used for the determination of serum drug concentration in each drug study, along with their corresponding accuracy and precision data, have been reported previously [11].

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_{lqc}, was calculated with the linear trapezoidal rule. The values of these pharmacokinetic parameters were compared with the values previously estimated after the administration of identical drug formulations/doses with 500 mL normal saline to the same dogs under identical conditions [11]. Differences in C_{max} and AUC_{lqc} values among the treatments 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, USA). Paired between treatments comparisons were performed with the Scheffe's *post hoc* test. T_{max} values were compared with the Friedman test (Statview®, Abacus Concepts, Berkeley, USA).

Results

The viscosity of the 1.5% UHMW HPMC solution and the average viscosity of the midgut contents after the administration of this solution in dogs are shown at three different shear rates in Table 2.

The apparent first order dissolution rate constants at 150 rpm in absence [11] and presence of HPMCs are presented in Table 3. The reductions in the dissolution rate constant resulting from the addition of 1.8% K8515 HPMC or 1.3% UHMW HPMC to the medium were more than 11-fold and 13-fold, respectively, for paracetamol, 10-fold and 8-fold for mefenamic acid, 7-fold and 4-fold for hydrochlorothiazide, and 17-fold and 8-fold for cimetidine. Similar reductions were observed at lower rotational speeds (data not presented). The decreases in the dissolution rate observed with HPMC are in accordance with previous studies on drug dissolution in viscous media [9,11].

The apparent diffusion rate constants of the four drugs in the absence [11] and presence of HPMC are presented in Table 4. The presence of 2% K8515 HPMC resulted in a reduction of the diffusion rate constant of paracetamol by 46% whereas the effect did not reach significance for the 1.5% UHMW HPMC case. The presence of K8515 HPMC and UHMW HPMC decreased the diffusion rate constants of mefenamic acid (by 34 and 33%, respectively), hydrochlorothiazide (by 43 and 34%, respectively) and cimetidine (by 38 and 39%, respectively).

In accordance with previous studies where guar gum was tested, the binding data indicated that none of the drugs interact to an appreciable extent with either K8515 HPMC or UHMW HPMC. For every drug, at all concentrations tested, the concentration of free drug remained within assay error of the original concentration.

The average serum concentration versus time profiles for each drug are shown in Figure 1, and the corresponding pharmacokinetic parameters are presented in Table 5. Coadministration of 2% K8515 HPMC or 1.5% UHMW HPMC in 500 mL normal saline with 500 mg of paracetamol resulted in a 38 and 54% reduction in the C_{max}, respectively, but had no significant effect on the AUC_{lqc} or T_{max}. No significant effects were observed on the three phar-

Table 3. 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 HPMC[a]

	Dissolution medium		
	Normal saline[b]	1.8% K8515 HPMC in normal saline	1.3% UHMW HPMC in normal saline
Paracetamol	0.02494 (0.00039)	0.00210 (0.00014)*	0.00192 (0.00006)*
Mefenamic acid	0.01482 (0.00057)	0.00144 (0.00007)*	0.00180 (0.00015)*
Hydrochlorothiazide	0.0341 (0.0030)	0.00474 (0.00014)*	0.00720 (0.00025)*
Cimetidine	0.02253 (0.00020)	0.00132 (0.00010)*	0.00276 (0.00022)*

[a] Standard error of estimation in the parentheses.
[b] These data have been taken from Reference [11].
* Statistically significant differences from normal saline at the 0.05 level.

Table 4. Apparent first-order diffusion rate constant (h^{-1}) for paracetamol, mefenamic acid, hydrochlorothiazide, and cimetidine determined with the Franz cell in the absence and presence of HPMC in the donor compartment[a]

	Solution of the donor compartment		
	Normal saline[b]	2% K8515 HPMC in normal saline	1.5% UHMW HPMC in normal saline
Paracetamol	0.188 (0.027)	0.1014 (0.0066)*	0.1284 (0.0078)
Mefenamic acid	0.250 (0.016)	0.165 (0.011)	0.1680 (0.0036)*
Hydrochlorothiazide	0.153 (0.018)	0.0870 (0.0090)*	0.1008 (0.0090)*
Cimetidine	0.1265 (0.0070)	0.0786 (0.0030)*	0.0774 (0.0024)*

[a] Standard error of estimation in the parentheses.
[b] These data have been taken from Reference [11].
* Statistically significant differences from normal saline at the 0.05 level.

macokinetic parameters for mefenamic acid and hydrochlorothiazide. Coadministration of 2% K8515 HPMC or 1.5% UHMW HPMC in 500 mL normal saline with 250 mg of cimetidine decreased the AUC_{lqc} (by 48 and 40%, respectively) and C_{max} (by 71 and 73%, respectively), but had no significant effect on T_{max} values.

Discussion

Selection of the 500 mL 2% K8515 HPMC and 500 mL 1.5% UHMW HPMC solutions was based on previous studies which showed that these HPMC combinations, administered as single doses of 10 or 7.5 g, respectively, are capable of regulating postprandial blood glucose levels in dogs [5] and humans [6] and blood lipid levels in humans [7,22].

The results in Table 2 indicate that the viscosity of the chyme recovered from canine midgut is 11–31% lower than the input viscosity of the 1.5% UHMW HPMC solution, depending on the shear rate used for the measurement. A reduction of about 50% had been previously observed for the K8515 HPMC solution [11]. Given the stability of HPMC in the acidic gastric environment [13], it seems likely that the decrease in viscosity is attributable to dilution of the solution by gastrointestinal (GI) secretions and/or interaction of HPMC with intralumenal components such as the bile salts [23,24]. Because of the significant decrease in viscosity during transit through the GI tract, we elected to conduct the *in vitro* dissolution experiments at viscosities reflective of the intralumenal conditions rather than the input viscosities. According to the manufacturers of the Methocels® [13], the equation which expresses the approximate relationship between solution viscosity and polymer concentration is:

$$n^{1/8} = (Cx\alpha) + 1$$

where n is the solution viscosity in centipoisse (cP), C is the polymer concentration in solution (expressed in percent) and α is a constant specific to the molecular weight. The value of α may be used to calculate the approximate viscosity at the desired concentration. For example, according to Table 2 the viscosity of a 1.5% UHMW solution at 37°C is about 29100 cP at 1 s^{-1}. Using the above equation, it can be calculated that $\alpha = 1.74$. Using this value of α, it can be calculated that for a viscosity of about 20200 cP (Table 2) the concentration of UHMW HPMC should be about 1.4%. The same result would be obtained if values at other shear rates were used. However, since the above equation expresses the 'approximate' relationship between solution viscosity and polymer concentration, similar calculations were performed using the actual viscosity data of 1% UHMW HPMC solution. These mean data were 10570 cP (at 1 s^{-1}) and 652 cP (at 100 s^{-1}) (not presented in the text). By using these data and the

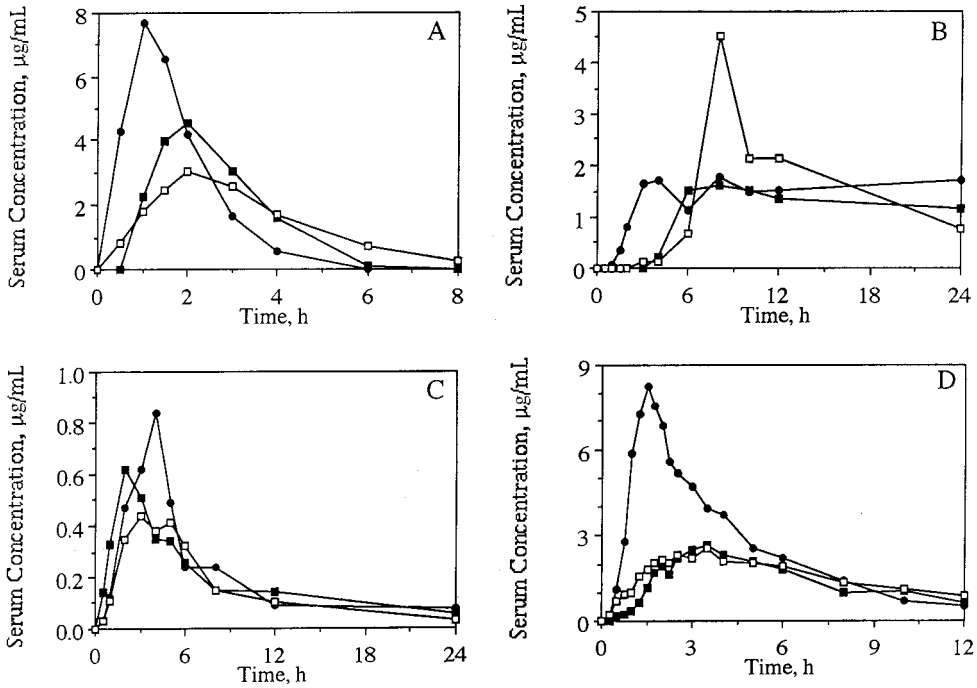

Figure 1. Average serum concentration versus time plots following the administration of (A) 500 mg paracetamol, (B) 250 mg mefenamic acid, (C) 50 mg hydrochlorothiazide, and (D) 300 mg cimetidine, to four dogs. ●, prototype capsule(s) with 500 mL normal saline [11]; ■, prototype capsule(s) with 500 mL of 2% K8515 HPMC in normal saline; □, prototype capsule(s) with 500 mL of 1.5% UHMW HPMC in normal saline

same equation it can be calculated that the viscosity values in mid-jejunum (Table 2) correspond to a 1.2% UHMW HPMC solution. It was concluded that a concentration of 1.3% would better simulate the intralumenal viscosity characteristics and, therefore, it was this concentration which was used in the dissolution studies. Using the same method it was further concluded that 1.8% K8515 HPMC should be used as the dissolution medium.

Binding of the four drugs to and their diffusion in presence of HPMCs were identical to those observed with guar [11]. Based on the binding data, for all drugs there is practically no drug-HPMC interaction. This observation in conjunction with the non-ionic nature of the HPMCs allowed us to use the solubility values in water (37°C) for estimation of the dissolution rate constants in all cases and regardless of the presence of HPMC in the medium. The dissolution data indicate that, for mefenamic acid and cimetidine, dissolution is suppressed to a greater extent by both HPMCs than by guar [11].

Paracetamol Study

Paracetamol levels peaked within 1–1.5 h after administration with the control solution (Table 5). These results, together with the almost complete absorption of paracetamol when dosed in dogs under fasted state conditions [25], indicates that paracetamol is rapidly and completely absorbed from the upper intestine. It has been further shown that the absorption kinetics of paracetamol are highly dependent on the gastric emptying pattern [26]. The results of this study are fully consistent with this behavior. The trend toward a longer T_{max} value and the significantly lower C_{max} observed with both HPMC formulations (Table 5) are consistent with an accompanying delay in gastric emptying. We have previously shown that 2% K8515 HPMC solution empties slower than normal saline from the canine stomach [14]. A lack of resultant effect on the AUC_{lqc} probably reflects the high capacity for absorption of this compound from the small intestine. Coadministration of 3% guar in 500 mL normal saline with the paracetamol dose [11] resulted in an even greater reduction in the C_{max} and a significant (28%) reduction in the AUC_{lqc}. The greater effect of the 3% guar gum may be linked to the greater viscosity achieved at that concentration of guar.

Mefenamic Acid Study

As in the previous studies with guar [11] the absorption of this drug was erratic (Figure 1B, Table 5) making it difficult to draw any conclusions from the data on a statistical basis. The long T_{max} values, even in the absence of HPMC administration, indicate that delays in gastric emptying would be unlikely to affect the absorption profile to any appreciable extent. When HPMCs were coadministered, there was a trend for the T_{max} values to be delayed, but neither these or the differences in C_{max} values were statistically significant. Likewise no differences were observed in the AUC_{lqc} values among the three phases. Mefenamic acid has an exceptionally high permeability (about 3 times as high as

caffeine) [27] and due to its lipophilicity it can be assumed that is well absorbed from all regions throughout the small and the large intestine. Therefore, the erratic absorption of mefenamic acid is most likely related to its low aqueous solubility [28] and the poor wetting properties of the micronized powder used in this study [11]. Although HPMCs decrease the dissolution rate of this compound even more than guar, it is likely that the continued absorption throughout the GI tract of this highly lipophilic drug would preclude the manifestation of any differences in dissolution rate in the AUC.

Hydrochlorothiazide Study

In contrast to mefenamic acid, absorption of this drug is limited by its low permeability rather than its dissolution characteristics [29]. T_{max} values were on the order of 3 h irrespective of HPMC coadministration (Table 5). These T_{max} values are consistent with slow absorption from the upper GI tract and indicate that changes in gastric emptying associated with administration of HPMCs are not very likely to be reflected in the absorption profile. As expected, no significant effects on T_{max}, C_{max} or AUC_{lqc} were observed. Coadministration of a 3% guar solution, in contrast, had been shown to reduce the C_{max} by 59% and AUC_{lqc} by 35% compared with the control solution [11]. As in the case of paracetamol, the difference between results with guar and HPMCs can probably be linked to the higher viscosity generated by the guar solution.

Cimetidine Study

Cimetidine, like paracetamol, is a highly soluble drug with a short T_{max}. Furthermore, it has been shown that the rate and pattern of cimetidine absorption is dependent on the gastric emptying profile [30]. Unlike paracetamol, however, it is not completely absorbed after oral administration. Recent studies have shown that the permeability of the gut wall to this compound is low [31], even though it has been shown that cimetidine is absorbed from the colon as well as the small intestine [32,33]. The trend toward longer T_{max} and the significantly lower C_{max} after administration with the HPMCs are reflective of the slower gastric emptying in presence of HPMCs. The extent of absorption also decreased, in contrast to the behavior in presence of guar. We hypothesize that this effect is related to the differences in fermentation between guar and HPMC. Guar, a natural polysaccharide, is fermented [12] to a far greater extent by bacteria in the colon than the semisynthetic HPMC [8]. Fermentation leads to a reduction in the viscosity of the fluids and thereby should permit better contact of the drug solution with the gut wall and subsequently more efficient drug absorption. Our hypothesis is supported by the relatively long T_{max} (*ca*. 7 h) after administration with guar [11], compared with that after administration with HPMCs (*ca*. 3 h).

In conclusion, it appears that the effects of the HPMCs on oral drug absorption in dogs are most pronounced for compounds with gastric emptying dependent absorption profiles, i.e. compounds that are highly water-soluble and that exhibit short T_{max}

Table 5. 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 HPMC) to four dogs[a]

Drug/HPMC	AUC_{lqc} ($\mu g \cdot mL\ h^{-1}$)	C_{max} ($\mu g\ mL^{-1}$)	T_{max} (h)
Paracetamol			
No HPMC[b]	15.1 (7.4)	8.1 (2.6)	1.2 (1.0–1.5)
2% K8515 HPMC	12.5 (4.9)	5.0 (1.4)*	1.9 (1.5–3.0)
1.5% UHMW HPMC	11.8 (5.6)	3.7 (0.9)*	2.0 (1.0–3.0)
Mefenamic acid			
No HPMC[b]	35 (15)	3.5 (0.7)	6.0 (3.0–10)
2% K8515 HPMC	26.1 (5.4)	2.2 (0.7)	11 (6.0–24)
1.5% UHMW HPMC	34 (10)	4.8 (1.9)	8.0 (8.0–10)
Hydrochlorothiazide			
No HPMC[b]	4.84 (0.74)	0.90 (0.11)	4.0 (4.0–5.0)
2% K8515 HPMC	4.42 (1.07)	0.68 (0.39)	2.5 (2.0–4.0)
1.5% UHMW HPMC	3.61 (1.71)	0.50 (0.21)	3.5 (2.0–5.0)
Cimetidine			
No HPMC[b]	30.9 (5.1)	9.9 (2.8)	1.4 (1.0–2.2)
2% K8515 HPMC	16.2 (2.1)*	2.9 (0.54)*	3.2 (2.0–3.2)
1.5% UHMW HPMC	18.6 (5.6)*	2.7 (0.81)*	3.0 (2.2–3.5)

[a] Values are mean (S.D.) for AUC_{lqc} and C_{max} and median (range) for T_{max}.
[b] These data have been taken from Reference [11].
* Significant differences from 'No HPMC' at the 0.05 level.

values. Compounds with long absorption profiles, whether these be due to low permeability (e.g. hydrochlorothiazide) or poor solubility (e.g. mefenamic acid) are less susceptible to changes in absorption behavior due to coadministration of HPMCs. To predict the effect of different water-soluble polymers on drug absorption, it appears that not only the pharmacokinetic properties of the drug must be considered, but also the sites of absorption of the drug within the GI tract and the viscosity achieved by the polymer in the gut, which in turn is dependent on the type and concentration of the polymer. Last but not least, extrapolation of these conclusions to humans should be made only in the light of quantitative differences in the GI physiology between dogs and humans [34].

Acknowledgements

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

References

1. W. Lund (Ed.), *The Pharmaceutical Codex, Principles and Practice of Pharmaceutics*, 12th edn, The Pharmaceutical Press, London, 1994, ISBN 0-85369-290-4.
2. E.M. Santos, Expert Panel. Final report on the safety assessment of hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose and cellulose gum. *J. Am. Coll. Toxicol.*, **5**, 1–59 (1986).
3. J.K. Seaman, Chapter 6. In *Handbook of Water-Soluble Gums and Resins*, R.L. Davidson (Ed), McGraw-Hill, New York, 1980, ISBN 0-07-015471-6.
4. *The United States Pharmacopeia* (USP 23), United States Pharmacopeial Convention, Rockville, MD, 1995, p. 774, ISBN 0-913595-76-4.
5. C. Reppas and J.B. Dressman, Viscosity modulates blood glucose response to nutrient solutions in dogs. *Diabet. Res. Clin. Pract.*, **17**, 81–88 (1992).
6. C. Reppas, C.H. Adair, J.L. Barnett, R.R. Berardi, D. DuRoss, S.Z. Swidan, P.F. Thill, S.W. Tobey and J.B. Dressman, High viscosity HPMC reduces postprandial blood glucose concentrations in NIDDM patients. *Diabetes Res. Clin. Pract.*, **22**, 61–69 (1993).
7. J.B. Dressman, C.H. Adair, J. Barnett, R.R. Berardi, V.A. Dunn-Kucharski, K.M. Jarvenpaa, D.D. Parr, C.A. Sowle, S.Z. Swidan, S.W. Tobey and C. Reppas, High-molecular-weight hydroxypropylmethylcellulose: a cholesterol-lowering agent. *Arch. Intern. Med.*, **153**, 1345–1353 (1993).
8. W.H. Braun, J.C. Ramsey and P.J. Gerling, The lack of significant absorption of methylcellulose viscosity 3300 from the gastrointestinal tract following single and multiple oral doses to the rat. *Food Cosmet. Toxicol.*, **12**, 373–376 (1974).
9. D.E. Greenwood, *Small Intestinal pH and Buffer Capacity: Implications for Dissolution of Ionizable Compounds*, Doctoral Thesis, University of Michigan, USA, 1994.
10. C. Reppas, D.E. Greenwood, L.C. Dermentzoglou, T.H. Meyer and J.B. Dressman, 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 (1992).
11. C. Reppas, G. Eleftheriou, P. Macheras, M. Symillides and J.B. Dressman, Effect of elevated viscosity in the upper gastrointestinal tract on drug absorption in dogs. *Eur. J. Pharm. Sci.*, **6**, 131–139 (1998).
12. M. Nyman and N.G. Asp, Fermentation of dietary fiber in the rat intestinal tract. *Br. J. Nutr.*, **47**, 357–366 (1982).
13. *Handbook on Methocel, Cellulose Ether Products*, p. 6.3, The Dow Chemical Company, Midland, MI, 1984
14. C. Reppas, J.H. Meyer, P. Sirois and J.B. Dressman, Effect of hydroxypropylmethylcellulose on gastrointestinal transit and luminal viscosity in dogs. *Gastroenterology*, **100**, 1217–1223 (1991).
15. V.G. Levich, *Physicochemical Hydrodynamics*, Prentice Hall, Englewood Cliffs, NJ, 1962, pp. 60–72.
16. P.J. Sirois, G.L. Amidon, J.H. Meyer, J. Doty and J.B. Dressman, Gastric emptying of nondigestible solids in dogs: a hydrodynamic correlation. *Am. J. Physiol.*, **258**, G65–G72 (1990).
17. S.A. Glantz, *Primer of Biostatistics*, McGraw-Hill Book, New York, 1981, ISBN 0-07-023370-5.
18. M.A. Etman and V.F. Naggar, Thermodynamics of paracetamol solubility in sugar–water cosolvent systems. *Int. J. Pharmac.*, **58**, 177–184 (1990).
19. H.P. Deppeler, Hydrochlorothiazide. In *Analytical Profiles of Drug Substances*, K. Florey (Ed.), Vol. 10, Academic Press, New York, 1981.
20. P.M.G. Bavin, Cimetidine. In *Analytical Profiles of Drug Substances*, K. Florey (Ed.), Vol. 13, Academic Press, New York, 1984.
21. T.J. Franz, Percutaneous absorption. On the relevance of *in vitro* data. *J. Invest. Dermatol.*, **64**, 190–195 (1975).
22. J.B. Dressman, S.Z. Swidan, C. Reppas and S.W. Tobey, Reduction of serum cholesterol concentration by HPMC. *Eur. J. Pharm. Sci.*, **2**, 106 (1994).
23. J.A.S. Nightingale, *Lipid Binding from Aqueous Solution by Lipid Conjugated HPMC*, Doctoral Thesis, University of Washington, USA, 1988.
24. N. Pandit, J. Kanjia, Z. Davidson and G. Rigoni, Interaction of HPMC with sodium cholate and deoxycholate. *Pharm. Res.*, **13**, S-338 (1996).
25. R.G. Sample, G.V. Rossi and E.W. Packman, Thiry-Vella dog as a biologic model for evaluation of drug absorption from the intestinal mucosa. *J. Pharm. Sci.*, **57**, 795–798 (1968).
26. J.A. Clements, R.C. Heading, W.S. Nimmo and L.F. Prescott, Kinetics of acetaminophen absorption and gastric emptying in man. *Clin. Pharmacol. Ther.*, **24**, 420–431 (1978).
27. L.C. Dermentzoglou, *Changes in Upper GI pH with Aging: Implication for Drug Absorption*, Doctoral Thesis, University of Michigan, USA, 1989
28. C.N. TenHoor, V. Bakatselou and J. Dressman, Solubility of mefenamic acid under simulated fed- and fasted-state conditions. *Pharm. Res.*, **8**, 1203–1205 (1991).
29. A. Collett, E. Sims, D. Walker, Y.L. He, J. Ayrton, M. Rowland and G. Warhurst, Comparison of HT29-18-Cl and Caco-2 cell lines as models for studying intestinal paracellular drug absorption. *Pharm. Res.*, **13**, 216–221 (1996).
30. R.L. Oberle and G.L. Amidon, 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 (1987).
31. K.M. Lee, *The Role of Time-Dependent Gastrointestinal Parameters in the Oral Absorption of Drugs*, Doctoral Thesis, University of Michigan, USA, 1991.
32. N. Kaneniwa, T. Funaki, S. Furuta and N. Watari, Study of the absorption site of cimetidine. *J. Pharmacobio-Dyn.*, **9**, 321–326 (1986).
33. V. Mummaneni, G.L. Amidon and J.B. Dressman, 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 (1995).
34. J.B. Dressman and K. Yamada, Animal models for oral drug absorption. In *Pharmaceutical Bioequivalence*, P.G. Welling, F.L.S. Tse and S. Dighe (Eds), Drugs and the Pharmaceutical Sciences, Vol. 48, Marcel Dekker, New York, 1991, ISBN 0-8247-8484-7.