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Drug interactions with diosmectite: a study using the artificial stomach–duodenum model

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Abstract

Drug interactions with diosmectite, a gastric-protective drug, were studied in vitro using an artificial stomach–duodenum model. The behavior of neutral and ionisable drugs with pK_a values ranging between 2 and 8 was monitored to determine the physicochemical characteristics of the interactions. The main neutral (digoxin) and acid (valproic acid) drug substances were moderately fixed by clay ($< 27\%$), in a pH-independent manner. Basic compounds with a p$K_a < 7$ (dapsone, metronidazole, cimetidine) were strongly fixed in acid medium ($> 62\%$), and fully released under neutral conditions. Amphoteric (fluoroquinolones) and basic compounds with a p$K_a \geq 7$ (ranitidine, pyrimethamine) were adsorbed by more than 81% by diosmectite in gastric and duodenal compartments. In the part of the model representing the distal duodenum, the potential site for drug absorption, only the active substances which remained positively charged (amphoteric and basic compounds) showed a large reduction ($\geq 80\%$) in their available free fraction. Ionisation of drug substances administered per os concomitantly with diosmectite plays a crucial role in these interactions.

Keywords: Drug–clay interaction; Clay; Diosmectite; pK_a

1. Introduction

Diosmectite is a clay preparation used as a gastric-protective drug in the treatment of gastrointestinal disorders (gastritis, diarrhea, etc). In addition to self-administration by patients, diosmectite is commonly co-prescribed with other drugs to patients with gastrointestinal disorders (H2 receptor blockers, antibiotics, etc) and with cardiovascular or neurological diseases, etc. Diosmectite avidly adsorbs certain compounds (Vatier et al., 1989).

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This is explained by its multilayer organisation, which creates a large surface for exchanges. In addition, the diffuse negative charges confer a large adsorption capacity for mineral and organic cations. In the interlayer space, water molecules, captured by aluminium silicates layers, are arranged in a partly ordered structure around the cation. Depending on the capacity of clay to swell, one to three sheets of water are present between the layers; this determines the space between the layers and that available for binding organic compounds (MacEwan and Wilson, 1980). The degree of adsorption of the drugs studied varied widely. This can be explained by the mechanisms involved. Different types of bonds are involved in the formation of complexes with organic compounds: ionic bonds with cations, ion–dipole bonds involving interlayer cations, hydrogen bonds, Van der Waals forces, Π bonds and, in some cases, covalent bonds (MacEwan and Wilson, 1980). Porubcan et al. (1979) have demonstrated the 'physical' adsorption of digoxin: at physiological pH, this interaction is sensitive to dilution and independent of pH. Similarly, with anionic compounds, there is a surface interaction involving physical mechanisms (McGinity and Lach, 1976). In neutral medium the appearance of a negative charge can lead to detrimental interactions, through electrostatic repulsion between drugs and the negatively charged surface of the layers. In the case of cationic and amphoteric compounds, a twin mechanism has been forwarded by McGinity and Lach (1976), Porubcan et al. (1978), involving 'physical' adsorption common to all organic compounds, and a chemical interaction (cation exchange). Cation exchange is pH-dependent. In vitro studies have demonstrated the adsorption of organic drug substances by clay (montmorillonite, attapulgite), including digoxin, tetracycline, clindamycin, amphetamine, propoxyphen, chlorpheniramine, theophylline, neomycin, quinidine and ciprofloxacin.

These interactions have been analysed by means of static physical methods (X-ray diffraction and IR absorption spectroscopy) as well as in studies of dissolution and dialysis (Khalil and Moustafa, 1973; McGinity and Hill, 1975; McGinity and Lach, 1976, 1977; Porubcan et al., 1978, 1979; Moustafa et al., 1987; Tunçel and Bergisadi, 1992).

The artificial stomach–duodenum model (Vatier et al., 1994) is a dynamic system which can be used to determine the physicochemical parameters of these interactions (gastroduodenal pH) and to predict their therapeutic impact. In this study we quantified interactions by testing neutral, acidic, basic and amphoteric compounds in this system.

2. Materials and methods

2.1. Artificial stomach–duodenum model

The model comprises a gastric reservoir (*S*), containing a fragment of hog stomach mucosa: it receives an acid secretory flux (HCl 0.1 N) and empties into compartments D1 and D2, which represent the proximal and distal duodenum, respectively. The latter have a fixed volume of 30 ml, and are spontaneously emptied; they receive simulated alkaline secretions (0.1 N $NaHCO_3$) from the proximal duodenum and pancreas. Influx and outflux are maintained at a constant rate (3 ml/min) by a microcomputer, allowing to establish the physicochemical characteristics of interactions. Influx and outflux can also be adjusted to simulate gastroduodenal flux in both healthy subjects and duodenal ulcer patients, in order to assess the therapeutic impact of interactions with clay. Under these conditions, the pH of *S* modulates gastric outflux and alkaline secretion from the duodenum in D1. The acid load penetrating into D1 modulates the flux of alkaline secretion from the pancreas in D2 (Fig. 1).

2.2. Experimental design

2.2.1. Constant flux model

At zero time, *S* was filled with 100 ml of 0.1 N HCl. Compartment D1 and D2 were filled with 30 ml of 0.1 N HCl and 30 ml of 0.1 N $NaHCO_3$, respectively. The fluxes of gastric secretion, of gastric emptying and alkaline secretion were kept constant at 3 ml/min throughout the experiment.

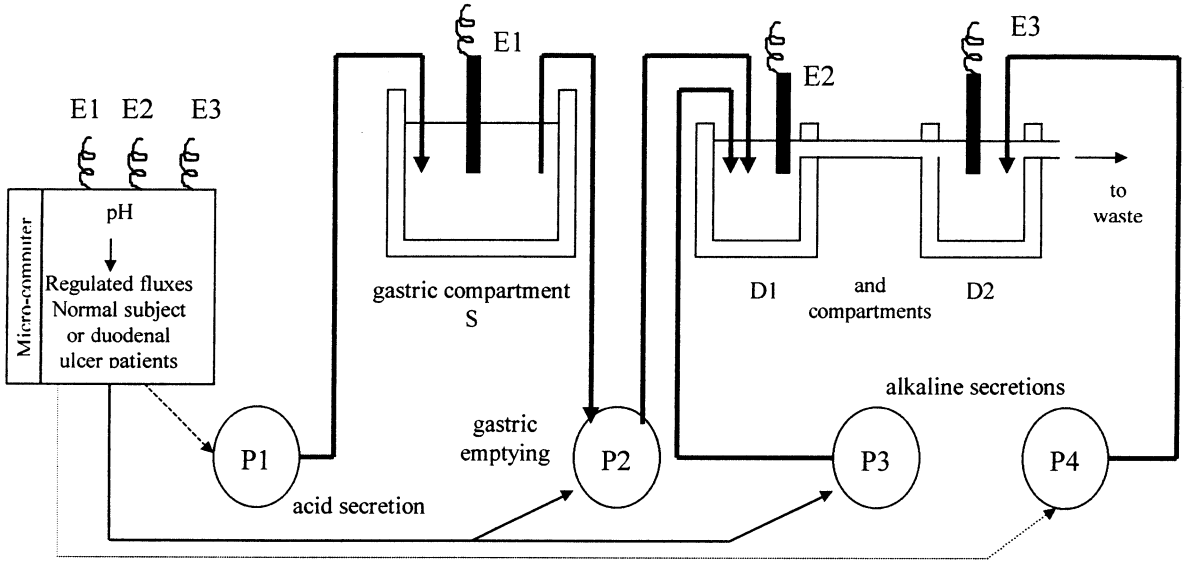

Fig. 1. Schematic representation of the model simulating gastroduodenal fluxes.

2.2.2. Simulation of gastro-intestinal flux regulation

A time t_0, *S* was filled with 200 ml of 0.1 N HCl. D1 and D2 were filled with 30 ml of 0.1 N HCl and 30 ml of 0.1 N $NaHCO_3$ respectively. Gastric emptying and D1 alkaline secretion were regulated according to intragastric pH, and D2 alkaline flux was regulated to the pH in D1.

The pH was recorded in each compartment throughout the 60-min experiment.

Samples were taken every 15 min from *S*, D1 and D2. After centrifugation, the supernatants were stored at −20°C for HPLC determination of the drug substances (Lee et al., 1972; Randolph et al., 1977; Carr et al., 1978; Carey and Martin, 1979; Kaye et al., 1980; Lagana, 1987; Meyers and Blumer, 1987; Le Coguic et al., 1988). Digoxin and valproic acid levels were measured by FPIA (TDX® Abbott)

A control was run with the test drugs alone (without clay) in the gastric reservoir. The clay–drug interaction was studied by adding to *S* a ground dose unit of the test drug simultaneously with 3 g of smectite (one sachet). Each combination was tested twice under the same conditions.

2.3. Drugs studied

(1) Clay: sachet of diosmectite (intergrade smectite of phyllitic structure) 3 g. The test drugs belonged to various pharmacologic classes (antimicrobial agents, H_2 receptor blockers, cardiotonic drugs and antiepileptic drugs) chosen for their physicochemical characteristics.

(2) Neutral compound: digoxin (250 μg)

(3) Acidic compounds: valproic acid (200 mg), nalidixic acid (250 mg).

(4) Basic compounds: dapsone (100 mg), metronidazole (250 mg), cimetidine (400 mg), pyrimethamine (50 mg) and ranitidine (150 mg).

(5) Amphoteric compounds: pipemidic acid (200 mg), ofloxacin (200 mg), norfloxacin (400 mg), ciprofloxacin (500 mg) and sparfloxacin (100 mg).

The pK_a and pHi values of the test drugs are given in Table 1 (Ross and Riley, 1992a,b; Budavari et al., 1989).

Five of these active substances (dapsone, metronidazole, cimetidine, pyrimethamine and ranitidine) were subsequently selected to study the potential therapeutic impact of interactions with clay in the variable-flux model (described previously).

Table 1
Ionization constants of the drugs studied[a]

	pK_a	pK_a1	pK_a2	pHi
Acidic compounds				
Valproic acid	5.0			
Nalidixic acid	6.0			
Basic compounds				
Dapsone	1.5			
Metronidazole	2.5			
Cimetidine	6.8			
Pyrimethamine	7.0			
Dibasic compound				
Ranitidine		2.3	8.2	5.25
Amphoteric compounds				
Pipemidic acid		5.8	8.7	7.25
Ofloxacin		6.1	8.2	7.15
Norfloxacin		6.3	8.4	7.35
Ciprofloxacin		6.1	8.7	7.40
Sparfloxacin		6.3	8.9	7.60

[a] Ross and Riley (1992a,b), Budavari et al., (1989).

2.4. Data analysis

Drug concentrations at each sampling time were used to construct a curve showing the quantities of active substance in solution as a function of time in the three compartments as well as to calculate the area under the curve (AUC) (mg 60 min). The free fraction of drug in each compartment was calculated as the ratio of the AUC measured in the presence or absence of clay.

Compartment D2 represents the main site at which drugs administered per os are absorbed, and the amount of free drug in D2 thus represents the fraction available for gastrointestinal absorption.

2.5. Adsorption isotherms

Cimetidine (12, 18, 36 mg), pyrimethamine (1, 2, 4 mg) and ranitidine (5, 10, 20 mg) were transferred into polypropylene tubes and dissolved in 4 ml of aqueous solutions at a defined pH (1, 4, 7 or 8). Clay (120 mg) was then added to each tube. The tubes were placed in a mechanical shaker at room temperature. After 2 h, the samples were centrifuged at 3000 rpm for 10 min. The equilibrium concentrations were determined in the supernatant by HPLC. Data have fitted the linear form of the Langmuir equation:

$$\frac{C_e}{X/M} = \frac{1}{a \cdot b} + \frac{C_e}{b},$$

where C_e is the equilibrium concentration; X/M the amount of drug adsorbed per mass unit of adsorbent; b, the limiting adsorptive capacity constant; a, the adsorption coefficient related to the forces involved in binding the drug to the clay.

3. Results

3.1. Constant flux model

Changes in gastroduodenal pH during a typical experiment are shown in Fig. 2. The presence of clay did not influence intragastric pH, which remained constant for 60 min (close to pH 1). In D1, the acid pH at $t = 0$ increased after 15 min to a mean of pH 5.5 due to the simulated bicarbonate secretion. The pH in D2 fell within a few minutes from 8.4 to 6.5, and remained at this mean value until the end of the experiment.

During control runs, the quantity of active substance in S fell, due to gastric emptying and dilution by simulated acid secretion. In D1 and D2, the quantities of drug increased for 20 min and subsequently fell. In the presence of diosmectite, the kinetics of certain drugs were modified, leading to a reduction in the quantity of drug in solution. The changes induced by clay varied widely among drug substances and from one compartment to the next (Fig. 3).

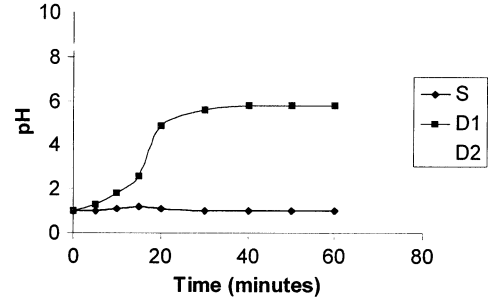

Fig. 2. pH changes with time in the three compartments.

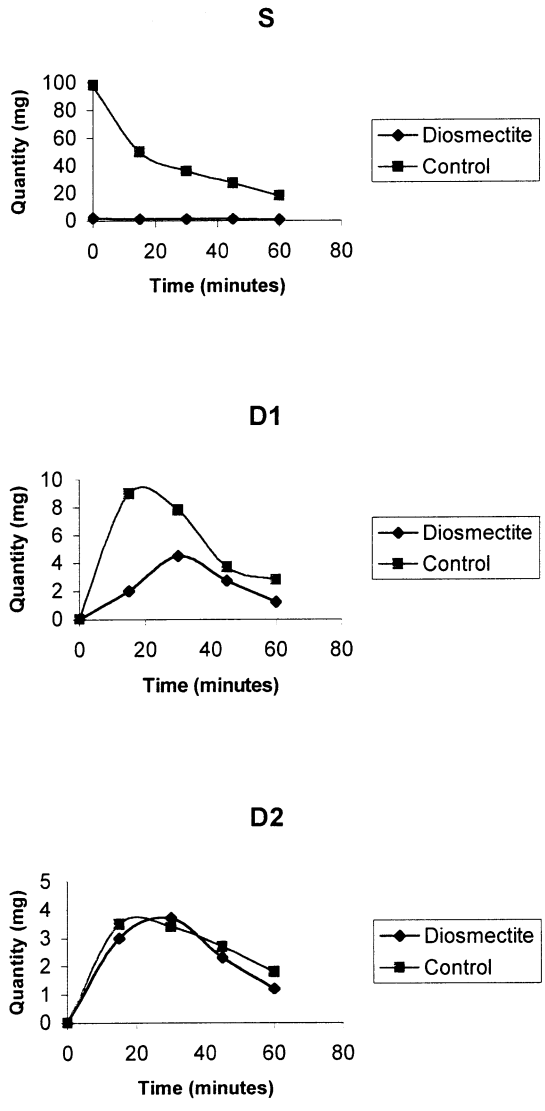

Fig. 3. Drug quantity changes with time in the three compartments in absence of diosmectite (control) or in presence of diosmectite (diosmectite). Example of dapsone.

After 1 h, 75% of clay or initial drug quantities had gone through the model, 19% remained in *S*, 3% in D1, and 3% in D2. Reproductibility has been estimated to be 7% (Vatier et al., 1994).

Table 2 shows the free fraction in the presence of diosmectite in *S*, D1 and D2 (expressed for each compound as a percentage of the control AUC value). Four main types of behavior were identified:

(1) In the case of dapsone and metronidazole, adsorption by diosmectite exceeded 79% in *S*, in acid medium. However, the increase in pH following passage into the duodenal compartments led to the release of both compounds. Finally, in D2, the free fraction exceeded 70%. Cimetidine was bound less extensively in *S* (62%), but it was also fully released in neutral medium.

In acid medium, these drugs were mainly present in ionized form (positively charged) and were strongly adsorbed. When the pH increased, the nonionized form became predominant and the drug was released.

(2) The fluoroquinolones and pipemidic acid were extensively adsorbed by clay ($\geq 92\%$) in an irreversible manner. This was also the case of ranitidine, a dibasic compound ($\geq 81\%$).

(3) At therapeutic doses, digoxin and valproic acid were poorly adsorbed to diosmectite ($\leq 27\%$ in the three compartments), independently of pH.

Table 2
Free fraction of the test drugs in the three compartments[a]

	S (pH = 1)	D1 (pH = 5)	D2 (pH = 7)
Acidic compounds			
Nalidixic acid	64	27	12
Valproic acid	88	87	101
Basic compounds			
Dapsone	1	54	70
Metronidazole	21	72	95
Cimetidine	38	89	90
Pyrimethamine	3	5	8
Dibasic compounds			
Ranitidine	7	10	19
Amphoteric compounds			
Pipemidic acid	1	2	4
Ofloxacin	0.1	0.5	3
Norfloxacin	4	3	6
Ciprofloxacin	3	2	1
Sparfloxacin	0.1	6	6
Neutral compounds			
Digoxin	73	100	79

[a] AUC in presence of clay, expressed as a percentage of the control AUC.

Table 3
Free fractions of the test drugs in the three compartments[a]

	Healthy subject			Duodenal ulcer		
	S	D1	D2	*S*	D1	D2
Mean pH	1	5.1	6.4	1	1.3	5.6
Dapsone	1	67	74	–	–	–
Metronidazole	13	59	76	16	18	68
Cimetidine	18	53	74	33	48	59
Pyrimethamine	10	11	12	–	–	–
Ranitidine	1	5	8	0.1	0.3	1.5

[a] AUC in presence of clay, expressed as a percentage of the control AUC. Comparison of conditions simulating the healthy subject and the duodenal ulcer patient.

(4) Nalidixic acid behaved differently in acid medium, where it was weakly bound by clay (36%), whereas in neutral medium it was extensively bound (88%), like the other quinolones.

3.2. Variable flux model

When physiological gastroduodenal flux was simulated, dapsone, metronidazole and cimetidine were adsorbed in acid medium and released in neutral medium, whereas pyrimethamine and ranitidine remained mainly bound to clay, as in the constant flux system. The amounts available for gastrointestinal absorption in D2 were, respectively, 74, 76, 74, 12 and 8% (Table 3).

In the duodenal ulcer simulation, emptying of a large amount of acid, together with the reduction of alkaline secretion, led to a D1 pH of less than 2. This led to the persistence of the drug substances in ionized form and to a 10 and 20% reduction in the release of metronidazole and cimetidine, respectively. Ranitidine remained adsorbed, such that the amount available for uptake was low (1.5%) (Table 3).

3.3. Adsorption isotherms

Table 4 shows the equation of the Langmuir isotherms, the limiting adsorptive capacities (b) and the adsorption coefficients (a) of cimetidine, pyrimethamine and ranitidine at different pH values.

These adsorption capacities vary from 0.05 to 0.72 mmol/g. Two types of variations can be distinguished: for cimetidine ($pK_a = 6.8$) or pyrimethamine ($pK_a = 7$), adsorption capacity decreases when pH increases; for ranitidine ($pK_a1 = 2.3$), adsorption capacity increases with increasing pH.

These adsorption coefficients vary from 0.84 to 1178. For pyrimethamine, the *a* values are very high.

Table 4
Equation of Langmuir adsorption isotherms, limiting adsorptive capacity (b) (mmol of drug/g of clay) and adsorption coefficient (a) for cimetidine, pyrimethamine and ranitidine by diosmectite at different pH-values[a]

	pH = 1	6 < pH < 8
Cimetidine	$y = 1.41 + 1.40\ C_e$ $r = 0.9996$ $b = 0.71$ $a = 0.99$	$y = 1.88 + 1.57\ C_e$ $r = 0.9999$ $b = 0.64$ $a = 0.84$
Pyrimethamine	$y = 0.64 + 7.69\ C_e$ $r = 0.9996$ $b = 0.13$ $a = 12.1$	$y = -0.018 + 21.68\ C_e$ $r = 0.9996$ $b = 0.05$ $a = 1178$
Ranitidine	$y = -0.97 + 7.19\ C_e$ $r = 0.9994$ $b = 0.14$ $a = 7.35$	$y = 0.87 + 1.64\ C_e$ $r = 0.9999$ $b = 0.61$ $a = 1.89$

[a] where $y = C_e\ (M/X)$ with X/M amount (mmol) of drug adsorbed per g of clay and C_e is expressed in mmol/g.

4. Discussion

The artificial stomach–duodenum is a dynamic model reproducing the range of gastroduodenal pH values and variations of gastroduodenal flux. It can be used to study drug interactions related to adsorption and pH. The constant flux model provides an approach to the physicochemical mechanisms of drug interactions, whereas the variable flux model allows to determine the likely therapeutic impact by simulating gastroduodenal flux in healthy subjects and in duodenal ulcer patients. The artificial stomach–duodenum model was used in this study to determine the parameters influencing interactions with clay.

Diosmectite was capable of adsorbing all the drug substances studied. This property results from its multilayer organisation, which confers a large external surface, and the presence of uncompensated negative charges on the border plane of the layers, which are a site of cation exchanges (Caillère et al., 1982). Between pH 3 and 7, the composition of clay is not modified and exchanges are independent of pH (Frysenberg and Thomas, 1960).

Interactions between drug and diosmectite are based on cationic exchange. Basic compounds are released into D1 and D2, as their positive charge disappears into neutral medium. Amphoteric compounds with pHi values between 6 and 8 are present in cationic or zwitterionic form at gastroduodenal pH values and thus remain bound to clay. Further experiments showed that ciprofloxacin is only released at pH 11.

Ionization of drug substances is thus a crucial parameter in determining interactions with clay. The involvement of a chemical mechanism of cation exchange induces stronger bonds and more extensive adsorption. 'Physical' adsorption is due to hydrogen bonds and ion–dipole interactions, which are weak links: the drugs are thus readily released, for example by dilution.

Other mechanisms can be involved, such as poor solubility and chelation of interlayer ions (Porubcan et al., 1979). This latter mechanism may be involved in the case of nalidixic acid, which behaved differently than the acidic compounds in neutral medium. In D2, in anionic form, nalidixic acid interacted strongly with clay, like the other quinolones. These compounds can all give rise to particularly stable chelates in neutral and alkaline medium (Ross and Riley, 1992b, 1993).

The artificial stomach–duodenum model reproduces the physiological pH and fluxes observed in vivo and revealed different interactions with diosmectite in therapeutic conditions. The degree of adsorption was highly variable, as it depends on multiple physical and chemical mechanisms (Albengres et al., 1985). These two types of interactions have very different therapeutic consequences. In the duodenum, neutral, acidic and basic compounds are eventually released: clay only delays gastrointestinal absorption, as demonstrated by McGinity in the case of amphetamine (McGinity and Lach, 1977). In contrast, amphoteric and dibasic compounds remained trapped by clay at physiologic pH. Diseases modifying gastroduodenal pH will influence these interactions. The flux of gastric emptying is greater in the duodenal ulcer model as compared to the normal subject model. This decreases the contact time between diosmectite and the drug in *S*. The low pH in D1 and D2 block the release of active basic or amphoteric compounds. In the case of the simulation of duodenal ulcer, the bioavailability of both amphoteric and basic compounds is reduced by the interaction with smectite.

Our conclusions concerning the influential parameters obtained with the constant flux model are in agreement with those of Albengres et al. (1985) who corellated in vivo and in vitro studies for phenylbutazone and diazepam. In contrast, for cimetidine Fredj et al. (1986) showed that AUC values of plasma concentrations were reduced by 54% in the presence of diosmectite. In the constant flux model, the free fraction in D2 was 90%. For the regulated flux models it was 74% for the normal subject model and 59% for the duodenal ulcer model. Using the constant flux model, the interaction was thus under estimated due to an underestimation of the Control test. Indeed, the concentrations obtained in *S* are close to the solubility limits of cimetidine at pH = 1 (3.6 g/l).

In order to better understand the behaviour of basic molecules, the isotherms of adsorption allow one to calculate the maximal adsorption capacity (AC) from the concentrations at equilibrium. For the three basic drugs studied, the AC's obtained varied greatly (5–72 mmol/100 g diosmectite). These complementary experiments in a static model also demonstrate that the adsorption of basic drugs is pH dependent. These results are in agreement with the AC's determined by Porubcan et al. (1978) for cindamycine or tetracycline, which behave like cimetidine or pyrimethamine.

In contrast, the correlation of adsorption isotherms with a dynamic system such as the artifical stomach–duodenum model is difficult. Indeed the three active compounds are strongly fixed by clay at a pH of 1 with AC's varying from 13 to 72 mmol/100 g. At a pH of about 7, the AC of cimetidine was only decreased by 12% while the free fraction of cimetidine increased nonetheless from 38 to 90%. In contrast, at pH 8, the AC of pyrimethamine was reduced by 64% but the drug remained fixed by clay. The force of the interaction, expressed by the adsorption coefficient, may explain these differences. In the dynamic model the interaction between cimetidine and diosmectite is more sensitive to the effects of dilution than is pyrimethamine because the forces involved between the latter and diosmectite are weaker. In additon at the level of *S* the drug/diosmectite ratio represents 50% of the AC for pyrimethamine and 75% for cimetidine. At the D2 level, this percentage is unfavorable for the release of pyrimethamine.

In conclusion, given the pH-dependent mechanism of adsorption of basic and amphoteric drug substances, their ionization state is the most important parameter determining their interactions with diosmectite. This provides a criterion for identifying drugs likely to show marked interactions with diosmectite. In addition, the artificial stomach–duodenum model can be used to predict the behavior of these drugs in the presence of clay, thereby avoiding the need for lengthy (and costly) studies of bioavailability.

References

Albengres, E., Urien, S., Tillement, J.P., Oury, P., Decourt, S., Flouvat, B., Drieu, K., 1985. Interactions between smectite, a mucus stabilizer, and acidic and basic drugs. In vitro and in vivo studies. Eur. J. Clin. Pharmacol. 28, 601–605.

Budavari, S., O'Neil, M.J., Smith, A., Heckelman, P.E. (Eds.), 1989. The Merck Index, Merck & Co, Rahway, pp. 444.

Caillère, S., Hénin, S., Rautureau, M., 1982. Minéralogie des argiles 1.structure et propriétés physico-chimiques, 2nd ed. Masson, Paris.

Carey, P.F., Martin, L.E., 1979. A high performance liquid method for the determination of ranitidine. J. Liquid. Chromatogr. 2, 1291–1303.

Carr, K., Oates, J.A., Nies, A.S., Woosley, R.L., 1978. Simultaneous analysis of dapsone and monoacetyl dapsone employing high performance liquid chromatography: a rapid method for determination of acetyl phenotype. Br. J. Clin. Pharmacol. 6, 421–427.

Fredj, G., Farinotti, R., Salvadori, C., Dauphin, A., Paillet, M., Doucet, D., Plantefève, J.C., Jouenne, P., 1986. Topiques digestifs à base d'argile. Influence sur l'absorption de la cimétidine. Thérapie 41, 23–25.

Frysenberg, M.M., Thomas, W.J., 1960. Adsorption studies on clay minerals. VII Yttrium–cesium and cerium(III)–cesium on montmorillonite. J. Soc. Chem. 64, 224–228.

Kaye, C.M., Sankey, M., Thomas, L., 1980. A rapid and specific semi-micro method involving high performance liquid chromatography for the assay of metronidazole in plasma, saliva, serum, urine and whole blood. Br. J. Clin. Pharm. 9, 528–529.

Khalil, S., Moustafa, M., 1973. The in-vitro-adsorption of some drugs on antacids. Pharmazie. 28, 116–118.

Lagana, A., 1987. High-performance liquid chromatography determination of norfloxacin in human tissues and plasma with fluorescence detection. J. Chromatogr. 417, 135–142.

Le Coguic, A., Bidault, R., Farinotti, R., Dauphin, A., 1988. Determination of ofloxacin in human plasma and urine by chromatography. J. Chromatogr. 434, 320–323.

Lee, F.H., Koss, R., O'Neil, S.K., Kullberg, M.P., MacGrath, M., Edelson, J., 1972. High-performance liquid chromatographic determination of plasma and urinary 1-ethyl-1,4-dihydro-4oxo-1,8- naphtyridine-3,7-dicarboxylic acid. J. Chromatogr. 152, 145–152.

MacEwan, D.M.C., Wilson, M.J., 1980. Interlayer and intercalation complexes of clay minerals. In: Brundley, G., Brown, G. (Eds.), Crystal Structure of Clay Minerals and their X-ray Identification. Mineralogy Society, London, pp. 197–248.

McGinity, J., Hill, J., 1975. Influence of monovalent and divalent electrolytes on sorption of neomycin sulfate to attapulgite and montmorillonite clays. J. Pharm. Sci. 64, 1566–1568.

McGinity, J., Lach, J., 1976. In vitro adsorption of various pharmaceuticals to montmorillonite. J. Pharm. Sci. 65, 896–902.

McGinity, J., Lach, J., 1977. Sustained-release applications of montmorillonite. Interaction with amphetamine sulfate. J. Pharm. Sci. 66, 63–66.

Meyers, C.M., Blumer, J.L., 1987. High-performance liquid chromatography of ciprofloxacin and its metabolites in serum, urine and sputum. J. Chromatogr. 422, 153–164.

Moustafa, M., Al-Shora, H., Gaber, M., Gouda, M., 1987. Decreased bioavailability of quinidine sulphate due to interactions with adsorbent antacids and antidiarrheal mixture. Int. J. Pharm. 34, 207–211.

Porubcan, L., Born, G., White, J., Hem, S., 1979. Interaction of digoxin and montmorillonite: mechanism of adsorption and degradation. J. Pharm. Sci. 68, 358–361.

Porubcan, L., Serna, C., White, J., Hem, S., 1978. Mechanism of adsorption of clindamycin and tetracyclin by montmorillonite. J. Pharm. Sci. 67, 1081–1087.

Randolph, W.C., Osborne, V.L., Walkenstein, S.S., Intoccia, A.P., 1977. High-performance liquid chromatographic analysis of cimetidine, a histamin H2-receptor antagonist, in blood and urine. J. Pharm. Sci. 66, 1148–1150.

Ross, D.L., Riley, C.M., 1992a. Physicochemical properties of the fluoroquinolone antimicrobials. II. Acid ionization constants and their relationship to structure. Int. J. Pharm. 83, 267–272.

Ross, D.L., Riley, C.M., 1992b. Physicochemical properties of the fluoroquinolone antimicrobials. III. Complexation of lomefloxacin with various metal ions and the effect of metal ion complexation on aqueous solubility. Int. J. Pharm. 87, 203–213.

Ross, D.L., Riley, C.M., 1993. Physicochemical properties of the fluoroquinolone antimicrobials. V. Effect of fluoroquinolone structure and pH on the complexation of various fluoroquinolones with magnesium and calcium ions. Int. J. Pharm. 93, 121–129.

Tunçel, T., Bergisadi, N., 1992. In vitro adsorption of ciprofloxacin hydrochloride on various antacids. Pharmazie 47, 304–305.

Vatier, J., Harman, A., Castéla, N., Droy-Lefaix, M.T., Farinotti, R., 1994. Interactions of cimetidine and ranitidine with aluminium containing antacids and a clay-containing gastric protective drug in an 'artificial stomach duodenum model'. J. Pharm. Sci. 83, 962–966.

Vatier, J., Olivier, J.F., Vitré, M.T., Papazian, A., 1989. Influence du pH dans la capacité d'adsorption des sels biliaires et des lysolécithines in vitro par les antiacides contenant de l'argile et/ou l'aluminium. Gastroenterol. Clin. Biol. 13, 445–451.