J. Pharm. Pharmacol. 1992, 44: 655–658
Received July 24, 1991

Adsorption of Paracetamol and Chloroquine Phosphate by Some Antacids

M. A. IWUAGWU AND K. S. ALOKO

The School of Pharmacy, University of Benin, P.M.B. 1154, Benin City, Nigeria

Abstract—The adsorption of paracetamol and chloroquine phosphate onto some antacids with adsorptive properties, has been studied. Dissolution of the drugs from commercial tablets was significantly retarded in the presence of the antacids. The adsorption and retardation of dissolution of both drugs by the adsorbent antacids studied followed the rank order magnesium trisilicate > magnesium oxide > aluminium hydroxide > edible clay. The concomitant administration of the drugs and antacid formulations containing any of these should be discouraged.

Magnesium trisilicate is known to interact in-vitro by adsorption with digoxin and digitoxin (Khalil 1974a) and some oral contraceptive steroids (Khalil & Iwuagwu 1978). The concomitant ingestion of some drugs with antacids possessing adsorptive properties caused a decrease in bioavailability of the drugs (Khalil 1974b; Bucci et al 1981; Gouda et al 1984; Moustafa et al 1986, 1987). The adsorption of chloroquine phosphate as well as the base by some pharmaceutical clays and tablet excipients has been reported (Udeala & Aly 1983). Edible clays are eaten in Papua, New Guinea for their nutritive value. Their consumption is popular amongst Nigerian females who consume substantial amounts ostensibly for their ability to stop diarrhoea, prevent nausea and vomiting as well as the discomfort associated with hyperacidity. Recent studies in our laboratory have shown that pyrimethamine is significantly adsorbed by edible clay (Iwuagwu & Anidu 1987). A comprehensive classification of some edible clays found locally in Papua, New Guinea has been published by Drover & Borrell (1980).

In this study we investigated the interaction between some antacid powders and paracetamol and chloroquine phosphate as well as the consequence of this interaction on the dissolution of the drugs from commercial tablets. The mechanisms of interaction between the drugs and the antacids were also investigated.

Materials and Methods

Paracetamol and chloroquine phosphate powders were gifts from Continental Pharmaceuticals, Lagos, Nigeria; paracetamol tablets (Panadol, BN. XI35BA, Sterling Products, Lagos, Nigeria) each containing 500 mg paracetamol, and chloroquine phosphate tablets (Resochin, BNs. 474B & 375Z, Bayer Pharmaceuticals, Lagos, Nigeria) each containing 250 mg chloroquine phosphate were purchased from a local pharmacy; magnesium trisilicate (BDH Chemicals, Poole, UK), aluminium hydroxide and magnesium oxide (both from Merck, Darmstadt, Germany) were used as supplied. Unsalted edible clay was purchased from a local market, ground and sifted through a 0·63 mm sieve. A modified BP 1980 dissolution testing apparatus was used. All spectrophotometric measurements were made on a Unicam SP 1800 UV/Vis spectrophotometer (Pye Unicam, Cambridge, UK); pH determinations were made with a Model 291 MK 2 pH meter (Pye Unicam, Cambridge, UK); surface areas were determined using a Flowsorb II 2300 instrument (Micromeritics Instrument Corp., Norcross, GA, USA); and X-ray diffractograms were obtained on a Philips PW1752 equipment.

Correspondence: M. A. Iwuagwu, The School of Pharmacy, University of Benin, P.M.B. 1154, Benin City, Nigeria.

Determination of surface area of adsorbents

The surface area of the adsorbents was determined by nitrogen adsorption. The results obtained are listed in Table 1.

Table 1. Specific surface area values of the adsorbents.

Adsorbent	Specific surface area ($m^2 g^{-1}$)
Magnesium trisilicate	1·64
Magnesium oxide	1·84
Aluminium hydroxide	2·04
Edible clay	1·64

Characterization of edible clay

Chemical analysis of the edible clay used in the study gave the following results in which the standard deviations are listed in parentheses: water of hydration 3·88 (0·24)%, silica 56·68 (0·82)%, sesquioxides ($Fe_2O_3 + Al_2O_3$) 37·59 (1·63)%, calcium carbonate 1·86 (0·25)%.

X-Ray diffraction analysis was carried out on the edible clay sample using cobalt irradiation. The patterns were collected at 40 Kv, 40 Ma and scan runs of approximately 3 degrees min^{-1}. The result confirmed a predominance of quartz and kaolinite in the clay sample.

Adsorption studies

An appropriate amount of antacid powder was weighed into a stoppered conical flask which was protected from light. Aqueous solutions of the drugs of various concentrations were added to each flask and shaken for 2 h in a thermostated

shaking incubator (Gallenkamp, UK) at 37±0·5°C. Previous experimentation had established that equilibrium was reached after 1 h for both drugs. At the end of the 2 h period, samples were centrifuged and the drug concentration in the supernatant was determined spectrophotometrically against a blank which was similarly prepared but without drug. The experiment was carried out in duplicate. The amount of drug adsorbed by the antacid powders was computed by subtracting the equilibrium concentration from the initial concentration.

Elution studies

The elution of the drugs from the adsorbents was determined as previously described (Miyazaki et al 1979) by digesting the residue obtained by centrifugation of the suspension after the adsorption run in 25 mL distilled water (pH 7·5), 0·01 M HCl (pH 2·0) or 0·1 M HCl (pH 1·2). The digested material was equilibrated at 37±0·5°C for 2 h, and the amount of drug desorbed was determined as a function of time. The experiment was carried out in duplicate after adsorption of the drugs onto 1% w/v magnesium trisilicate and edible clay.

Disintegration time testing

The disintegration times of the tablets in distilled water and in adsorbent suspensions were determined at 37±0·2°C in a BP disintegration test unit (Mk IV. Manesty Machines Ltd, UK). Average values were computed for five tablets.

Dissolution studies

Dissolution profiles were obtained for the paracetamol and chloroquine phosphate tablets in 1L distilled water which was previously flushed with nitrogen and maintained at 37±0·2°C. The effect of antacids on dissolution was studied by adding various amounts of the antacid powders to the dissolution medium. Samples were withdrawn at suitable time intervals, filtered, and the filtrate suitably diluted (where necessary), and the concentration of the drug in the sample determined spectrophotometrically at 245 nm (for paracetamol) or at 257 nm (for chloroquine phosphate). Equal amounts of fresh dissolution medium were added to replace those withdrawn for analysis. The experiments were carried out in triplicate.

Results

The results of adsorption studies of paracetamol and chloroquine phosphate onto the adsorbents are illustrated in Fig. 1 which is plotted according to Langmuir's relationship:

$$c/x/m = 1/ab + c/ab \quad (1)$$

where c is the equilibrium concentration of drug, x/m is the amount of drug adsorbed per unit weight of adsorbent, and a and b are adsorption constants. The adsorptive capacities of the various adsorbents for paracetamol and chloroquine phosphate are listed in Table 2. For both drugs the adsorptive capacities followed the rank order: magnesium trisilicate > magnesium oxide > aluminium hydroxide > edible clay.

The degree of desorption achieved was dependent on the acidity of the medium used. The lower the pH of the desorption medium the higher the desorption achieved

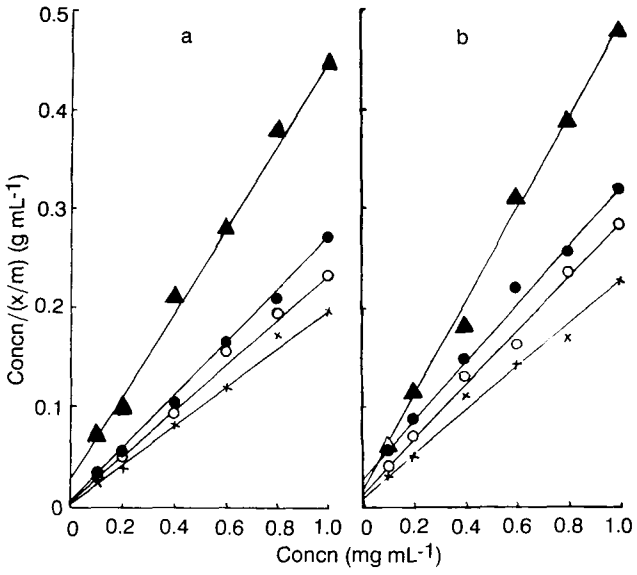

FIG. 1. Langmuir plots for the adsorption of paracetamol (a) and chloroquine phosphate (b) onto edible clay (▲), aluminium hydroxide (●), magnesium oxide (○), and magnesium trisilicate (×).

Table 2. Adsorptive capacities of the adsorbents for paracetamol and chloroquine phosphate.

	Adsorptive capacity (mg g^{-1})	
Adsorbent	Paracetamol	Chloroquine phosphate
Magnesium trisilicate	5·204	4·721
Magnesium oxide	4·342	4·175
Aluminium hydroxide	4·127	3·911
Edible clay	2·324	2·140

(Fig. 2). Since the magnesium trisilicate was decomposed in 0·01M and 0·1 M HCl with the formation of an adsorptive silica gel, some of the drug molecules may have been readsorbed. Both paracetamol and chloroquine phosphate were not completely desorbed from the clay.

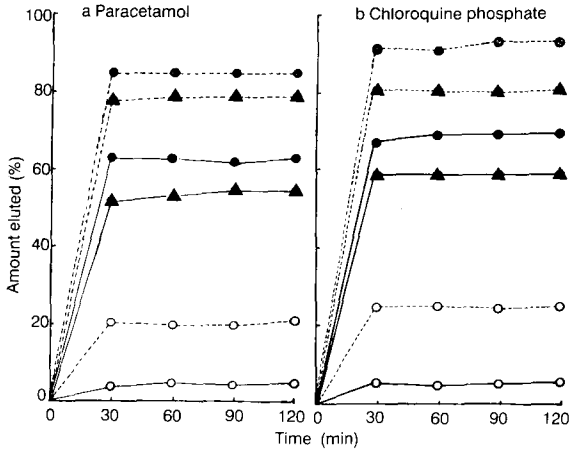

FIG. 2. The elution of paracetamol (a) and chloroquine phosphate (b) from magnesium trisilicate ——, and edible clay - - - - - with water (○), 0·01 M HCl (▲) or 0·1 M HCl (●) at 37°C.

Table 3. Disintegration times of paracetamol (Panadol) and chloroquine phosphate (Resochin) tablets in various media at 37±0·2°C.

Disintegration medium		Disintegration times (min:s) Panadol	Resochin
Distilled water		2:30	3:25
Magnesium trisilicate (% w/v)	0·5	3:40	5:50
	1·0	4:25	6:50
	2·0	5:10	7:45
Magnesium oxide (% w/v)	0·5	3:32	5:04
	1·0	4:05	5:10
	2·0	5:00	6:12
Aluminium hydroxide (% w/v)	0·5	4:33	6:40
	1·0	4:38	6:48
	2·0	5:05	7:20
Edible clay (% w/v)	0·5	3:40	5:15
	1·0	4:26	6:08
	2·0	4:50	6:56

The paracetamol and chloroquine phosphate tablets disintegrated within the BP 15 min time limit for uncoated tablets in spite of delayed disintegration in the presence of the adsorbents (Table 3).

The effect of the adsorbents on the dissolution characteristics of paracetamol and chloroquine phosphate from tablets is illustrated in Fig. 3. The curves show that dissolution of both drugs from the commercial tablets decreased in the presence of all the antacids studied. At all the concentrations studied the rank order of retardation of dissolution of both drugs from the tablets was magnesium trisilicate > magnesium oxide > aluminium hydroxide > edible clay. The degree of retardation of dissolution from both tablets increased as the amount of adsorbent increased (Fig. 4). Hence, after 2 h, 41% of the paracetamol and 45% of the chloroquine phosphate were found in solution in the presence of 0·5% w/v magnesium trisilicate; 32% of the paracetamol and 30% of the chloroquine phosphate were found in solution after 2 h in the presence of 1% w/v magnesium trisilicate; after the same time period, 15% of the paracetamol and 12% of the chloroquine phosphate were found in solution in the presence of 2% w/v magnesium trisilicate. However, in the absence of antacids from the dissolution medium the two tablet formulations gave 100% dissolution in less than 2 h.

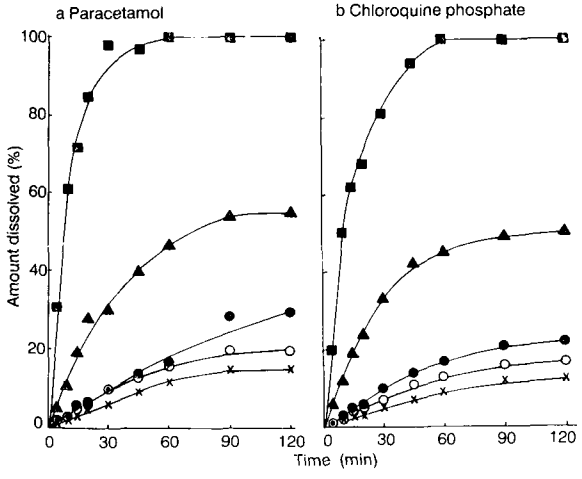

FIG. 3. The dissolution of paracetamol (a) and chloroquine phosphate (b) from tablets in water (■), and in 2% w/v aqueous suspension of edible clay (▲), aluminium hydroxide (●), magnesium oxide (○), and magnesium trisilicate —×— at 37°C.

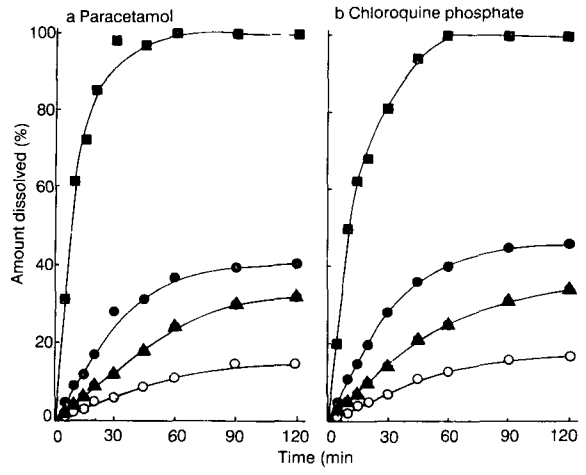

FIG. 4. (a) The dissolution of paracetamol from tablets in various concentrations of aqueous magnesium trisilicate suspensions: (■) water, (●) 0·5% w/v, (▲) 1·0% w/v, (○) 2·0% w/v. (b) The dissolution of chloroquine phosphate from tablets in various concentrations of aqueous magnesium oxide suspensions (symbols as in Fig. 4a).

Discussion

The buffer capacity, porosity, internal surface and availability of adsorption sites may affect the adsorptive capacities of adsorbents (Naggar 1981). It has been shown that adsorption is also affected by the ionic state (Sorby 1965) and the solubility (Blaug & Gross 1965) of the solute. Both paracetamol (pK_a 9·5) and chloroquine (pK_a 10·8) are weak bases. At the pH values of the aqueous suspensions of the adsorbents (Table 4) both drugs will exist mainly in the un-ionized (less soluble) form in the magnesium oxide suspension. In aluminium hydroxide suspension, paracetamol is mainly un-ionized while chloroquine phosphate is ionized. In the clay and magnesium trisilicate suspensions both drugs exist mainly in the ionized state. Considering the above, it would be expected that the adsorption of both drugs will follow the rank order: magnesium oxide > aluminium hydroxide > edible clay > magnesium trisilicate. Magnesium trisilicate deviates from this by having the highest adsorptive

Table 4. pH values of 1% w/v aqueous suspensions of the adsorbents.

Adsorbents	pH
Magnesium trisilicate	8·83
Magnesium oxide	10·80
Aluminium hydroxide	9·95
Edible clay	8·86

capacities for both drugs. Therefore, some other contributory forces may also account for adsorption of solutes onto adsorbents.

Since adsorption is a surface phenomenon it would be expected that the degree of adsorption will be related to particle size of the adsorbents. A larger particle surface will be associated with increased adsorption and vice versa. From the values of the specific surface area listed in Table 1 it would be expected that the propensity for adsorption of solutes by the adsorbents used in this study will follow the rank order: aluminium hydroxide > magnesium oxide > magnesium trisilicate = edible clay. Again, magnesium trisilicate deviates from this rank order since it has the highest adsorptive capacities for both paracetamol and chloroquine phosphate.

It may be inferred therefore, that the apparent retardation of dissolution from the paracetamol and chloroquine phosphate tablets in the presence of antacids may be due to the significant interaction which occurred between the drugs that dissolved out of the compacts and the antacids studied via relatively strong adsorptive forces.

In the disintegration time determination, some antacid particles may have been attracted onto the tablet surface, blocking pores through which water would have entered into the tablet by capillary action and thereby delaying disintegration. Blocking of the tablet pores would be expected to occur with all types of tablet irrespective of whether the tablets contain active compounds capable of interacting via adsorptive forces with adsorbents present in the disintegration medium. Such non-specific antacid-particle interaction after disintegration of the tablet would be expected to further delay dissolution. The study showed that dissolution of active compounds from commercial tablets of paracetamol and chloroquine phosphate was retarded in the presence of the antacids studied. Apart from the delayed disintegration of the tablets, the drugs may have been adsorbed by the antacids soon after normal dissolution occurred from the tablets, leading to the observed retardation of dissolution.

The clinical implications of this interaction must be further confirmed by in-vivo studies. It is, however, suggested that the concomitant administration of antacids which possess adsorptive properties and the drugs studied should be discouraged.

Acknowledgements

The authors gratefully acknowledge Dr Peter Roeder of the Department of Geological Sciences and Dr Augustine Okhamafe of the Department of Chemical Engineering of Queen's University, Kingston, Canada, for the X-ray diffractography and surface area determination.

References

Blaug, S. M., Gross, M. R. (1965) Adsorption of some anticholinergic drugs by various antacids. J. Pharm. Sci. 54: 289–294

Bucci, A. J., Myre, S. A., Tan, H. S. I., Shenouda, L. S. (1981) In vitro interaction of quinidine with kaolin and pectin. J. Pharm. Sci. 70: 999–1002

Drover, D. P., Borrell, O. W. (1980) Analysis of two edible clays from East Sepik, Papua, New Guinea. Sci. New Guinea. 7: 6–11

Gouda, M. W., Hikal, A. H., Badhair, S. A., El-Hofy, S. A., Mahrous, G. M. (1984) Effect of sucralfate and antacids on the bioavailability of sulpiride in humans. Int. J. Pharm. 22: 257–263

Iwuagwu, M. A., Anidu, S. O. (1987) The in vitro interaction between pyrimethamine and some adsorbents. Nig. J. Pharm. Sci. 3: 64–72

Khalil, S. A. H. (1974a) The uptake of digoxin and digitoxin by some antacids. J. Pharm. Pharmacol. 26: 961–967

Khalil, S. A. H. (1974b) Bioavailability of digoxin in the presence of antacids. J. Pharm. Sci. 63: 1641–1643

Khalil, S. A. H., Iwuagwu, M. (1978) In vitro uptake of oral contraceptive steroids by magnesium trisilicate. Ibid. 67: 287–289

Miyazaki, S., Inoue, H., Nadai, T. (1979) Effect of antacids on the dissolution behaviour of tetracycline and methacycline. Chem. Pharm. Bull. 27: 2523–2527

Moustafa, M. A., Al-Shora, H. I., Gaber, M., Gouda, M. W. (1987) Decreased bioavailability of quinidine sulphate due to interactions with adsorbent antacids and antidiarrhoeal mixtures. Int. J. Pharm. 34: 207–211

Moustafa, M. A., Gouda, M. W., Tariq, M. (1986) Decreased bioavailability of propranolol due to interaction with adsorbent antacids and antidiarrhoeal mixtures. Int. J. Pharm. 30: 225–228

Naggar, V. F. (1981) An in vitro study of the interaction between diazepam and some antacids or excipients. Pharmazie 36: 114–117

Sorby, D. L. (1965) Effect of adsorbents on drug absorption. I. Modification of promazine absorption by activated attapulgite and activated charcoal. J. Pharm. Sci. 54: 677–683

Udeala, O. K., Aly, S. A. S. (1983) The adsorption of chloroquine phosphate and base by some pharmaceutical clays and tablet excipients. Paper presented at the 3rd International Conference on Pharmaceutical Technology, Paris (A.P.G.I., V, 26–34)