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In vitro availability of promethazine-HCl in the presence of some commercial antacids

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Summary

The dialysis and dissolution dialysis rates of promethazine-HCl alone or in the presence of 4 commercial antacid suspensions and 3 commercial antacid powders in either 0.1 HCl or distilled water, was studied at 37°C. The commercial products caused a substantial decrease in the percentage drug dialyzed especially in water. Adsorption, viscosity effects as well as pH effects on both the drug and ingredients of the formulations, may be responsible for the observed decrease in the dialytic rate constant. Adsorption experiments on the main ingredients of the products were carried out. Kaolin showed a high adsorption power for the drug in both HCl and water; bismuth carbonate had a much higher adsorption capacity in HCl than in water while aluminium hydroxide showed a rather low adsorption property especially in HCl. The clinical significance of such interactions needs further biological investigation.

Introduction

Promethazine is a widely used antihistaminic drug belonging to the phenothiazine family. Phenothiazine derivatives have been shown to exhibit surface tension lowering effects (Zografi and Zarenda, 1966). This property gives them a tendency to accumulate at solid–liquid interfaces as readily as at solution–air interfaces. It was also suggested that the phenothiazine ring may hold an orientation on solid surfaces (Nogami et al., 1970). Various medicinally active phenothiazine derivatives were in fact found to be adsorbed to a great extent on many types of surfaces (Franz and Peck, 1982).

Antihistamines and phenothiazine derivatives are commonly used in the treatment of nausea and vomiting. Therefore, antacids may be recommended for concurrent therapy with such compounds. Antacids may affect the gastrointestinal (g.i.) absorption of other drugs and many modes of interactions have been described (Hurwitz, 1977). Moreover, the relatively small dose of antihistamines makes their potential interaction with other substances of significant importance on their bioavailability. Therefore, it was deemed of interest to determine if an in vitro interaction was evident between promethazine and some marketed antacid preparations via dialysis or simultaneous dissolution dialysis experiments. Adsorption of the

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drug on some components of the commercial formulations is also examined for elucidation of interaction mechanisms.

Experimental

Materials

Promethazine-HCl [1] was used as received. The commercial antacid preparations were used as provided from the manufacturer and are listed in Table 1. Common ingredients of the commercial products tested were: kaolin, bismuth carbonate, aluminium hydroxide, calcium carbonate and magnesium oxide, all of B.P. or B.P.C. grade, screened to a particle size of 90–100 μm. Avicel [2], Sta-Rx 1500 starch [3], magnesium stearate (B.P.) were also used in the present study.

Methods

Tablet preparation. Tablets were prepared by directly compressing 100 mg accurately weighed mixture consisting of 10% promethazine-HCl, 44% avicel, 44% Sta-Rx 1500 starch and 2% magnesium stearate using a hydraulic press [4] adjusted to 3217 kg/cm^2 pressure into flat-faced tablets (0.6 cm diameter). The average hardness [5] of the tablets was 4 kg, their disintegration time was 4 min in distilled water [6]. The drug content of the tablets was determined in 0.1 N HCl and was found to be within the range specified by the U.S.P.

Dialysis and dissolution-dialysis experiments. Segments of cellophane tubing [7] (15 cm long), thoroughly washed and hydrated, were carefully tied at one end. Internal medium consisted of 10 ml of 0.1 N HCl, distilled water, commercial antacid suspension I, II, III or IV or prepared suspension of the commercial antacid powder V, VI or VII (20% w/v in 0.1 N HCl or distilled water). 1 ml of the drug solution in 0.1 N HCl or distilled water was then placed inside the bag. The closed bags were attached around the baskets of a 6-channel dissolution apparatus (50 rpm) [8] and immersed into 1000 ml of 0.1 N HCl or distilled water, kept at 37°C. At various time intervals, 5 ml samples were automatically withdrawn and assayed spectrophotometrically at 250 nm [9]. Blanks of antacid preparations underwent the same procedure to correct for any absorption due to component in the formulation or to extraneous materials eluted from the antacid surface. It was checked that the absorbance of commercial preparations, if any, was relatively low, additive to drug solution and did not shift the λ_{max} of the drug. The pH values inside and outside the bags were checked before and at the end of the experiments. The relative viscosity of each antacid preparation was also determined. [10].

Adsorption experiments. 2 g quantities of adsorbent were placed in 100 ml glass stoppered conical flasks, then 50 ml of drug solution in either 0.1 N HCl or distilled water (ranging in concentration from 0.5 to 3.0 mg/100 ml) were added. Flasks were shaken (45 strokes per minute) at 37°C for 90 min. The suitably filtered samples, appropriately diluted, were analyzed for the remaining drug as previously mentioned. Control series containing identical initial concentrations of promethazine-HCl were treated similarly. A blank suspension of the adsorbent was prepared as well. The pH of the filtrates were also determined. In the case of aluminium hydroxide suspension in 0.1 N HCl, it was necessary to perform equilibrium dialysis experiments because of the difficulty in filtration of the colloidal supernatant. This was carried out by immersing the bags containing the suspension (0.8 g in 10 ml of 0.1 N HCl) into 10 ml of the drug solution in 0.1 N HCl, present in 50 ml stoppered conical flasks and shaken as mentioned above. After equilibrium, the drug content

[1] May and Baker, Ltd., Dagenham, Essex, U.K.
[2] F.M.C. Corp., U.S.A. (PH 101).
[3] Alexandria Pharmaceutical Company, Egypt.
[4] Carver Laboratory Press Model C, Fred S. Carver Inc., U.S.A.
[5] Erweka Apparatabeau, Frankfurt, F.R.G.
[6] U.S.P. Disintegration Apparatus.
[7] Spectrapor standard dialysis tubing (dry cylindrical diameter 16 mm, M.W.cutoff: 12,000–14,000); Fisher Scientific Co., 711 Farbes Ave. Pittsburgh, PA 15219, U.S.A.
[8] Hanson Research Corp., Northridge, CA 91324, U.S.A.
[9] Unicam SP 1800 spectrophotometer.
[10] Thomas-Stormer Viscometer, 9730-F10; Arthur H. Thomas Co., Philadelphia, PA 19105, U.S.A.

TABLE 1

AMOUNTS OF MAIN INGREDIENTS IN COMMERCIAL ANTACID PREPARATIONS (mg per 5 ml or 5 g)

Product	Symbol	Dosage form	Main ingredients					
			Aluminium hydroxide	Calcium carbonate	Bismuth carbonate	Magnesium carbonate	Magnesium hydroxide	Others
Mucaine [a]	I	suspension	300	–	–	–	100	–
Riopan [b]	II	suspension	–	–	–	–	–	magaldrate, 400
Gelcocaine [c]	III	suspension	405	–	–	–	70	–
Neogelco [c]	IV	suspension	405	–	–	–	70	–
Biskaol [c]	V	powder	–	1250	401	1125		sodium bicarbonate 625 kaolin 1000
Takazyma [d]	VI	powder	–	q.s.	480	830	–	–
Antazyme [e]	VII	powder	–	3350	440	750	–	–

[a] John Wyeth and Brother Ltd., Havant, U.K.
[b] Ayerst Laboratories, Montreal, Canada.
[c] Kahira Pharm. and Chem. Ind. Co., Cairo, A.R.E.
[d] Parke, Davis & Co., Hounslow, London, U.K.
[e] Misr. Co. for Pharm. Ind., Mataria, Cairo, A.R.E.

was then determined outside the bag. There was no significant change in the volumes of both the inside and outside media.

It is to be noted that the drug solutions used in the present study were freshly prepared, protected from light and were fairly stable under the experimental conditions used as regards time, temperature, pH and concentration which was below the stated c.m.c. (Attwood et al., 1974; Meakin et al., 1978; Stavchansky et al., 1983).

Results and Discussion

The results of the dialysis study of promethazine-HCl alone or in the presence of commercial antacid preparation, in either 0.1 N HCl or distilled water, are shown in Figs. 1 and 2 and Table 2. The pH values of the media used were considered to approximate those of the stomach and duodenum. In the latter, absorption of weak bases is expected to be optimum. The dialysis rate was

TABLE 2

COMPILED PARAMETERS OF DIALYTIC RATE CONSTANTS OF PROMETHAZINE HCl IN THE PRESENCE OF VARIOUS ANTACID PREPARATIONS; pH VALUES AND RELATIVE VISCOSITIES OF THE ANTACID SUSPENSIONS

Antacid *	K_1	K_2	K_f	$t_{50\%}$ (min)	pH_a	pH_b	η
Drug alone	0.2297	0.1758	0.0102	67.94	–	–	–
I	0.0203	0.0930	0.0019	364.74	7.5	5.5	145
II	0.0290	0.1020	0.0063	110	7.0	5.5	49
III	0.0097	0.0838	0.0055	126	9.0	5.5	1.8
IV	0.0203	0.0948	–	–	9.0	5.5	2.0
V	–	0.1312	0.0040	169.02	8.0	5.5	2.2
VI	–	0.0927	–	–	7.0	6.0	1.4
VII	–	0.0609	–	–	7.0	5.0	1.1

K_1 = apparent dialytic rate constant of the aqueous solution of the drug in water; K_2 = apparent dialytic rate constant of 0.1 N HCl solution of the drug in 0.1 N HCl; K_f = apparent dialytic rate constant of the drug tablets in 0.1 N HCl; $t_{50\%}$ = half life of promethazine-HCl tablets; pH_a = pH of the dialysis solution before starting the run in the presence of 0.1 N HCl; pH_b = pH of the dialysis solution at the end of the run in the presence of 0.1 N HCl; η = relative viscosity of the suspension in water.

* Symbols of antacid preparations used, as explained in Table 1.

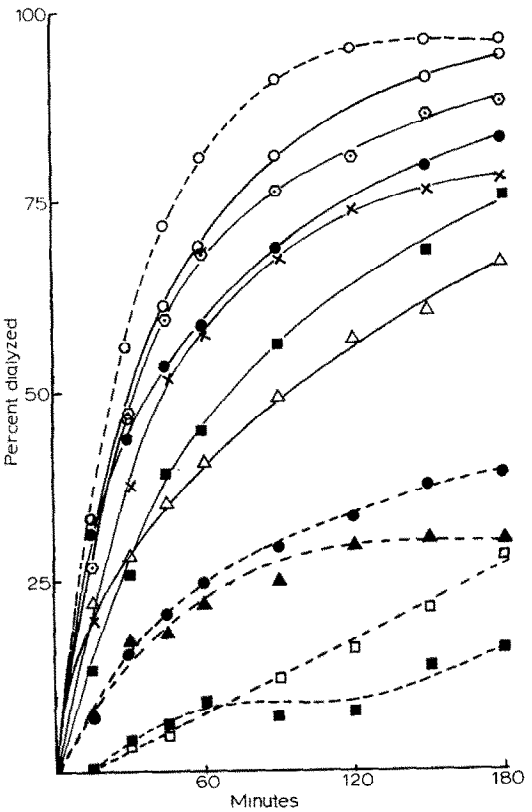

Fig. 1. Dialysis of promethazine-HCl in water (— — —) and in 0.1 N HCl (———), alone (○) and in the presence of I (▲), II (●), III (■), IV (□), V (⊙), VII (×) and VI (△).

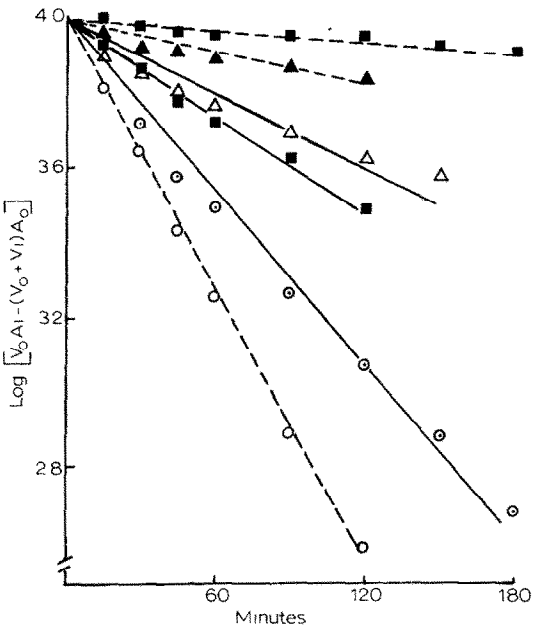

Fig. 2. Dialysis of promethazine HCl in water (— — —) and in 0.1 N HCl (———); alone (○) and in the presence of I (▲), III (■) and VI (△).

evaluated in terms of dialytic rate constant, an appropriate parameter for assessing the amount of drug available for absorption in the gastrointestinal test (Shah and Sheth, 1976).

The calculation of the dialytic rate constant K was carried out according to Davis et al. (1971) using an expression of Fick's law as follows:

$$\log[V_o \cdot A_i - (V_o + V_i)A_o] = -\frac{V_o + V_i}{2.3 \cdot V_i \cdot V_o} K \cdot t + \log(V_o + A_i) \qquad (1)$$

where t = time (in minutes); V_o = volume of the outside reservoir; V_i = volume inside the dialysis bag; A_o = amount of drug dialyzed into outside medium; A_i = amount of drug inside the bag.

In the present study, the ratio of the inside medium to the outside medium was 11/1000 so that sink conditions were maintained (Davis et al., 1971; Barzegar-Jalali and Richards, 1979). The straight lines obtained for all the dialysis experiments by plotting $\log[V_o A_i - (V_o + V_i)A_o]$ against t (Fig. 2), at least for 2–3 half-lives (Davis et al., 1971) demonstrate the appropriateness of the model. The values of K (Table 2) were calculated from the slope of the lines using the least-squares method.

The rate of dialysis is a function of the concentration of the drug in solution, the diffusion coefficient of the drug and the surface area of the dialyzing membrane. The dialysis of the drug alone in water showed a slightly higher rate than in HCl (Fig. 1). Previous studies (Davis et al., 1971; McGinity and Lach, 1976) on weak bases reported a higher dialysis rate for the uncharged drug moiety. Promethazine is a weak base ($pK_a = 9.08$) (Sorby et al., 1966). Therefore, the percent unionized drug will be slightly more in distilled water (pH = 5.5) than in 0.1 N HCl (pH = 1.2).

The commercial antacid preparations caused a

substantial decrease in the percentage drug dialyzed especially in water (Fig. 1). In fact, practically no drug was detected in the outside water in some cases e.g. with V, VI and VII during the whole time of the experiment. The values of K (Table 2) obtained in the presence of antacid preparations were consequently lower than those for the drug alone. The lowering effect of these preparations on the K value was as follows: V, VI, VII > III > I and IV > II. The corresponding sequence in HCl was: VII > III > VI > I > IV > II > V.

Possible adsorption of drug molecules on the surface of solid ingredients present in the commercial preparations tested could be responsible, in a great part, for the reduction observed in the dialysis rate. In addition, the commercial preparations may increase the bulk viscosity of the medium due to their gel properties, thus modifying the diffusion coefficient of the drug. Reduced dialysis rates as a result of an increase in the relative viscosity were reported previously (Shah and Sheth, 1976). From the results of viscosity measurement (Table 2), it could be seen that product I exhibited the highest relative viscosity. Although product III has the same formulation, its relative viscosity was substantially lower than product I. Moreover, its pH was higher (Table 2). The main ingredient of both I and III is aluminium hydroxide which has a diverse nature. Even batch-to-batch variation in the sedimentation volume, the viscosity, the caking and hence, in the surface charge density or zeta potential at the pH of the suspension, and in the zero point charge are known to exist in the manufacture of aluminium hydroxide suspensions (Shott, 1977).

The values of the dialytic rate constant obtained in 0.1 N HCl in the presence of the commercial products, were in all cases higher than in water (Table 2). The alkalinity imparting effect of the preparations might have an influence on the solubility of the drug (the pH values of the suspensions supernatant before and at the end of the experiment are shown in Table 2). It was observed that precipitation of the drug from solution (100 mg/100 ml) began to occur at pH $\simeq$ 8.5 at room temperature.

The pH of the medium (Table 2) may also affect the adsorption process through an influence on the physicochemical properties of both the drug and the ingredients of the formulation. At the lower pH obtained in HCl, the ionization of the drug will increase. The protonated form being more soluble is expected to have a lower tendency for adsorption unless a specific interaction with adsorption sites takes place.

Regarding the effect of pH on the adsorbance themselves, some changes in their physical properties were apparent at the end of the experiment, e.g. flocculaton in case of II and V, probably decreasing the number of available sites for adsorption. Also partial dissolution occurred in the case of IV and III, accompanied by a small increase in the volume of the inside medium due to osmotic effect. This latter effect would slightly modify the concentration gradient and therefore affect the dialysis rate.

The viscosity imparted to the medium by the ingredients of the commercial preparations may also be influenced by pH changes, due to change in the extension and cross-linking network of particles. A small pH change in the region of the zero point of charge of aluminium hydroxide was shown (Feldkamp et al., 1981) to produce a large change in the apparent viscosity.

The results of the dissolution-dialysis study are shown in Figs. 3 and 4 and Table 2. Conventional dissolution rate measurement methods are sometimes unsuitable for determination of the dissolution behaviour of drugs (Shah and Sheth, 1976). The rate of dialysis should serve as a more reliable index of the dissolution behaviour of the drug from tablets than dissolution rate (Papadimitriou and Sheth, 1978). A better discrimination between different systems is possible in the dialysis method because dissolution must first occur in a small volume of liquid and the dissolved drug must then be transported through a membrane; whereas in conventional dissolution methods, dispersal of the particles occurs and subsequent dissolution of the drug can take place in a large volume of dissolution medium. Moreover, the addition of the antacid suspensions to a large volume of agitated medium would lead to the fairly rapid dilution of the suspension ingredients. Thus, the effects of these ingredients on the dissolution of the drug are

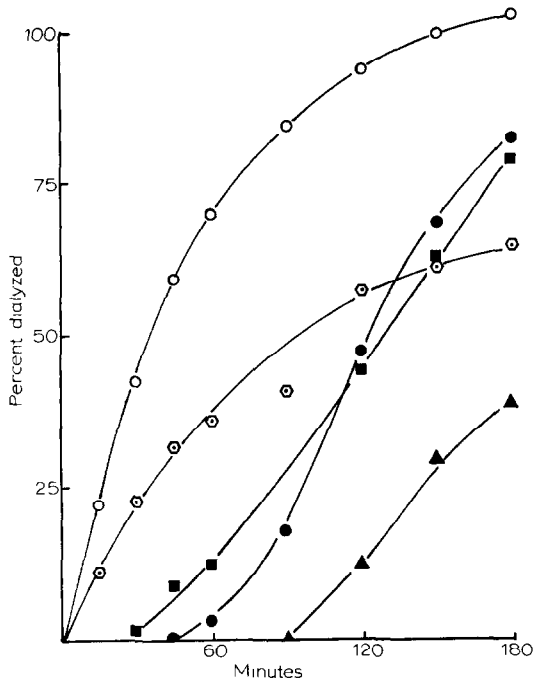

Fig. 3. Dissolution dialysis of promethazine HCl tablets in 0.1 N HCl alone (○) and in the presence of I (▲), II (●), III (■) and V (⊙).

likely to be much reduced when compared with their effects in the in vivo situation, particularly if the suspension is administered to fasting subjects. In the present method, the volume of liquid inside the dialysis sac is only 11 cm^3. A similar volume was used in a previous study (Barzegar-Jalali and Richards, 1979). Also the area of the dialyzing membrane should not be too small to prevent concentration build-up of dissolved drug inside the sac. Dialysis rate should be dissolution dependent and not permeation dependent (Papadimitriou and Sheth, 1978). In our work, the ratio of the area of the dialyzing membrane to the volume of liquid inside the sac $\simeq 5$. A ratio of ~ 3 was used by others (Barzegar-Jalali and Richards, 1979). Eqn. 1 was again applied but the amount of drug in solution at zero time (A_i) was taken as the amount of drug added to the system (10 mg of promethazine-HCl tablet) for the data treatment. Hence the values of K represent apparent dialytic rate constants. According to Barzegar-Jalali and Richards, Eqn. 1 may be rewritten as follows:

$$\log[V_o \cdot A_T - (V_o + V_i)A_o] = -\frac{K_F \cdot t}{2.303} + \log(V_o \cdot A_T) \quad (2)$$

K_F is a first-order rate constant for the release of drug into the liquid on the outside of the dialysis sac. The term $\log[V_o \cdot A_T - (V_o + V_i)A_o]$ represents the amount of drug remaining at any time. The constant K_F is related to K according to the equation:

$$K_F = \left[\frac{V_o + V_i}{V_o \cdot V_i}\right] K \quad (3)$$

The data obtained for the systems involved in this study gave linear graphs when plotted in accordance with Eqn. 1 or 2. The values of the apparent first-order rate constant K_F are given in Table 2 together with the corresponding half-lives ($t_{1/2}$) which were calculated from Eqn. 4:

$$t_{1/2} = \frac{0.693}{K_F} \quad (4)$$

In turn, the presence of commercial antacid preparations obviously reduced the percentage dialysis and therefore K_F of the drug especially in

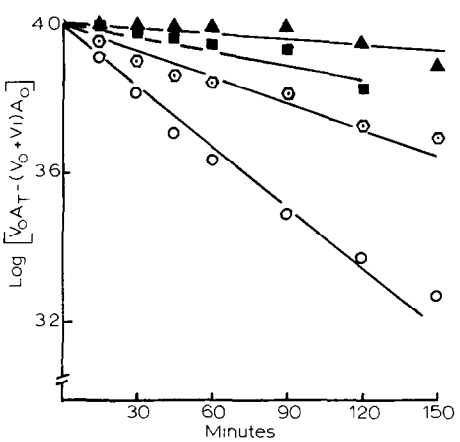

Fig. 4. Plot of the dissolution dialysis data for 10 mg tablets of promethazine-HCl in 0.1 N HCl; alone (○) and in the presence of I (▲), III (■) and V (⊙).

water where no measurable drug concentration could be detected outside the bag at any time of the experiment. Regarding the results obtained in HCl, the lowering effect of selected antacid preparations on K_F value of the drug was as follows: I > V > III > II. A lag period was observed in case of I > II > III (Fig. 3). However, steady-state diffusion was reached in time period ranging from 30 to 90 min (Fig. 4). This lag period was probably due to a retardation of the disintegration of the tablet and consequently of the dissolution of the drug, as a result of viscosity effects from the commercial preparations (Table 1). Drug particles may be entrapped in the gel structure of the antacids preventing easy access of the solvent. Also a higher viscosity in the microscopic regions surrounding the dissolved drug molecules would make them encounter a resistance in the diffusion process from the matrix to the dissolution medium.

Adsorption effects on the dialysis rate are expected to be more prominent in dissolution-dialysis experiments than in sink dialysis experiments, since in the latter case, the rapid dialysis of the drug from concentrated solution would not permit sufficient time for adsorption equilibrium to be achieved in the dialysis bag. An interesting case was that observed in the presence of product V (using HCl). Here, the K value for dialysis of the drug was 0.044 min^{-1}, whereas the corresponding K_F value for the dissolution-dialysis was only 0.004 min^{-1} (Figs. 1 and 3, and Table 2). This result could be due to effective adsorption probably occurring on the main components of the formulation, namely, kaolin and bismuth carbonate. It is to be noted that the pH inside the bag was $\simeq 5.5$ at the end of the experiment, showing that pH effect on drug solubility was not very important when HCl was used.

Adsorption studies in both distilled water and 0.1 N HCl were undergone to check for the previous assumption that adsorption of the drug on solid ingredients of the commercial preparations, may be for a great part, responsible in retarding drug dialysis. It is to be noted that drug concentrations used in adsorption experiments were small, thus minimizing the possibility of pH effect on drug solubility. Moreover, antacids like magnesium oxide, magnesium carbonate and calcium carbonate, exhibiting a high buffer capacity, adsorbed the drug to a lower extent than other ingredients of low buffer capacity, e.g. bismuth carbonate and kaolin in either HCl or water.

Phenothiazines are believed to have a strong tendency to leave an aqueous environment for a more non-polar medium (Zografi and Zarenda, 1966).

It could be seen that kaolin in both acid and water, gave a high percentage adsorption of the drug (98%) from an initial concentration of 1 mg/100 ml. The high adsorptive capacity of kaolin for phenothiazine derivatives was previously reported by Sorby (Sorby et al., 1966) who concluded that the adsorption results could not be attributed to one specific mechanism. Armstrong and Clarke (1976) indicated that the adsorptive mechanism of kaolin for basic drugs is believed to occur through the electrostatic charge on the kaolin surface and to a lesser extent to physical adsorption. A large number of negative sites capable of adsorbing cations is available on the larger area of the cleavage surface of the clay, outweighing the positive charge on the smaller edge face area. Moreover, the cleavage plane negative charge is unaffected by pH changes. Therefore, adsorption was about equally high in HCl and in water (pH of suspension 1.1 and 6, respectively). Preliminary elution test using water showed that practically no drug was released from the surface of the adsorbent.

In the case of bismuth carbonate, the high adsorption in HCl, relatively to water (Fig. 5) may indicate that the tendency for adsorption is higher for the protonated form of the drug (pH of the suspension in acid and water ~ 1.9 and ~ 6, respectively.

The shape of the isotherm obtained in HCl was substantially different from that obtained in water (Fig. 5(a)). A plateau region was formed early in case of water, giving rise to a Langmuir-type isotherm characterized by monolayer formation (Giles et al., 1960). In the case of HCl, the curve rose steadily without inflection to a level representing adsorption of several layers deep. The difference in the shape of isotherm arises from difference in the orientation adopted by the adsorbate molecules on the surface of the adsorbent as a result of

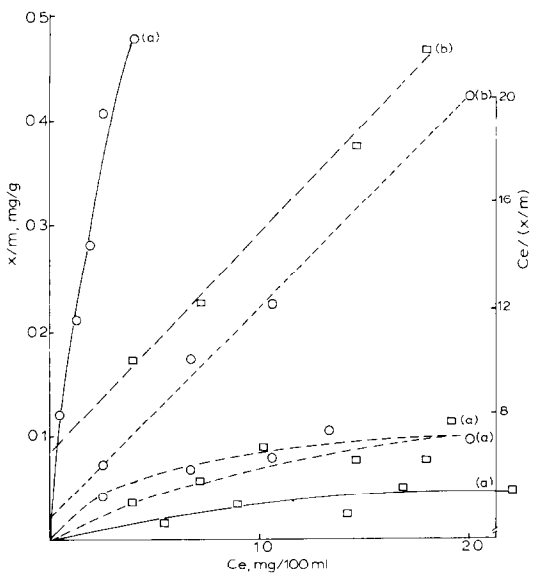

Fig. 5. Adsorption isotherm for promethazine-HCl on bismuth carbonate (○) and on aluminium hydroxide (□), in water (— — —) and in 0.1 N HCl (———). Key: (a) x/m vs Ce; (b) Ce/(x/m) vs Ce.

their affinity for both the adsorbent and the external medium. In the case of water, the drug molecules may get adsorbed on the adsorbent surface in such a way that when the monolayer is complete, they present to the solution, a new surface which has less attraction for bombarding drug molecules than the original surface had. Thus, a second layer builds up with difficulty. In the case of HCl, we may suggest a close packing of adsorbed molecules so that the surface they expose after adsorption has almost as high affinity for additional promethazine molecules as the original surface has. If the molecules in each subsequent layer are oriented as they are in the first, the affinity of the outer surface for an additional layer of drug will remain almost constant.

Kaolin and bismuth carbonate are the main ingredients of biskaol which showed itself about 97% adsorption for the drug in water, from an initial concentration of 1 mg/100 ml.

The results of adsorption of promethazine-HCl on aluminium hydroxide, indicated a rather poor adsorption capacity of the antacid compared to either kaolin or bismuth carbonate. The values obtained were lower than in water. This may be related to the intensity of the surface charge (Shott, 1977) present on aluminium hydroxide and to the amount of protonated promethazine molecules in relation to the pH of the medium (pH of suspension in HCl and water is ~ 3.35 and ~ 6, respectively). It is possible that the higher intensity of positive charge of both the drug and antacid at the lower pH value, decreased the adsorption tendency due to mutual repulsion. Moreover, the solubility of aluminium hydroxide varies with the pH of the medium (Kaehny et al., 1977). However, no substantial difference in the shape of the adsorption isotherms (Fig. 5(a)) could be detected when either HCl or water was the medium used.

The Langmuir plots for the adsorption of promethazine-HCl on either bismuth carbonate or aluminium hydroxide (using water) are shown in Fig. 5(b). The monolayer capacity was 0.125 and 0.122 mg/g, respectively, and were consistent with the values obtained from the plateau region of the adsorption isotherms. The affinity constant was 1.88 and 1.23 for the bismuth carbonate and aluminium hydroxide systems, respectively.

From these in vitro results, we may predict a possible interference in the adsorption of promethazine-HCl when co-administered with commercial antacid preparations. This interference may be serious since the ratio of the dose of the antihistamine to the amount of antacid is rather low. However, the clinical significance of such interaction needs further biological investigation.

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