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The uptake of ampicillin and amoxycillin by some adsorbents

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Summary

The in vitro uptake of ampicillin and amoxycillin by attapulgite, magnesium trisilicate, veegum and 3 types of kaolin has been studied. Adsorption data were obtained under conditions simulating in vivo with respect to changes in pH values, and the presence of electrolytes, a viscosity-imparting agent and a surfactant. Under all the conditions examined, amoxycillin was much less adsorbed than ampicillin. Desorption experiments at 37°C and pH values 2.0 and 6.5 showed only partial release of the adsorbed antibiotics; the maximum percentage was about 37 after 4 h. The presence of either veegum (1 g) or kaolin (4 g) in the dissolution medium (900 ml) did not significantly alter the level of ampicillin or amoxycillin in solution during dissolution testing of the capsule. The data obtained emphasize the importance of investigating in vitro adsorption of drugs under conditions simulating in vivo.

Introduction

Antacids and adsorbents in antidiarrhoeal products represent a potential source of interaction with co-administered drugs (Stockley, 1981). Wagner (1966) reported that the presence of a solid adsorbent can interfere with the absorption of drugs. Kaolin was found to affect the bioavailability of concurrently-administered drugs such as lincomycin (McCall et al., 1967; McGehee et al., 1968), digoxin (Albert et al., 1978) and oral hypoglycemic agents (Said and Al-Shora, 1980). Attapulgite, a

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recently introduced adsorbent in the BP, was found to adsorb a number of drugs (Sorby, 1965; Barr and Arnista, 1957; Evcim and Barr, 1955), and one report (Sorby and Liu, 1966) showed decreased absorption of phenothiazine derivatives in the presence of attapulgite. The ability of a grade of magnesium aluminium silicate (veegum) to adsorb a number of drugs (Nakashima and Miller, 1955; El-Nakeeb and Youssef, 1968) has been reported. Munzel (1971) showed that diazepam was adsorbed by veegum present in a liquid formulation, but in mice desorption occurred. Adsorbents such as kaolin and attapulgite are sometimes used with antibiotics (e.g. ampicillin) for the treatment of bacterial diarrhoea and cases of food poisoning and hence, the possible adsorption between the components cannot be ruled out.

Although in vivo testing appears to be the decisive approach in assessing drug–adsorbent interactions, the test may not be feasible in most cases. Properly designed in vitro experiments may be useful as a screening tool in drug–adsorbent interactions. The objective of the present work has been to examine the uptake and desorption of the two structurally-related antibiotics, ampicillin and amoxycillin, by some adsorbents under factors simulating in vivo condition.

Materials and Methods

Materials

Ampicillin (anhydrous) and amoxycillin (trihydrate) were of BP grade. The adsorbents used were: attapulgite, (regular grade [1]); 3 types of kaolin, namely, light kaolin (BP), natural kaolin (BP) and white fine kaolin (DAB7) [2]; a grade of magnesium aluminium silicate [3] and magnesium trisilicate (U.S.P.). The electrolytes used were of A.R. quality and other materials were of B.P.C. grade.

Adsorption experiments

In vitro adsorption studies were carried out at 37 ± 0.2°C by dissolving either ampicillin or amoxycillin in solutions having different pH values (2.1–7). Appropriate concentrations of either hydrochloric acid or sodium hydroxide were used to adjust the pH values. The use of buffer was avoided in view of the effect of buffer species on the extent of adsorption. Fifty ml of a solution containing 20–500 mg/100 ml of either drug were placed in a 100-ml stoppered conical flask containing the adsorbent (1 g). Attapulgite, magnesium trisilicate and veegum were pretreated with varying volumes of 0.3–0.6 N HCl for 1 h at 37 ± 0.2°C, to adjust the medium to the required pH value. The suspensions were shaken in a constant temperature water bath until equilibrium was attained (2 h). After centrifugation, the drug concentration remaining in the supernate was determined chemically by the method proposed by Angelucci and Baldieri (1971). Two replicate runs were made and the results averaged. To examine the effect of heat sterilization of kaolin on the extent of

[1] Pharmasorb Regular, Engelhard, Edison, N.J.
[2] E. Merck, Darmstadt.
[3] Veegum H.V. grade, Vanderbilt, N.Y.

adsorption, the 3 types of kaolin were heated at 160°C for 3 h. Adsorption experiments were performed on the heated and unheated samples.

Effect of electrolytes

The effect of some electrolytes on the extent of adsorption was examined over the concentration range 0–100 mmole at pH 2.1. Sodium chloride, sodium sulphate, sodium phosphate, calcium chloride, aluminium chloride and citric acid were used.

Effect of methylcellulose and polysorbate 80

The effects of 0.5% w/v methylcellulose and 50 mg% polysorbate 80 on the extents of adsorption of ampicillin and amoxycillin (on veegum) and ampicillin (on kaolin) were investigated at pH 2. The polymer and surfactant were separately equilibrated with the adsorbent for 1 h before addition of the drug solution.

Desorption experiments

The extent of elution of the adsorbed antibiotic was determined in two media of pH values 2.0 and 6.5. The residue obtained by cetrifugation of the suspension after the adsorption run, was digested in varying volumes of the desorption medium at 37°C. The amount of drug eluted was determined in an aliquot, after centrifugation, by the method of Angelucci and Baldieri (1971), over a period of 4 h.

In vitro availability in presence of adsorbents

Dissolution runs of capsules containing either ampicillin or amoxycillin were carried out in presence and absence of either veegum or kaolin. The dissolution experiments were performed in 0.01 N HCl using the U.S.P. paddle-stirrer apparatus at 100 rpm (1980). The dissolution medium (900 ml) containing either 1 g veegum or 4 g kaolin was maintained at 37 ± 0.2°C. At zero time, one capsule (size 0) containing 500 mg of either drug was allowed to sink to the bottom of the dissolution vessel before starting rotation. A small, loose piece of stainless steel wire was attached to the capsule to prevent it from floating. Samples were withdrawn at various time intervals and immediately replaced by fresh volumes of the dissolution medium to maintain a constant volume. The amount of the drug in solution was determined chemically.

Dialysis experiments

To investigate the possible binding of either drug with methylcellulose, the following dialysis experiment was carried out. Cellophane bags [4], prepared from Visking tubing 24/32 inch, were filled with 10 ml of solutions (pH 2.1) containing either 20 or 200 mg% of the antibiotic and 0.5% w/v solution of methylcellulose. The bags were immersed in 10 ml solution (pH 2.1) and shaken at 37 ± 0.2°C for 2 h. The volumes of both inside and outside solutions were accurately measured and the drug contents in both solutions were determined. Duplicate experiments were carried out and the results averaged. Preliminary experiments showed that no binding occurred of either ampicillin or amoxycillin to the membrane.

[4] The Scientific Instrument Centre (London).

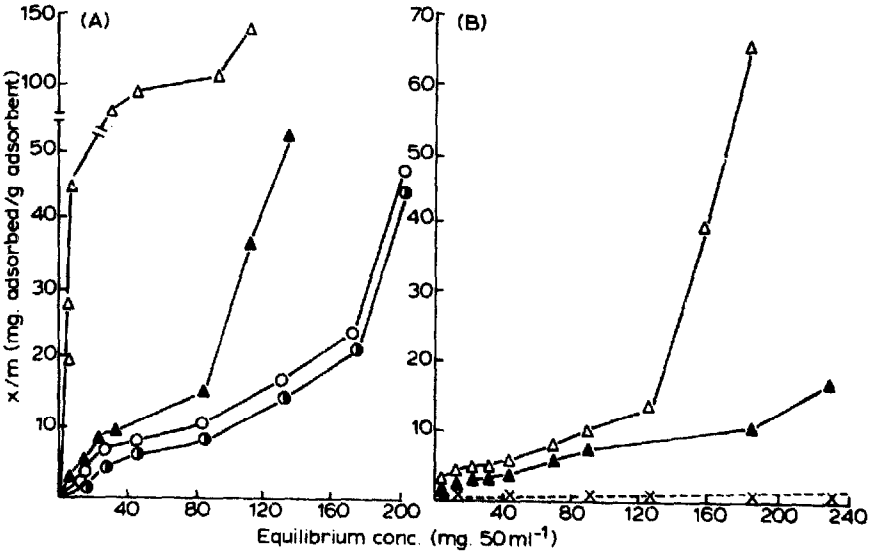

Fig. 1. Adsorption of ampicillin (A) and amoxycillin (B) at pH 2.1 by the adsorbents: (△) veegum; (▲) attapulgite; (⊙) light and natural kaolin; (◑) white kaolin; (×------×) composite plot for the 3 types of kaolin.

Results

Adsorption testing

Fig. 1 shows the adsorption plots of ampicillin and amoxycillin on the various adsorbents at pH 2.1. Ampicillin was adsorbed by veegum, attapulgite and the 3 types of kaolin whilst amoxycillin was adsorbed only by veegum and attapulgite but not by kaolin. For magnesium trisilicate, it was found that the hydrated silica gel,

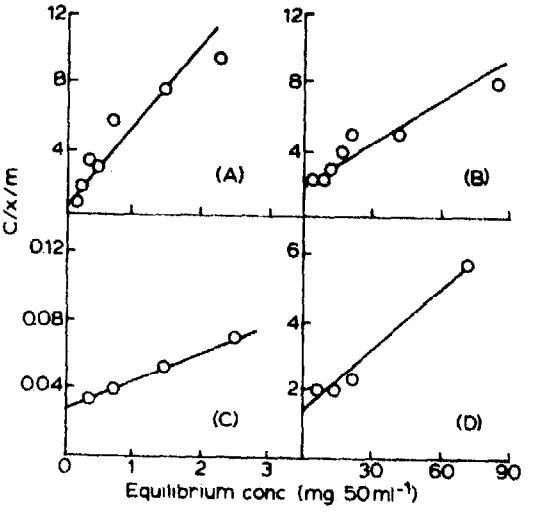

Fig. 2. Langmuir plots for the adsorption of ampicillin at pH 2.1: (A) combined plots for light and natural light kaolin; (B) white kaolin; (C) veegum; and (D) attapulgite.

TABLE 1

CALCULATED VALUES OF THE LANGMUIR CONSTANTS a AND b OF AMPICILLIN AND AMOXYCILLIN ADSORBED ONTO VARIOUS ADSORBENTS AS A FUNCTION OF pH

Parameter	Ampicillin								Amoxycillin			
	Light kaolin	Natural kaolin	White kaolin		Veegum				Attapulgite	Attapulgite	Veegum	
pH	2.1	2.1	2.1	3.2	2.1	3.2	4.3	5.2	2.1	2.1	2.1	3.2
a ($\times 10^3$)[a]	250	170	60	180	502	322	95	40	30	30	110	40
b ($mg \cdot g^{-1}$)[b]	8.5	8.3	12.0	4.0	66.3	51.8	24.6	13.7	19.6	8.4	5.6	7.2
r[c]	0.99	0.99	0.92	0.96	0.98	0.99	0.98	0.89	0.99	0.98	0.98	0.94

[a] The adsorption coefficient of the Langmuir plot.

[b] The reciprocal of the slope of the Langmuir plot (the limiting adsorptive capacity).

[c] Correlation coefficient.

formed from the decomposition of the antacid at pH 2.1, had no adsorptive effect on both drugs.

The adsorption data obtained fitted a Langmuir plot (Fig. 2). The Langmuir's constants 'a' and 'b' are shown in Table 1. At pH 2.1, the efficacy of the adsorbents followed the sequence: veegum > attapulgite > kaolin. Comparing the efficacy of the 3 types of kaolin, both light and natural types gave almost identical results whilst white kaolin showed slightly higher adsorptive property (Table 1).

Since heat sterilization is specified when kaolin is used in mixtures not freshly prepared, the effect of heating, at 160°C for 3 h, on the extent of adsorption was studied. For the 3 types of kaolin, no significant difference was found between the heated and unheated samples towards their adsorptive capacity of ampicillin.

On all the adsorbents studied, amoxycillin was found to be much less adsorbed when compared to ampicillin (Table 1).

The effect of pH on the extent of adsorption of ampicillin and amoxycillin is shown in Fig. 3. Within the pH range studied (2.1–7), both drugs were stable when maintained at 37°C for 2 h and decomposition did not exceed 2% at pH 2.1. The extent of ampicillin adsorption onto veegum and kaolin was pH-dependent; it decreased as the pH was increased. Ampicillin adsorption onto kaolin was insignifi-

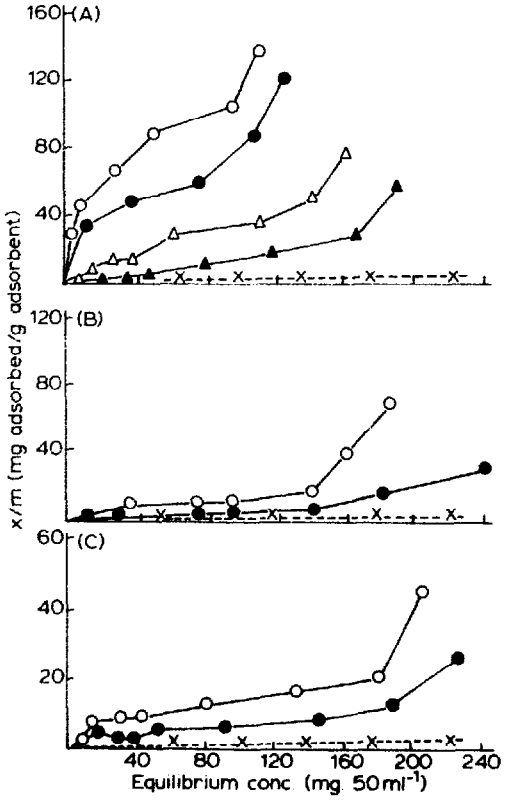

Fig. 3. Effect of pH on the extent of adsorption of ampicillin on veegum (A), amoxycillin on veegum (B) and ampicillin on kaolin (C). pH values: (⊙) 2.1, (●) 3.2; (△) 4.3; (▲) 5.2 (×- - - - - -×) composite plots for pH 6 and 7.0 (Fig. 3A). and for pH 4.3–7.0 (Fig. 3B and 3C).

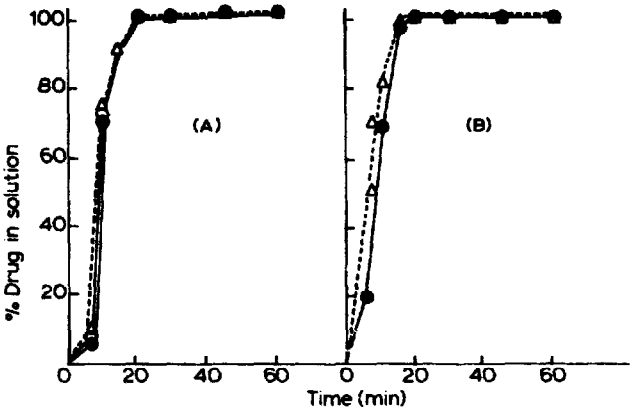

Fig. 4. Effect of the presence of adsorbents on the in vitro availability of ampicillin (A) and amoxycillin (B) during dissolution rate testing of 500 mg capsule of the drug in 900 ml of 0.01 N HCl (pH 2.1) at 37°C, using the paddle method (100 rpm). (Δ·–·–·Δ) no adsorbent; (○) is presence of 4 g light kaolin; (●) in presence of 1 g veegum.

cant within the pH range 4.3–7 (Fig. 3C). Relatively higher x/m values (mg adsorbed/g adsorbent) were obtained onto veegum over the pH range 2.1–5.2 (Fig. 3A). Again, amoxycillin was much less adsorbed than ampicillin on veegum (Fig. 3B). Also amoxycillin was not adsorbed to any significant extent by kaolin at all the pH values studied.

The effect of the presence of either kaolin (4 g) or veegum (1 g) on the in vitro availability of ampicillin or amoxycillin from hard gelatin capsules is shown in Fig. 4. The presence of both adsorbents in the dissolution medium had no apparent effect on the level of drug in solution; hence suggesting no uptake of either drug by the adsorbents under the conditions of the dissolution rate test.

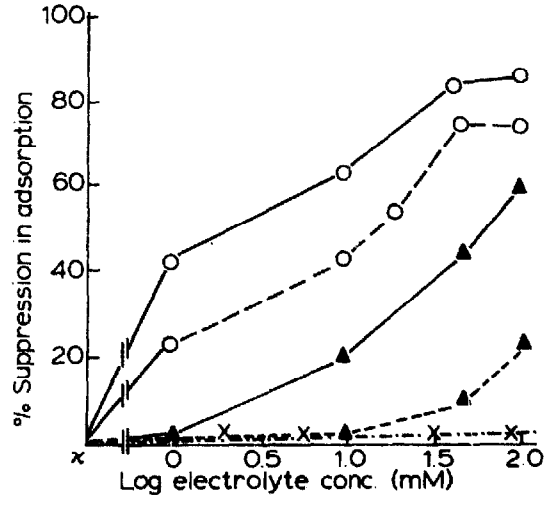

Fig. 5. Effect of some electrolytes on the percent suppression of adsorption of ampicillin (- - - - -) and amoxycillin (———) on veegum at pH 2.1. Electrolytes: (○) aluminium chloride; (▲) sodium dihydrogen phosphate; (× ·–·–· ×) composite plot for sodium chloride, sodium sulphate and citric acid. Initial drug concentration: 20 mg·100 ml^{-1}.

TABLE 2

EFFECTS OF 0.5% METHYLCELLULOSE AND 0.05% POLYSORBATE 80 ON PERCENT SUPPRESSION OF ADSORPTION OF AMPICILLIN (ONTO KAOLIN AND VEEGUM) AND AMOXYCILLIN (ONTO VEEGUM)

	% Suppression in adsorption of		
	Ampicillin on:		Amoxycillin on:
	Kaolin	Veegum	Veegum
0.5% methylcellulose	42.1	4.0	33.0
0.05% polysorbate 80 ($\gamma = 38.0\ N \cdot m^{-1}$)	34.5	16.6	43.3

Initial drug concentration: 400 mg·100 ml^{-1}.

Fig. 5 shows the effect of some electrolytes on the extent of adsorption of ampicillin and amoxycillin. Over the concentration range studied (1–100 mmoles) sodium chloride, sodium sulphate and citric acid had no apparent effect. On the other hand, both aluminium chloride and dihydrogen sodium phosphate suppressed the adsorption of both drugs; the effect being dependent on the electrolyte concentration and was more pronounced in ampicillin system.

Table 2 shows the effects of methylcellulose and polysorbate 80 on the percent suppression in adsorption of both drugs. Percentages suppression ranged from 4 to 42 in the presence of 0.5% of the polymer. Also, a reduction in the surface tension value from 69 to 38 $N \cdot m^{-1}$ suppressed the adsorption of the two drugs; percentages suppression ranged between 16.60 and 43.3.

Desorption testing

Table 3 shows the percent desorption at 37°C after 4 h as a function of the

TABLE 3

DATA OF PERCENT ELUTION AFTER 4 h AT 37°C OF AMPICILLIN AND AMOXYCILLIN ADSORBED ON KAOLIN AND VEEGUM, AS A FUNCTION OF VOLUME OF DESORPTION MEDIA

Volume of desorption medium (ml)	% Ampicillin eluted from kaolin		% Ampicillin eluted from veegum		% Amoxycillin eluted from veegum	
	pH 2.0	pH 6.5	pH 2.0	pH 6.5	pH 2.0	pH 6.5
50	6.3	11.9	14.4	33.0	16.3	35.1
250	6.5	11.9	15.9	33.7	15.5	35.1
500	7.5	12.7	19.1	35.9	16.3	36.5
900	6.7	12.8	22.8	34.1	15.2	35.4

Conditions of adsorption experiments were: 1 g adsorbent, 250 mg drug in 50 ml N/100 HCl (pH 2.1).

volume of desorption medium. In media of pH 2.0 and 6.5, only partial release of the adsorbed drug occurred (maximum of about 37%). Values obtained at pH 6.5 were about double those at pH 2.0. The percent drug desorbed was only slightly affected by changing the volume of the desorption medium from 50 to 900 ml.

Discussion

The mechanism of uptake of drugs by solid adsorbents is mainly dependent on the physicochemical properties of both the adsorbents and the drugs in the medium tested. In the present work, the two structurally-related antibiotics, ampicillin and amoxycillin, were found to be adsorbed differently by the various adsorbents

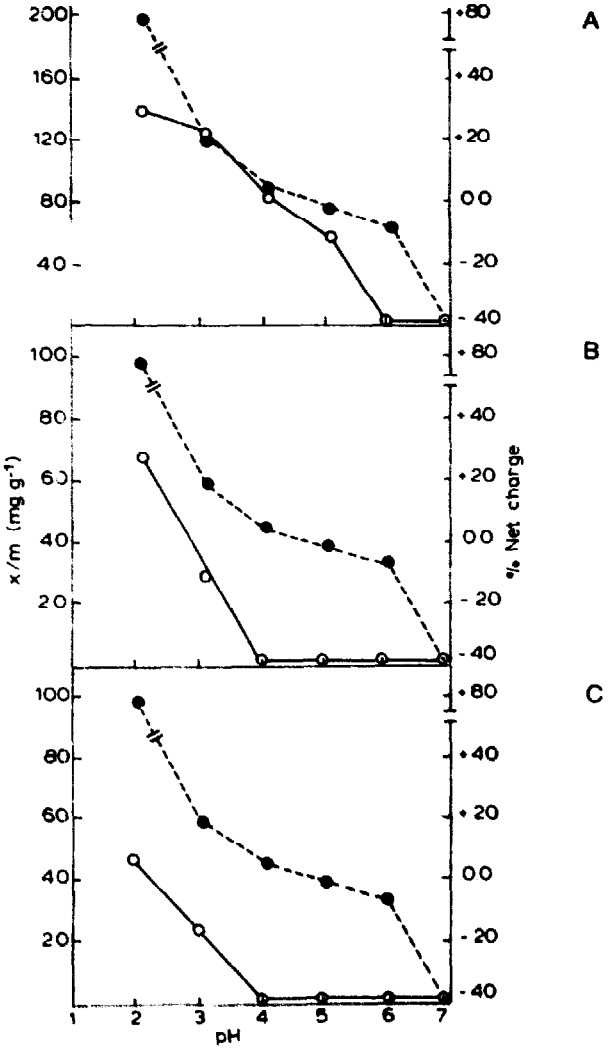

Fig. 6. Relationship between x/m values (O——O) and percent net charges on the drug (●- - - - -●) as a function of pH. Initial drug concentration: 500 mg·100 ml^{-1}. (A) ampicillin/veegum; (B) amoxycillin/veegum; (C) ampicillin/kaolin.

examined. Possible chemisorption occurred between the negatively charged silicate adsorbents and the cationic drugs. Since the two drugs possess the same pK_a values for the carboxyl and α-amino groups (2.6 and 7.2, respectively), it follows, therefore, that the percent ionization of both ionic groups (and hence the net charge) will be the same within the pH range studied. The presence of the polar phenolic group in amoxycillin structure was reponsible for the observed reduction in the uptake of the antibiotic by the various adsorbents.

Polar groups often suppress the extent of drug adsorption. This was evidenced when the extent of adsorption of the following drug pairs were compared: hyoscine–atropine (El-Masry and Khalil, 1974), digoxin–digitoxin (Khalil, 1974) and ethinyloestradiol–mestranol (Khalil and Iwuagwu, 1978). The presence of an ether oxygen (in hyoscine), an –OH group at C_{12} (in digoxin) and a phenolic –OH group (in ethinyloestradiol) produced significant reduction in the extent of adsorption of these drugs when compared to atropine, digitoxin and mestranol, respectively.

The effect of pH on the extent of adsorption revealed that the degree of protonation of the drugs significantly influenced the extent of adsorption. As shown in Fig. 6, an increase in the percent net positive charge caused an increase in the extent of adsorption on both veegum and kaolin, hence suggesting chemisorption between the cationic drug and the negatively charged silicate adsorbents. In addition, possible ion-exchange mechanism between the cations of the adsorbents (mainly Al^{3+}) and the cationic drugs is suggested. This is particularly the case for ampicillin adsorption at pH values 4.3 and 5.2 on veegum where the percent net charges on the drug will be 4(+) and 0.8(−), respectively. Under such conditions, ion-exchange is the possible mechanism of adsorption.

The observed suppression in adsorption in the presence of some electrolytes (Fig. 5) can be ascribed to the insulation of the ionic groups on both the drugs and the adsorbents by the oppositely charged ions of the electrolytes. Significant suppression was only caused by the trivalent aluminium and phosphate ions.

The incorporation of a hydrophilic colloid (methylcellulose) in the systems produced a significant reduction in the extent of adsorption. This is probably due to either drug binding by the polymer or coating of the adsorbent surface by the polymeric film. The results of dialysis experiments revealed no significant binding of either drugs to methylcellulose. Therefore, the observed suppression in adsorption can be attributed to the property of the polymer as a protective colloid. A similar finding was found for the suppressive effect of some polymers on the adsorption of benzoic acid by sulphadimidine (Khalil and Nasipuri, 1973). A reduction in the surface tension from 69 to 38 $N \cdot m^{-1}$ produced a reduction in the extent of adsorption. Again, this is due to the positive adsorption of the surface active agent on the adsorbent thus reducing the extent of drug adsorption.

The partial desorption of both drugs in the presence of increasing volumes of the medium (from 50 to 900 ml) suggests a chemisorption mechanism. Also, the increase in the level of drug desorbed by increasing the pH value from 2.0 to 6.5 supports the above suggestion.

The data reported in the present work emphasize the need for investigating in

vitro adsorption of drugs under conditions simulating in vivo. Some factors such as pH, and the presence of a hydrophilic polymer and a surfactant were found to influence the extent of adsorption of the drugs in the systems studied. In vivo evaluation of the interactions cited here should be done in order to assess the level of such interactions.

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