Retardation of stem elongation and inhibition of plant growth were greater with the combination of retardant and DMSO than when the retardant was employed alone. The phytotoxicity of the CCC was increased with DMSO. The total alkaloid content per plant of the groups receiving the combined treatment was reduced to a greater extent than when retardant was used alone. The greatest decrease, 55%, was found in the group treated with CCC plus DMSO.

B995 is preferred to CCC when growth retardation by the spray method is desired in *Datura* spp. Phytotoxicity is lacking with B995 solutions up to a 2% strength (20,000 p.p.m.), and the inhibition of plant growth (dry weight) is not so drastic as that noted with CCC. DMSO appears to potentiate the response of plants to the retardant. In all cases, the dry matter content of the treated groups was less than the controls. This indicates that the biosynthesis and/or accumulation of carbohydrates, proteins, or similar components were depressed. The shoot–root ratios of the treated groups were generally less than controls. Some of the effects noted on plants treated with either retardant suggest that the mechanism of action of the growth retardant is antigibberellin in nature.

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In Vitro Adsorption of Some Anticholinergic Drugs by Various Antacids

By SEYMOUR M. BLAUG and MILTON R. GROSS*

The adsorption of some anticholinergic drugs from aqueous solution by six different antacids was studied. The results obtained were plotted and interpreted according to the Langmuir adsorption isotherm. The adsorptive power of the six antacids varied with the anticholinergic drug being studied. Of the nine anticholinergics investigated, atropine sulfate, methantheline bromide, propantheline bromide, and oxyphenonium bromide were adsorbed to the greatest extent. Magnesium trisilicate showed the highest adsorptive capacity of the antacids studied. The reversibility of the adsorption process was studied using methantheline bromide and propantheline bromide. Magnesium trisilicate retained the largest amount of either of the two drugs. The effect of pH and ionic strength on the adsorption of methantheline bromide and propantheline bromide was investigated.

IN MODERN therapeutics, anticholinergic drugs are often administered in combination with antacids. The adsorption effect of certain antacids on atropine and other anticholinergics has been reported in the literature. Schloss (1) noted the adsorption and destruction of atropine by magnesium oxide. Dey and Haar (2) found that after grinding belladonna extract or powdered belladonna leaves with magnesium oxide, not all the atropine was recovered and that the amounts recoverable decreased with time. Heubner and Haas (3) found that when belladonna extract was combined with bismuth subnitrate or magnesium oxide, the loss in atropine activity was 93–97%. However, even before destruction, atropine was so firmly held that only a slight amount was released by 0.1 *N* hydrochloric acid. Experiments carried out on rats showed that when atropine was administered with adsorbing powders, half of the activity was retained (4) at the most.

The effect of dry aluminum hydroxide gel and dihydroxy aluminum aminoacetate on the acetylcholine action of atropine has been evaluated (5). Both were found to decrease the activity of atropine. Ogakurayama *et al.* (6) found that oral administration of preparations containing adsorbents with atropine must be avoided since the alkaloid was not released in the stomach or intestine and thus was ineffective.

Seifter *et al.* (7) evaluated the effect of aluminum hydroxide gel and hydrated alumina powder on the intensity and duration of action of

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anticholinergic drugs in rats. The gel retarded slightly the intestinal absorption of the drugs but did not influence the activity.

Grote and Woods (8, 9) conducted a study of the adsorption effects of various aluminum antacids upon simultaneously administered anticholinergic drugs. Their method consisted of determining the mouse LD_{90} dose for the drug to be tested, then giving the same dose of drug in admixture with the aluminum preparation to determine if the same LD effect was obtained after admixture as previously. Aluminum hydroxide magmas showed marked adsorption with atropine sulfate, homatropine hydrobromide, and belladonna alkaloids as sulfates and had little or no effect with homatropine methylbromide. Dihydroxy aluminum aminoacetate showed less adsorption. Neither of these two antacids showed marked adsorption with propantheline bromide. However, there was a marked adsorption of tridihexethyl chloride by aluminum hydroxide magmas and only slight adsorption by dihydroxy aluminum aminoacetate.

Zupko (10) investigated the adsorption effects of hydroxy aluminum magnesium aminoacetate and other aluminum antacids for six anticholinergics. The greatest adsorption was shown by a freshly prepared magma made from aluminum hydroxide dried gel. The least adsorption was with hydroxy aluminum magnesium aminoacetate and dihydroxy aluminum aminoacetate.

This study was undertaken to investigate *in vitro* the adsorption phenomena that had been reported in animal studies. The purpose was to determine the extent of adsorption of the anticholinergics by the antacids, the reversibility of the adsorption process, and the effect of pH, ionic strength, and concentration. This type of *in vitro* data is significant in respect to formulation of dosage forms containing combinations of these types of drugs. It also indicates possible unforeseen complications when the individual drugs are exposed to each other in the gastrointestinal tract by virtue of simultaneous or proximal administration.

EXPERIMENTAL

Reagents.—Aluminum hydroxide dried gel U.S.P., light magnesium carbonate U.S.P., calcium carbonate U.S.P., magnesium trisilicate U.S.P., dihydroxy aluminum aminoacetate[1] (DAA), dihydroxy aluminum sodium carbonate[1] (DASC), methantheline bromide,[2] propantheline bromide,[2] trihexyphenidyl hydrochloride,[3] tridihexethyl chloride,[3] oxyphenonium bromide,[4] amprotropine phosphate,[5] ambutonium bromide,[6] homatropine methylbromide, and atropine sulfate were employed.

Method.—The procedure used to study the adsorption of various anticholinergics from aqueous solution by solid adsorbents was similar to that reported (11–13) in the literature. One-gram quantities of antacid powder were weighed accurately and transferred to 125-ml. glass-stoppered bottles. A standard aqueous solution was prepared for each anticholinergic drug. An accurate volume of the standard solution was added to each bottle to give the desired anticholinergic concentration, approximately 1.0 to 4.0 mg. per milliliter, and the volume of each bottle was brought to 50 ml. with distilled water. The bottles were placed in a mechanical shaker in a constant-temperature bath and equilibrated at 30 ± 0.1° for 24 hours. It was established previously that equilibrium was attained within this period. At the end of this time, an aliquot portion of the supernatant liquid was removed and analyzed spectrophotometrically for residual anticholinergic drug concentration using a Beckman model DU spectrophotometer.

The quantity of anticholinergic drug adsorbed by the antacid was determined by subtracting the equilibrium concentration from the initial concentration. For each anticholinergic studied, a control bottle was prepared which differed from the other bottles only because the control bottles contained no antacid. Drug concentration in each control bottle remained constant; hence, no degradation of drug occurred at the temperature and equilibration time used in the study.

It was impossible to study adsorption or elution using artificial gastric juice U.S.P. since, with the addition of acidic solvent, the antacid dissolved slowly.

For the determination of atropine sulfate, the modified spectrophotometric method of Kondritzer and Zvirblis (14) was used.

All the adsorbent powders were in a fine state of subdivision. The average diameters fell in the colloidal dispersion range of 0.5 to 5 μ determined with the Fisher subsieve sizer according to the method of Gooden and Smith (15).

To ascertain the effect of ionic strength on the adsorption, methantheline bromide and propantheline bromide were selected for further study. Sodium chloride, sodium sulfate, and sodium citrate, in concentrations ranging from 0.1 to 1.0 M, were added to the bottles and allowed to equilibrate 24 hours. Aliquots were withdrawn and assayed as described above.

A series of determinations was carried out to discover if either methantheline bromide or propantheline bromide was held irreversibly by any of the adsorbents. The samples were equilibrated as before, and the amount initially adsorbed was determined. The supernatant liquid was filtered off; 50 ml. of distilled water was added to the remaining adsorbent–adsorbate mixture, and this new suspension was agitated in the constant-temperature bath. After a suitable length of time, this supernatant was analyzed for any anticholinergic drug that

[1] Supplied by the Brayten Pharmaceutical Co., Chattanooga, Tenn.
[2] Supplied as Banthine Bromide and Pro-Banthine Bromide, respectively, by G. D. Searle and Co., Chicago, Ill.
[3] Supplied as Artane Hydrochloride and Pathilon Chloride, respectively, by Lederle Laboratories, Pearl River, N. Y.
[4] Supplied as Antrenyl Bromide by Ciba Pharmaceutical Products, Summit, N. J.
[5] Supplied as Syntropan Phosphate by Roche Laboratories, Nutley, N. J.
[6] Supplied by Wyeth Laboratories, Philadelphia, Pa.

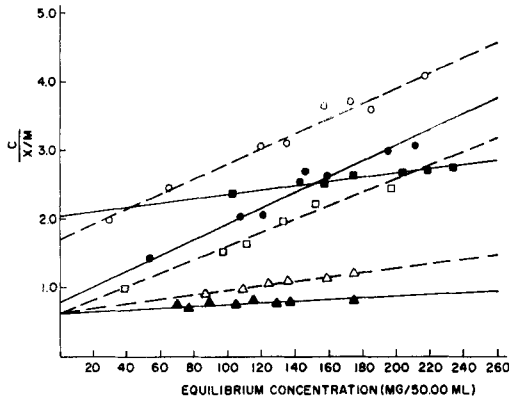

Fig. 1.—Adsorption isotherms for atropine sulfate by various antacids. Key: O- - -O, $Al(OH)_3$; ●——●, DASC; □- - -□, $CaCO_3$; ■——■, DAA; △- - -△, magnesium trisilicate; ▲——▲, $MgCO_3$.

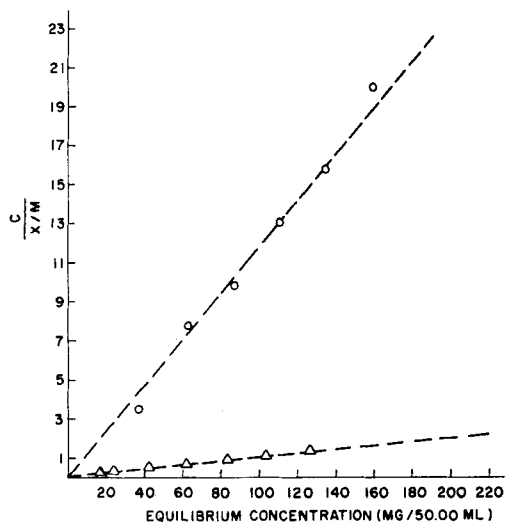

Fig. 2.—Adsorption isotherms for tridihexethyl chloride. Key: O- - -O, $Al(OH)_3$; △- - -△, magnesium trisilicate. No adsorption for $CaCO_3$, $MgCO_3$, DASC, or DAA.

might have been eluted from the antacid. This procedure was repeated a number of times until there was no further drug in the supernatant, or the amount was minute.

The effect of pH on the adsorption of methantheline bromide and propantheline bromide on aluminum hydroxide was studied using 0.3 *M* phosphate buffer to adjust the pH of the final antacid suspension to various pH values. The samples were equilibrated and assayed as described previously.

RESULTS AND DISCUSSION

The data obtained can be represented best by the Langmuir equation (16)

$$\frac{x}{m} = \frac{abc}{1 + ac} \qquad \text{(Eq. 1)}$$

where x/m is the weight of drug in milligrams adsorbed per gram of adsorbent, c is the equilibrium concentration of drug in milligrams, and a and b are constants. Constant a is related to the forces involved in binding the adsorbate molecules to the surface of the adsorbent, and constant b is the maximum amount of drug which can be adsorbed per gram of adsorbent; hence, it is a measure of the adsorptive capacity of adsorbents. According to Brunauer (17), these constants are not empirical or arbitrary.

The linear form of the Langmuir equation derived from Eq. 1 is

$$\frac{c}{x/m} = \frac{1}{ab} + \frac{c}{b} \qquad \text{(Eq. 2)}$$

Linear curves with a slope of $1/b$ and an intercept of $1/ab$ are obtained by plotting $c/(x/m)$ against c. Adsorption isotherms for the compounds used in this study were plotted according to Eq. 2. Figures 1 and 2 are typical of the phase diagrams obtained.

These isotherms show that the extent of adsorption by any one antacid depends on the compound being adsorbed. For example, adsorption by calcium carbonate ranged from absence of adsorption to definite adsorption, while magnesium trisilicate exhibited marked adsorption for all the compounds studied.

In addition to the isotherms themselves which reveal to a certain extent the degree of adsorption, the b values or limiting adsorptive capacities were calculated. The results are shown in Table I.

TABLE I.—LIMITING ADSORPTIVE CAPACITIES OF ANTACIDS FOR ANTICHOLINERGIC DRUGS, mg./Gm.

	$MgCO_3$	DAA	Mag. Tri.	$CaCO_3$	$Al(OH)_3$	DASC
Atropine sulfate	955[a]	312	308	105	92	91
Methantheline bromide	100	51	191	89	94	74
Propantheline bromide	27	[b]	154	14	38	15
Oxyphenonium bromide	43	[b]	118	43	35	177
Tridihexethyl chloride	[c]	[c]	100	[c]	8	[c]
Homatropine methylbromide	57	42	111	9	28	84
Amprotropine phosphate	49	[b]	61	49	[b]	[b]
Ambutonium bromide	[c]	85	118	[c]	[c]	[c]
Trihexyphenidyl hydrochloride	[d]	103	[d]	[d]	152	[d]

[a] High value probably due to decomposition of atropine at pH of suspension. [b] Adsorption not determined. [c] No adsorption. [d] Trihexyphenidyl hydrochloride precipitated at pH of suspension.

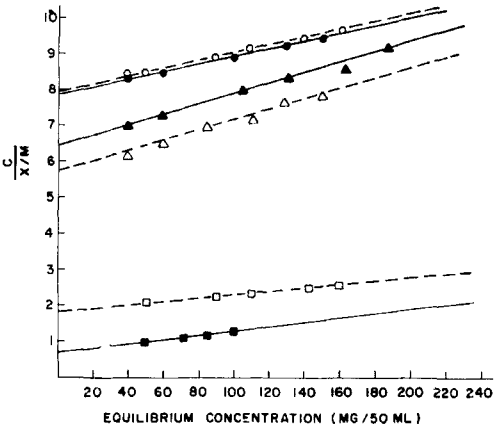

Fig. 3.—Adsorption isotherms for methantheline bromide by various antacids at different concentrations. Key: ●———●, $MgCO_3$ (1.0 Gm.); O- - -O, $MgCO_3$ (0.25 Gm.); ▲———▲, DASC (0.25 Gm.); Δ- - -Δ, DASC (1.0 Gm.); ■———■, magnesium trisilicate (1.0 Gm.); □- - -□, magnesium trisilicate (0.25 Gm.).

It was necessary in most cases to use 1-Gm. samples of the antacid adsorbents to find adherence to the Langmuir equation over a wide anticholinergic concentration range. When less than 1 Gm. of adsorbent was used, deviations from linearity occurred at low concentrations of anticholinergic drug. However, in some cases, less than 1 Gm., 250 mg., did adsorb the compounds in conformity to the equation. Figure 3 shows a comparison of the isotherms plotted for these two concentrations of adsorbents.

With DAA, propantheline bromide, and oxyphenonium bromide, it was impossible to analyze the supernatant liquids since neither filtration or centrifugation resulted in a solution sufficiently clear to analyze with the spectrophotometer. This phenomenon has been noted by the "Merck Index" for DAA (18). The same problem was encountered with amprotropine phosphate and all three of the aluminum antacids; this might be due in part to the effect of the phosphate ion.

From the foregoing data, the adsorption of the anticholinergics by the antacids used in this study shows a variable quantity; *i.e.*, with the antacids used, no single compound was the superior adsorbent for all the anticholinergics. On the whole, magnesium trisilicate showed the highest adsorptive capacity on the basis of amounts actually adsorbed and the calculated *b* values. The other antacids, in most cases, adsorbed the drugs to a lesser extent; this too was reflected in lower *b* values.

Chemically, the anticholinergics studied varied considerably. Four were esters containing quaternary ammonium salt functions: methantheline bromide, propantheline bromide, oxyphenonium bromide, and homatropine methylbromide. Tridihexethyl chloride was a quaternary ammonium alcohol, ambutonium bromide was an amide with a quaternary ammonium function, trihexyphenidyl hydrochloride an *N*-substituted piperidine, and atropine sulfate and amprotropine phosphate were esters containing tertiary amino groups. Each of these compounds contains a powerful anchoring group and one or more additional groups sufficiently polar to anchor to some extent to a hydrophilic receptor site.

With atropine sulfate and magnesium carbonate, the unusually high value calculated for *b*, the limiting capacity, can probably be explained on the basis of the effect of the pH of the suspension. The final pH of the magnesium carbonate–atropine sulfate mixture was such that some loss of atropine occurred due to hydrolysis of the ester (19). Thus, if some atropine hydrolyzed, it would not show up in the spectrophotometric assay procedure, and it would be impossible to determine if disappearance of atropine from the supernatant liquid was due to adsorption or hydrolysis.

It might be suspected that the alkalinity of the magnesium trisilicate suspension would account for its strong adsorptive capacities. In an alkaline suspension, the acid salts of the anticholinergic drugs would be converted to some extent, depending on their individual pKa values, to their respective free bases. The free bases, less soluble than the salts in water, would be more readily adsorbed since it has been previously shown (20, 21) that the ability to be adsorbed is inversely proportional to solubility. However, this cannot account entirely for this effect with magnesium trisilicate, as suspensions of magnesium carbonate and DASC also have high pH values, and their adsorptive capacities were not comparable to those of magnesium trisilicate. It would seem that other factors are involved.

Aside from the unusually high value obtained with magnesium carbonate, most of the antacids showed relatively high adsorptivity for atropine compared to the other anticholinergic drugs. The two other carbonate type antacids produced relatively similar adsorption isotherms, a result that was also found with the other anticholinergic drugs. The similarity in chemical structure, suspension pH, and other properties no doubt accounted for this. DAA and magnesium trisilicate had the highest adsorptive capacities for atropine, an indication that pH was not entirely responsible for high adsorption. The pH of a DAA suspension was lower than that of a magnesium trisilicate suspension.

Homatropine methylbromide, structurally similar to atropine, was adsorbed to a lesser extent by all the antacids studied. For example, the *b* value with calcium carbonate for atropine was 105; that for homatropine was only 9. In a consideration of the close chemical structure, it was assumed that quaternization of the nitrogen in the molecule affected its adsorption.

Again in a consideration of the similarity in molecular structure, it might have been anticipated that methantheline bromide and propantheline bromide would be adsorbed to the same extent. However, the results show that methantheline bromide, both from the actual amounts adsorbed and the calculated *b* values, was adsorbed to a greater extent than propantheline bromide. There was greater diversity in the *b* values, as shown in Table I, than in the amounts actually adsorbed.

The difference in the calculated limiting adsorption capacities might be explained on the basis of a steric effect caused by the different substituents on the nitrogen atom in the structures. The two bulky isopropyl groups on propantheline bromide (β-diisopropylaminoethyl 9-xanthene carboxylate metho-

TABLE II.—ADSORPTION COEFFICIENTS FOR METHANTHELINE BROMIDE AND ANTACIDS

Antacid	Adsorption Coefficient, $a \times 10^3$
Magnesium trisilicate	7.0
DASC	2.3
Calcium carbonate	1.6
Aluminum hydroxide	1.3
Magnesium carbonate	1.2

bromide) occupy a greater area in space than the relatively smaller ethyl groups of the methantheline bromide (β-diethylaminoethyl 9-xanthene carboxylate methobromide). This might offer greater resistance to the weak adsorptive forces, and it might also be expected that fewer propantheline bromide molecules can be adsorbed onto a similar surface area of adsorbent compared to the methantheline bromide molecules.

Tridihexethyl chloride (3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol ethochloride) and trihexyphenidyl hydrochloride [3-(1-piperidyl)-1-cyclohexyl-1-phenyl-1-propanol hydrochloride] also are similar structurally since both are amino alcohols; the only difference is the substitution on the nitrogen atom. Yet tridihexethyl chloride was not adsorbed by DAA, whereas trihexyphenidyl hydrochloride exhibited a *b* value of 103 mg./Gm. of DAA.

Again, steric effects probably accounted for the differences in *b* values noted for tridihexethyl chloride and trihexyphenidyl hydrochloride. The three ethyl groups reaching out into space may offer resistance to the adsorptive forces and occupy greater space than the piperidyl group, which has a somewhat streamlined effect, because the carbon atoms attached to the nitrogen are under a strain and are in effect pinned back and out of the way.

Unfortunately, it was impossible to demonstrate this conclusively with all the antacids since the pH of the suspensions of magnesium trisilicate, magnesium carbonate, calcium carbonate, and DASC was sufficiently high to force the trihexyphenidyl hydrochloride out of the solution. However, with aluminum hydroxide, which adsorbs both compounds, there was definitely lower adsorption with tridihexethyl chloride. There was no adsorption of tridihexethyl chloride by calcium carbonate, magnesium carbonate, DASC, or DAA.

Oxyphenonium bromide and amprotropine phosphate are both esters; the former is a quaternized compound. However, there was no correlation between the adsorption of these compounds and the other compounds similar in chemical structure.

Ambutonium bromide, which also possesses a quaternized nitrogen in its molecule, was adsorbed only by DAA and magnesium trisilicate. It was the only compound studied that contained an amide function. However, it has approximately the same spatial relationship of polar and nonpolar groups as the other compounds studied.

The results obtained in this *in vitro* study of the adsorption of anticholinergic drugs by antacids can be compared to a certain extent to the *in vivo* work of other investigators when the combination of compounds used was the same. However, the ratios of antacids to anticholinergics employed in this study were not the same as those reported in the *in vivo* studies.

Grote and Woods (8, 9), using the mortality rate of mice as in indication of adsorption, found that aluminum hydroxide had a marked adsorption for tridihexethyl chloride, while DAA showed only slight adsorption. This agreed with the findings in this study, where DAA did not adsorb tridihexethyl chloride, while aluminum hydroxide did. They also found that propantheline bromide was only slightly adsorbed by aluminum hydroxide; this study found that only about 5% of added propanthline bromide was adsorbed. In both studies, homatropine methylbromide was adsorbed to a lesser degree than atropine sulfate by all the antacid drugs tested.

The results with atropine sulfate differed because this study had a higher adsorption with DAA than with aluminum hydroxide. The opposite was true in the *in vivo* study. However, this may be explained on the basis of retention ability of the respective antacids for atropine.

Zupko (10), using a similar procedure, found that almost twice as much methantheline bromide was adsorbed by aluminum hydroxide as by DAA. This agreed with the *b* values calculated for these combinations in this study. For aluminum hydroxide, *b* was 97 mg./Gm.; for DAA, *b* was 51 mg./Gm.

The retention of methantheline bromide by the six antacids used in this study was correlated with the calculated adsorption coefficients, *a*. Correlation would seem likely since the adsorption coefficient is related to the force of binding between adsorbent and adsorbate. Adsorption coefficient values are shown in Table II. Thus, magnesium trisilicate showed the highest adsorption coefficient and retained the largest amount of methantheline bromide. Magnesium carbonate had the lowest adsorption coefficient and the weakest retentive powers. The results of the retention studies are shown in Fig. 4.

From the ease with which most of the adsorbed molecules were desorbed, it can be concluded that adsorption was probably of the type known as physical or van der Waals adsorption. This type of adsorption is characterized by weak adsorptive forces.

When two different initial concentrations of the same drug on the same antacid were eluted by the above procedure, the final concentration retained approached the same value.

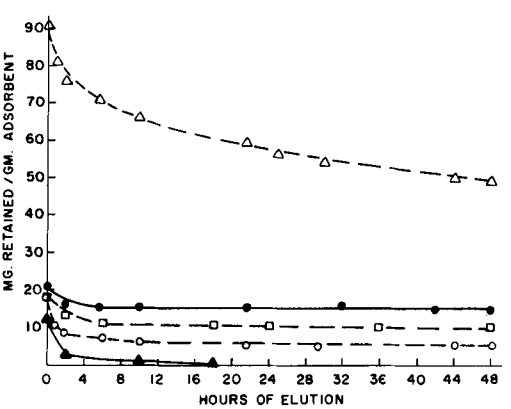

Fig. 4.—Retention of methantheline bromide by 1.0 Gm. of antacids. Key: O- - -O, $Al(OH)_3$; ●- - -●, DASC; □- - -□, $CaCO_3$; △- - -△, magnesium trisilicate; ▲——▲, $MgCO_3$.

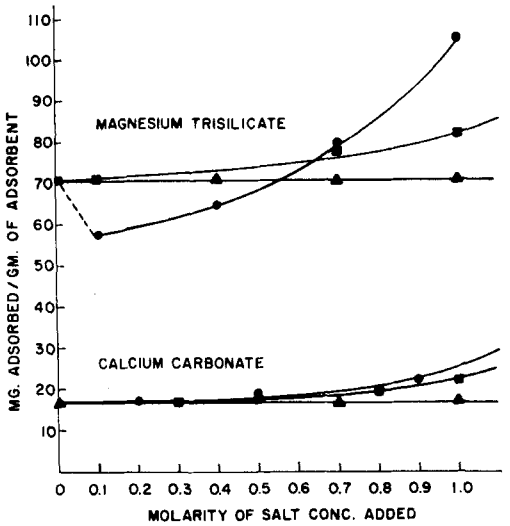

Fig. 5.—Effect of salts on adsorption of methantheline bromide. Key: ●——●, Na citrate; ■——■, Na_2SO_4; ▲——▲, NaCl.

From the results of the ionic strength studies, shown in Fig. 5, it can be seen that adsorption definitely was affected by salt concentration.

It has been shown previously (22) that adsorption is greatly dependent on the amounts of electrolytes present in the solution and that the two parts of an ionizable molecule tend to be adsorbed to different extents. For example, Rona and Michaelis (23) have shown that the quantity of hydrogen atoms adsorbed by charcoal in a solution of hydrochloric acid is increased greatly when 1 *N* potassium chloride is added.

It is relatively easier for a noncharged molecule to be adsorbed onto a surface than it is for highly charged molecule. This is due to the repulsion of the like charges when drawn together or near to each other during the process of adsorption. Also, in the event that the surface of the adsorbent is charged, molecules of similar charge would find great difficulty in being adsorbed. However, if for any reason the cationic portion of the molecule were to have some of its charge density reduced, it would probably show increased adsorption.

It is possible that the above mechanism was responsible for the results observed in this study, as the anions tested caused increased adsorption according to their valence. The order of effectiveness thus followed the Hofmeister or lyotropic series of anions since citrate was more effective than sulfate which was more effective than the chloride anion.

Low concentrations of citrate ion decreased the adsorption of methantheline bromide and propantheline bromide by magnesium trisilicate. Citrate ion, in low concentrations, may have displaced the drug molecules from their adsorption sites; while at high concentrations, the charge density of the cationic portion of the drug molecule was reduced sufficiently to increase adsorption.

Adsorption of propantheline bromide and methantheline bromide on aluminum hydroxide increased with a rise in the pH of the suspension. For example, at a pH of 6.7, 11 mg. out of an initial concentration of 150 mg. of propantheline bromide was adsorbed by 1 Gm. of aluminum hydroxide. At a pH of 8.5, 15.5 mg. was adsorbed. At a pH of 6.7, 13 mg. of methantheline bromide was adsorbed, which was increased to 18 mg. at pH 8.4. A rise in the pH above 8.5 did not increase adsorption.

The increased adsorption at higher pH's was indicative of the formation of additional drug as the free base which, less soluble than the salt, resulted in higher adsorption. This occurred up to the point where further increase in pH did not produce additional free base. The isotherm obtained in an unbuffered suspension was similar to the one obtained in a suspension buffered to a pH the same as that of the unbuffered suspension. Alteration of the pH to either side of this pH resulted in either an increase or decrease in the amount of drug adsorbed.

Throughout this paper, the results have been interpreted in light of adsorbents showing strong adsorptive properties for the anticholinergic drugs. For the most part, this property is a distinct disadvantage. The adsorbents with the strongest adsorptive properties should have this noted as a detriment to their use in combination with other drugs, unless it is proven conclusively that pharmacological activity of the combination is no less than that of the individual compounds. This applies to combinations arrived at by formulation techniques or by simultaneous administration of individual drugs. This type of easily collected data can serve as a useful indication of the reactivity tendencies of any combination of solid adsorbent and adsorbate.

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