Adsorption of Phenothiazine Derivatives by Solid Adsorbents

By DONALD L. SORBY, ELMER M. PLEIN*, and JOSEPH D. BENMAMAN

In simple aqueous media, the extent of adsorption of various phenothiazine derivatives by kaolin, talc, and activated charcoal is significant. Adsorption by talc and kaolin is dependent upon pH of the medium, while adsorption by activated charcoal is less affected by pH. Adsorption of promazine hydrochloride by all three adsorbents is sensitive to the electrolyte concentration of the medium. A variety of evidence suggests that adsorption of the phenothiazine derivatives by activated charcoal is a result of physical forces related to the tendency of the solute to accumulate at the air–water interface. Adsorption of these compounds by talc and kaolin occurs through more complex mechanisms which cannot be completely elucidated from knowledge obtained in this experiment. The effects of pH and electrolyte concentration may be important to the previously observed action of adsorbents in modifying absorption of promazine from the gastrointestinal tract.

A PREVIOUS publication (1) presented a partial report of results obtained in this experiment. Various medicinally active phenothiazine derivatives were found to be adsorbed to a significant extent by kaolin, talc, and activated charcoal. The purpose of this report is to describe various aspects of the adsorption process in further detail and to present results of studies concerned with attempts to elucidate the mechanisms of the adsorption interaction. In addition, there is interest in adsorption as a potential means of altering drug absorption from the gastrointestinal tract (2, 3). Certain factors have been studied for their ability to produce release of the absorbed material from the surface of the adsorbate complex. *In vivo* experiments have involved the use of promazine hydrochloride. Thus, several experiments reported here feature this compound. Results obtained for promazine hydrochloride should be qualitatively similar for other phenothiazine derivatives.

EXPERIMENTAL

Preparation of Compounds for Study.—The phenothiazine derivatives used in this study were obtained from various sources of supply.[1] Each compound was recrystallized from an appropriate solvent until the melting point agreed with the accepted value.[2] The 15 compounds studied during various phases of the experiment are listed in Table I.

All adsorption studies were performed using compounds in the form of their hydrochloride salts. Compounds not available as the hydrochloride salt, *viz.*, methoxypromazine maleate, acepromazine maleate, trimeprazine tartrate, and prochlorperazine ethanedisulfonate, were converted to the hydrochloride form by passing 1.1×10^{-2} *M* solutions through an ion exchange column charged with a strongly basic polystyrene quaternary amine type ion-exchange resin[3] in the chloride cycle. The nonaqueous titration procedure described below was used to determine the exact concentration of the solution recovered from the ion-exchange column. The effluent solutions were tested for completeness of anion exchange by a paper chromatographic procedure (4). Ethanedisulfonate could not be detected by this method. For other compounds mentioned, no evidence of the original acid anion could be found in the effluent from the ion exchange columns. Conversion to the hydrochloride salt form was considered to be complete in all cases.

Preparation of Adsorbents for Study.—Adsorbent materials were procured from commercial sources. Activated charcoal[4] was obtained from the American Norit Co., Jacksonville, Fla.

Average screen analysis data, supplied by the manufacturer, showed that 98% is passed through a 100-mesh U. S. standard screen, 90% through a 200-mesh, and 85% through a 300-mesh screen. Talc was U.S.P. grade, 99.5% passes a 100-mesh screen. Kaolin was N.F. grade, 99.5% passes a 325-mesh screen.

The total content of commercial packages of each adsorbent was blended in a twin shell blender, dried at 120° for 5 hr., and stored in air-tight bottles until used. The total amount of each adsorbent used in this study came from one single production lot of material.

Aqueous extracts of the kaolin and talc adsorbents

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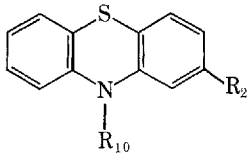
[2] Melting point data were furnished by the supplier of each compound. Isopropanol was used as the recrystallizing solvent for all compounds except acepromazine maleate and prochlorperazine ethanedisulfonate. Ethyl acetate was used for the former and water–ethanol for the latter. Ethopropazine hydrochloride and thioridazine dihydrochloride were not recrystallized.

[3] Marketed as Amberlite IRA-400 by Rohm & Haas Co. Philadelphia, Pa.

[4] Marketed as Norit A.

TABLE I.—PHENOTHIAZINE DERIVATIVES INCLUDED IN THIS RESEARCH



Compd.	No. 2 Substituent (R_2)	No. 10 Substituent (R_{10})
Promazine	Hydrogen	3-Dimethylaminopropyl
Mepazine	Hydrogen	(*N*-Methyl-piperidyl)-methyl
Trimeprazine	Hydrogen	3-Dimethylamino-2-methylpropyl
Promethazine	Hydrogen	2-Dimethylamino-2-methylethyl
Ethopropazine	Hydrogen	2-Diethylamino-2-methylethyl
Pyrathiazine	Hydrogen	2-(1-Pyrrolidyl)-ethyl
Chlorpromazine	Chlorine	3-Dimethylaminopropyl
Methoxypromazine	Methoxy	3-Dimethylaminopropyl
Triflupromazine	Trifluoromethyl	3-Dimethylaminopropyl
Acepromazine	Acetyl	3-Dimethylaminopropyl
Prochlorperazine	Chlorine	3-(1-Methyl-4-piperazinyl)-propyl
Thiopropazate	Chlorine	3-[1-(2-Acetoxyethyl)-4-piperazinyl]-propyl
Trifluoperazine	Trifluoromethyl	3-(1-Methyl-4-piperazinyl)-propyl
Fluphenazine	Trifluoromethyl	3-(2-Hydroxyethyl-4-piperazinyl)-propyl
Thioridazine	Methylmercapto	2-(1-Methyl-2-piperidyl)ethyl

contained small amounts of ultraviolet absorbing impurities. The magnitude of this absorption was small, however, and was nearly constant in the range of the ultraviolet absorption spectrum where the phenothiazine derivatives show absorption maxima. The aqueous extracts showed a negative potassium ferrocyanide test for ferric ion.

Analytical Methods.—Two analytical methods were employed in this research.

Nonaqueous Titration Procedure.—The concentration of all stock solutions of phenothiazine derivatives was confirmed by a nonaqueous titration procedure adapted from the method of Milne *et al.* (5, 6). Aqueous solutions containing a particular phenothiazine derivative were made strongly basic with sodium hydroxide and then were extracted[5] with four 20-ml. portions of *n*-hexane. Sufficient acetone was added to the extract to make a solvent containing a 2:1 ratio of hexane to acetone. This solution was titrated with perchloric acid, 0.05 *N* in dioxane. The end point was determined potentiometrically using a Leeds & Northrup pH indicator equipped with glass indicator and calomel reference electrodes. The end point was taken as the point of maximum inflection of a curve representing observed E.M.F. plotted against volume of titrant added. A blank correction was made for a similar system containing no phenothiazine derivative. The method was used for all phenothiazine derivatives listed in Table I except ethopropazine. Accuracy of the method was within a range of ±3% of theoretical at the 1×10^{-2} *M* concentration level. Quantitative recovery of thiopropazate could not be obtained using this procedure.

Spectrophotometric Procedure.—The nonaqueous titration procedure lacked sufficient sensitivity to be used at the concentration ranges employed in experiments which measure adsorption isotherms. In such cases, an ultraviolet spectrophotometric procedure was used to measure equilibrium concentrations of the phenothiazine derivatives. The method was adapted from a background cancellation technique proposed by Flanagan *et al.* (7) for chlorpromazine. A Beckman DU spectrophotometer was used to measure absorbance of the samples at three different wavelengths. Absorbance at the wavelength of maximum absorbance ($\lambda_{max.}$) was always measured. The other two absorbance measurements were made at wavelengths where the sample absorbed less strongly. One measurement was always made at a shorter wavelength (λ_{short}) than $\lambda_{max.}$ and one at a longer wavelength (λ_{long}). Corrections for background absorbance were made in the fashion described by Flanagan *et al.* (7). However, they were calculated algebraically.

The following expressions illustrate this method of correcting for "background" interference in samples.

$$\text{Background correction (B.C.)} = As\ \lambda_{high} + \left[(As\ \lambda_{short} - As\ \lambda_{long}) \times \frac{\lambda_{max.} - \lambda_{long}}{\lambda_{short} - \lambda_{long}}\right]$$

$$\text{Corrected absorbance } (As^*) = \text{measured } As \text{ at } \lambda_{max.} - \text{B.C.}$$

A "corrected" molar absorption coefficient was calculated for each compound from the "corrected" absorbance of samples of known concentrations measured in the absence of adsorbent. The concentration of solute in test samples was calculated from the relationship

$$C = \frac{As^*}{(l)\ (e^*)}$$

where, As^* is the corrected absorbance of the sample at $\lambda_{max.}$, l is the path length of the solution, and e^* is the "corrected" molar absorption coefficient for the compound. Table II lists the wavelengths used in determining As^* and the values of e^* for compounds studied in this experiment. The range of usefulness of this method of assay is 5×10^{-6} *M* to 4×10^{-5} *M*.

[5] A benzene–dinitromethane solvent was recommended (5) for extracting dibasic compounds. Personal communication with the author indicated that the hexane–acetone mixture also worked well with dibasic compounds. Results obtained during this research have confirmed the hexane–acetone solvent as being suitable for extracting both monobasic and dibasic compounds.

TABLE II.—WAVELENGTHS USED FOR ANALYSIS AND THE CORRECTED MOLAR ABSORPTION COEFFICIENTS FOR VARIOUS PHENOTHIAZINE DERIVATIVES

Compd.[a]	Wavelengths for Absorption Measurements λ_{low}, mμ	$\lambda_{max.}$, mμ	λ_{high}, mμ	"Corrected" molar Absorption Coefficient × 10^{-5}
Methoxypromazine	232	251	270	0.155
Pyrathiazine	230	250	260	0.174
Triflupromazine	230	256	270	0.209
Acepromazine	230	242	290	0.099
Trifluoperazine	237	257	267	0.179
Trimeprazine	226	251	262	0.179
Thiopropazate	230	254	266	0.214
Chlorpromazine	236	255	265	0.196
Promethazine	225	250	260	0.188
Promazine	230	248	262	0.182
Prochlorperazine	234	255	266	0.213
Fluphenazine	234	256	268	0.200
Mepazine	234	253	262	0.188
Thioridazine	246	262	278	0.232
Ethopropazine	230	249	258	0.156

[a] All compounds were studied as the hydrochloride salt. All solutions also contained 0.01% sodium bisulfite.

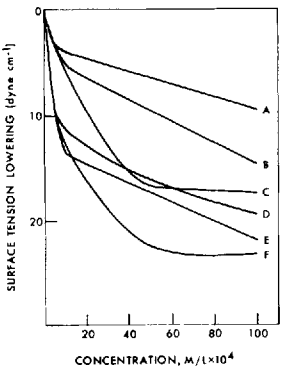


Fig. 1.—Surface tension lowering-concentration relationships. Key: A, promazine hydrochloride; B, mepazine hydrochloride; C, thioridazine hydrochloride; D, trifluoperazine; E, thiopropazate dihydrochloride; F, triflupromazine hydrochloride.

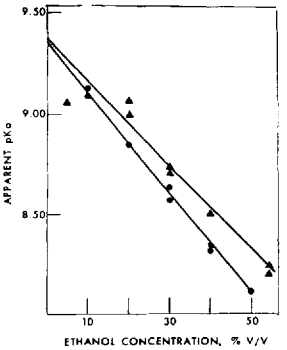


Fig. 2.—Apparent pKa as a function of ethanol concentration. Key: ▲, promazine hydrochloride; ●, pyrathiazine hydrochloride.

Preparation of Solutions.—Stock solutions of each compound were prepared on the day the adsorption isotherm was determined. Each solution was prepared to contain a 1×10^{-2} *M* concentration of the particular compound under study. Each solution also contained 0.01% sodium bisulfite.

Determination of Adsorption Isotherms.—The procedure for determining adsorption isotherms was reported elsewhere (1). Except where specified, all adsorption experiments were made at 20.0°.

Surface Tension Lowering Measurements.—The change in surface tension with concentration was measured for six phenothiazine derivatives. Dilutions of each compound in distilled water, ranging between 5×10^{-4} *M* and 1×10^{-2} *M*, were prepared. Surface tensions of the solutions were measured at 20 ± 1° with a Cenco-DuNoüy interfacial tensiometer, precision direct reading model. Fresh surfaces were prepared by flooding a small glass dish with solution, and two readings of the surface tension were immediately taken. This procedure was repeated until a total of six readings had been obtained at each concentration tested. The mean value was calculated from the six readings. A value for the surface tension of water was measured in a similar fashion. Figure 1 shows the variation of surface tension lowering with concentration for the compounds tested.

Determination of Apparent pKa.—Apparent pKa values for several compounds were measured by a titrimetric procedure similar to one employed by Marshall (8). Hydroalcohol solutions of the hydrochloride form of the appropriate phenothiazine derivative were prepared at a concentration of 1×10^{-3} *M*. These solutions were titrated with standard sodium hydroxide solution, 0.0500 *N*, at 20.0° under a nitrogen atmosphere. After each addition of titrant, the pH was measured with the instrument mentioned under *Nonaqueous Titration Procedure*. The apparent pKa was calculated at each pH reading on the titration curve using the relationship

$$\text{pKa} - \text{pH} - \log \frac{C_{R_3N}}{C_{R_3NH^+}}$$

where C_{R_3N} is the concentration of amine base, and $C_{R_3NH^+}$ is the concentration of the protonated species present at the particular pH value. Values for C_{R_3N} and $C_{R_3NH^+}$ were calculated from the amount of amine salt initially present and the amount of titrant added. An average of the several pKa values calculated in this fashion was taken as the apparent pKa for the compound in the particular hydroalcohol solvent. Titrations and apparent pKa calculations were made in duplicate for each compound at each alcohol strength, usually 10, 20, 30, 40, and 50% by volume ethanol.

The apparent pKa values measured for each compound in the various hydroalcohol solutions were plotted against alcohol concentration. The zero alcohol concentration intercept, calculated from the linear portion of the curve by the method of least squares, yielded the apparent pKa of the compound in water. Figure 2 shows a plot of apparent pKa *versus* alcohol concentration for pyrathiazine hydrochloride and chlorpromazine hydrochloride and is typical of the over-all results.

In certain cases, the amine base began to precipitate from the hydroalcohol system before a complete titration curve could be obtained. In such cases, the apparent pKa was calculated by assuming the concentration of the amine base actually in solution to be constant after the point where precipitation first occurred. The concentration of free base present at the point of precipitation was estimated from the amount theoretically present at the cloud point when a sample of identical concentration with respect to both alcohol and drug was titrated with a more dilute titrant solution. Using this method, apparent pKa values could be determined for most

TABLE III.—APPARENT pKa VALUES FOR VARIOUS PHENOTHIAZINE DERIVATIVES

Compd.	Measured pKa	pKa Reported in Lit.[a]
Promazine hydrochloride	9.39	9.52
Mepazine hydrochloride	9.25	...
Chlorpromazine hydrochloride	9.21	9.30
Thioridazine hydrochloride	9.45	...
Pyrathiazine hydrochloride	9.36	8.96
Fluphenazine dihydrochloride[b]	8.05	...
Trifluoperazine dihydrochloride[b]	8.36	...
Promethazine hydrochloride	...	9.08
Ethopropazine hydrochloride	...	9.50

[a] Values reported by Marshall (8). [b] These values are for dissociation of the second basic group. For pK_1, values of 3.90 and 4.10 were obtained for fluphenazine and trifluoperazine, respectively.

of the compounds in hydroalcohol solutions containing as little as 10% v/v alcohol. Where calculations could be made from data collected both before and after the point of precipitation, good agreement was obtained between apparent pKa values.

Values of the apparent pKa for several compounds are reported in Table III.

Adsorption at Constant pH.—Adsorption of promazine hydrochloride and fluphenazine dihydrochloride was studied at pH 2.5 and 6.5. Phosphate buffers were prepared to contain 0.03 *M* total phosphate. For the pH 6.5 buffer, 4.23 Gm. of dibasic sodium phosphate and 2.0 ml. of hydrochloric acid were made to a volume of 1000 ml. with carbonate-free distilled water. For pH 2.5 buffer, 4.13 Gm. of monobasic sodium phosphate and 1.0 ml. of hydrochloric acid were made to 1000 ml. with carbonate-free distilled water. The pH of each buffer was brought exactly to the desired values, by addition of acid or base, before adjustment to volume. Stock solutions of each phenothiazine derivative in the appropriate buffer were prepared, and the isotherms were determined by the procedure described previously (1). The method employed here differed only with respect to the fact that buffer was used as the solvent for all systems. Limited adsorption experiments carried out in varying concentrations of phosphate buffer showed that the observed effects on adsorption were not due to competition between the buffer components and the phenothiazine derivative for sites on the adsorbent surface.

Effect of Electrolyte on Adsorption.—Adsorption of promazine by the various adsorbents was measured in the presence of 0.01 and 0.10 *N* sodium chloride. Stock solutions were prepared by dissolving promazine hydrochloride in the appropriate sodium chloride solution. Isotherms were determined in a manner similar to that described previously (1) except the appropriate sodium chloride solution was used as the solvent in place of distilled water. The pH of all samples was measured at the time of analysis with a Beckman model G pH meter equipped with glass indicator and calomel reference electrodes.

Effect of Temperature on Adsorption.—Adsorption was measured at 37.0° for chlorpromazine hydrochloride and thiopropazate dihydrochloride by the method described previously (1).

RESULTS AND DISCUSSION

All of the phenothiazine derivatives were adsorbed to a significant extent by the adsorbents tested. The experimental data were plotted according to the following form of the Langmuir equation:

$$\frac{C_{EQ}}{x/m} = \frac{1}{k_1 k_2} + \frac{C_{EQ}}{k_2}$$

where C_{EQ} is the concentration of the phenothiazine derivative remaining in solution at equilibrium, x/m is defined as the amount of compound adsorbed by the quantity of adsorbent used,[6] 1.00 Gm. for kaolin and talc, 0.100 Gm. for activated charcoal, and k_1 and k_2 are constants. The constant k_1 is sometimes called the adsorption coefficient and is related to the force of the interaction between the adsorbent and the bound molecules. The value of k_2 gives the maximum amount of compound which can be adsorbed by the weight of adsorbent used in the experiment. It must be assumed that only a monomolecular layer of solute molecules can be found in order to correctly apply the Langmuir equation.

The best straight line through the experimental data was calculated by the method of least squares. The values of the constants, k_1 and k_2, were obtained from the reciprocals of the slope and intercept values of the regression equation calculated from the experimental data. In each case, linear conformity of the data to the Langmuir equation was checked by graphic plots before calculating the regression equation. In most cases, the data could be expressed in linear form by the Langmuir equation. Values of the Langmuir constant, k_2, are summarized in Table IV. Figure 3 shows the Langmuir isotherms obtained for promazine hydrochloride and fluphenazine dihydrochloride which are typical of the over-all results.

Values of k_2 show that in unbuffered media, kaolin has the weakest adsorbent capacity. Talc possesses adsorbent capacity which is similar to kaolin, although approximately twice as great for any given compound. The similarity in adsorbent capacity between kaolin and talc is not especially surprising since both are basic aluminosilicates although they do differ with respect to physical structure and exchangable cations. Adsorption of all compounds by activated charcoal is much greater in magnitude. Compared on a weight basis, the adsorbent power of charcoal ranges from 20 to 80 times that of kaolin and talc.

Values for the adsorption coefficient, k_1, are not shown in Table IV. In most cases, adsorption approached surface saturation at very low concentration ranges. As a result, due to the lack of data at low degrees of surface saturation, calculation of k_1 values from intercept values of the Langmuir equation is potentially subject to some error. A procedure recommended by Finger *et al.* (9) is equally unsatisfactory for determining k_1 values from these data. The values of k_1 were found to increase from kaolin to talc to charcoal and were generally of a similar order of magnitude within a particular adsorbent series.

The intercept value of the Langmuir equation may also be used for comparing affinities between adsorbents and the phenothiazine derivatives. At the

[6] Since x/m is determined from concentration difference measurements, it is actually the apparent amount adsorbed. Adsorption of solvent by the adsorbent may also alter the solute concentration and hence produce some uncertainty in the value obtained for x/m. Due to the relatively large ratio of solvent to adsorbent in the test systems, the effect of solvent adsorption should be minimal and the values of x/m are considered to be subject to little error from this effect.

TABLE IV.—VALUES OF LANGMUIR CONSTANTS EXPRESSING ADSORPTION OF VARIOUS PHENOTHIAZINE DERIVATIVES BY KAOLIN, TALC, AND ACTIVATED CHARCOAL AT 20°

Compd.	Kaolin Adsorbent		Talc Adsorbent		Charcoal Adsorbent	
	$k_2 \times 10^3$	$k_1k_2 \times 10^{-3}$	$k_2 \times 10^3$	$k_1k_2 \times 10^{-3}$	$k_2 \times 10^3$	$k_1k_2 \times 10^{-3}$
Promazine	21.9	0.299	49.5	1.00	116.	4.08
Mepazine	26.2	0.119	52.9	10.3	91.7	4.76
Trimeprazine	23.0	0.175	47.8	1.15	91.7	2.53
Promethazine	22.4	0.227	44.8	1.11	103.	1.86
Ethopropazine	24.0	0.098	...[a]	...[a]	...[a]	...[a]
Pyrathiazine	18.9	0.267	39.7	1.09	101.	4.24
Chlorpromazine	24.0	0.194	51.8	0.744	102.	4.18
Methoxypromazine	12.0	−2.09	21.0	− .486	75.2	−3.65
Trifluprom azine	19.3	1.39	61.3	2.07	80.0	18.9
Acepromazine	21.8	0.476	35.2	0.825	90.9	1.93
Prochlorperazine	15.2	0.478	...[b]	...[b]	81.3	6.37
Thiopropazate	14.1	0.452	...[b]	...[b]	58.5	2.29
Trifluoperazine	14.5	1.07	...[b]	...[b]	65.8	1.58
Fluphenazine	15.1	0.239	...[b]	...[b]	64.9	3.32
Thioridazine	35.9	2.61	74.1	3.31	72.5	3.53

[a] Evidence indicated a decomposition of the sample with these adsorbents. [b] Data plotted according to the Langmuir equation produced a nonlinear curve, hence the value of the constants k_1 and k_2 could not be determined.

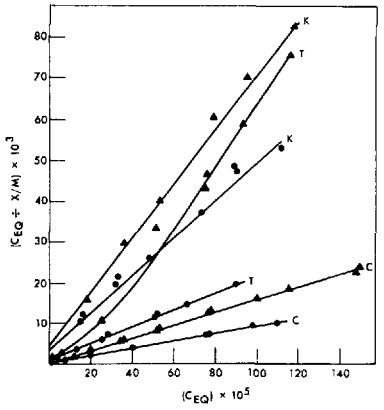


Fig. 3.—Langmuir plots for adsorption in simple aqueous media. Key: ●, promazine hydrochloride; ▲, fluphenazine dihydrochloride; K, kaolin; T, talc; C, activated charcoal. With exception of the curve expressing adsorption of fluphenazine dihydrochloride by talc, the various curves represent regression lines calculated by method of least squares.

lower equilibrium concentrations, *viz.*, at infinite dilution, the Langmuir equation reduces to

$$x/m = k_1k_2\, C_{EQ}$$

The product, k_1k_2, would be the initial slope of the adsorption isotherm and would, in a sense, be an equilibrium constant for adsorption of phenothiazine derivatives in systems well below saturation of the adsorbent surface. Thus, the k_1k_2 values should be useful in comparing the relative strength of interaction between the adsorbents and the various phenothiazine derivatives. Values of k_1k_2 taken from the reciprocals of intercept values of the Langmuir equations expressing experimental data are shown in Table IV. These values are subject to some of the uncertainty discussed for k_1 values, and it is seen that occasionally unexpectedly large variations within a particular adsorbent series are encountered. On the other hand, for a particular adsorbent, the k_1k_2 values are relatively similar and probably reflect essentially similar adsorption affinities. The values generally increase from kaolin to talc to charcoal. It must be remembered, however, that the k_1k_2 value only tells that the three adsorbents have different affinity for the compounds, and one cannot assume much about the mechanism of the interaction from these values.

Adsorption may occur as a result of several possible mechanisms (10–13). Certain mechanisms may involve a specific interaction between the surface of the solid and the adsorbed molecule. On the other hand, solutes which exhibit surface tension lowering properties are often strongly adsorbed by a wide variety of solids since these solutes often tend to accumulate at the solid–liquid interface as readily as at the solution–air interface (10, 12). Phenothiazine derivatives have been shown to exhibit surface tension lowering properties (14–16). Figure 4 presents plots of surface tension lowering *versus* extent of adsorption for the phenothiazine compounds shown in Fig. 1. The coefficient of correlation between extent of adsorption by activated charcoal and surface tension lowering is −0.843. This value is significant at the $P = 0.05$ level. Such correlation does not exist for kaolin and talc adsorbents. This suggests that the ability to accumulate at the solid–solution interface may be responsible for the charcoal–solute interaction. Such a condition is favored by the very large surface area of activated charcoal which offers an extensive interface to the solution phase.[7] The failure of talc and kaolin to exhibit adsorptive properties which correlate to surface tension lowering can be interpreted as indicating that the tendency of solute molecules to accumulate at an interface is not the sole reason why adsorption onto these substances takes place. Since surface areas of kaolin and talc are generally much smaller than for activated charcoal, a smaller interface is offered for accumulation of surface-active solute molecules. Adsorption by interfacial effects cannot be entirely ruled out for kaolin and talc, however, as it is possible that some adsorption occurs *via* this mechanism, but it is obscured by the effects of other factors also facilitating adsorption at the same time.

If adsorption of solute by charcoal is mediated primarily through ability of the solute to accumulate

[7] Cassidy reports (10) surface areas in the range of 15 M.²/Gm. for kaolin, and 500–1700 M.²/Gm. for activated charcoal. Talc could be expected to have a surface area somewere in the range below 50 M.²/Gm. While surface areas were not measured for the specific adsorbents used in this study, they would probably be of a similar order of magnitude.

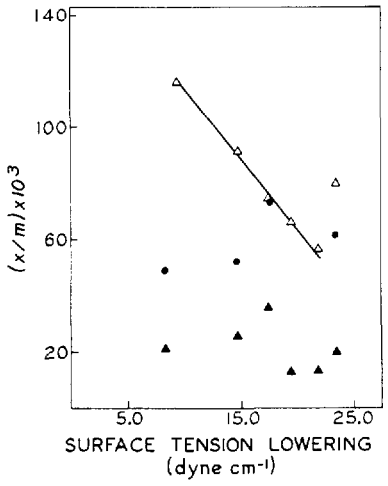


Fig. 4.—Limiting adsorptive capacity as a function of surface tension lowering produced by 1×10^{-2} M solutions of various phenothiazine derivatives. Key: △, charcoal adsorbent; ●, talc adsorbent; ▲, kaolin adsorbent.

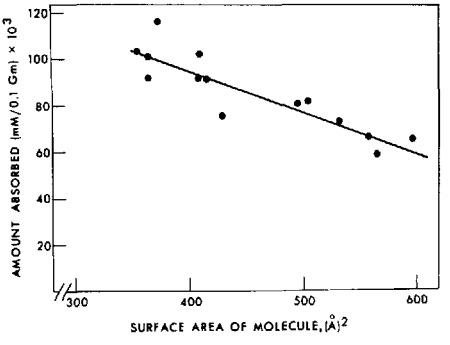


Fig. 5.—Limiting adsorptive capacity as a function of planar surface area of various phenothiazine derivatives adsorbed by activated charcoal.

at the solid–solution interface, a relationship might be expected to exist between the maximum extent of adsorption and the area occupied by the molecules in the interface. Figure 5 shows the apparent relationship between molecular surface area of the various phenothiazine derivatives and the Langmuir constant k_2.[8] The coefficient of correlation for the relationship in Fig. 5 is −0.861 and is significant at the $P = 0.001$ level. A coefficient of correlation equal to −0.886, significant at the $P = 0.01$ level, was obtained when k_2 values were compared to molecular volumes of the solutes. The total surface area of adsorbed molecules corresponds well with surface areas commonly encountered for activated charcoals. In the case of promazine, the total surface area of the molecules adsorbed at saturation of the adsorbent surface is 690 M.²/Gm. activated charcoal.

[8] Space-filling atomic models were used in calculating approximate surface areas of solute molecules. Areas were calculated on the basis of the smallest trapezoid which would contain the model. Molecular volumes were calculated as the smallest truncated pyramid which would contain the model.

Since the phenothiazine derivatives studied are capable of existence entirely or at least partially in a protonated form at the pH ranges of this experiment, it is possible that, in some cases, adsorption may be mediated by ion-exchange interactions. Both kaolin and talc particles would be expected to carry a negative charge (10) on their surface due to deficiencies in certain cations within the crystal structure of these substances. The negative charges are neutralized by exchangeable cations such as sodium and potassium. It is a well-established fact (10–13) that high molecular weight organic cations can displace these inorganic cations and preferentially adsorb to the particle surfaces. Such mechanisms would not account for the high adsorptive capacity of activated charcoal. Although certain charcoals can have some ion-exchange abilities (10), this cannot account for the high affinity of charcoal for solute molecules in the system under study.

The effect of electrolyte on promazine adsorption

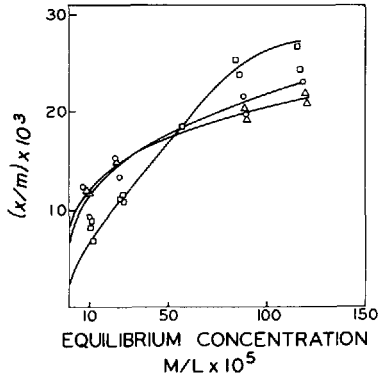


Fig. 6.—Isotherms for adsorption of promazine by kaolin. Key: ○, distilled water; △, 0.01 N sodium chloride; □, 0.10 N sodium chloride.

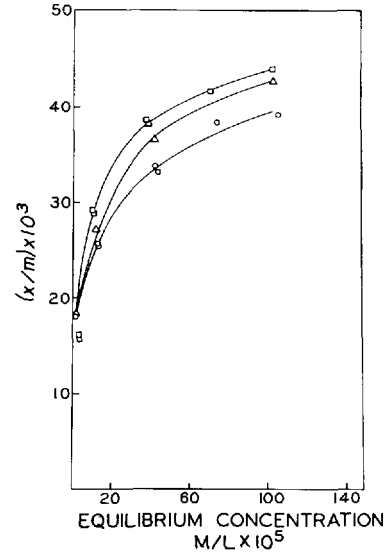


Fig. 7.—Isotherms for adsorption of promazine by talc. Key: ○, distilled water; △, 0.01 N sodium chloride; □, 0.10 N sodium chloride.

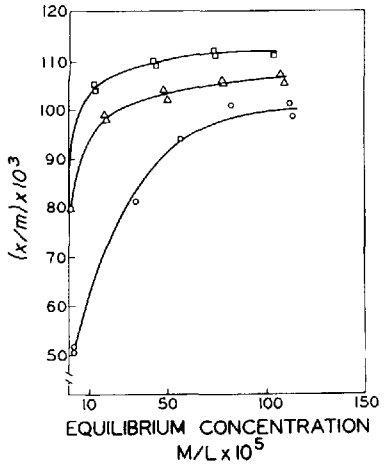


Fig. 8.—Isotherms for adsorption of promazine by activated charcoal. Key: O, distilled water; △, 0.01 *N* sodium chloride; □, 0.10 *N* sodium chloride.

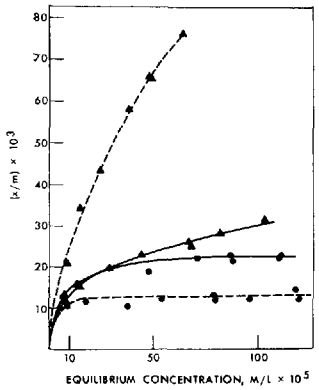


Fig. 9.—Adsorption of promazine hydrochloride (——) and fluphenazine dihydrochloride (- - - - -) by kaolin at pH 2.5 (●) and pH 6.5 (▲).

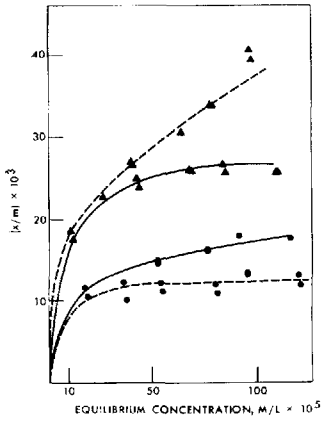


Fig. 10.—Adsorption of promazine hydrochloride (——) and fluphenazine dihydrochloride (- - - - -) by talc at pH 2.5 (●) and pH 6.5 (▲).

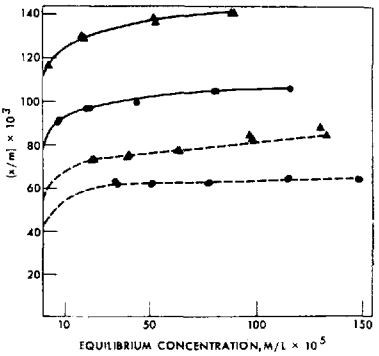


Fig. 11.—Adsorption of promazine hydrochloride (——) and fluphenazine dihydrochloride (- - - - -) by activated charcoal at pH 2.5 (●) and pH 6.5 (▲).

is shown in Figs. 6, 7, and 8. It is seen that increasing the electrolyte concentration increases the adsorptive capacity of the adsorbent.[9] In addition, at any given solute concentration below that necessary to achieve apparent saturation of the adsorbent surface, the extent of adsorption is increased. Measurements showed that pH remained unchanged in the presence of increasing amounts of sodium chloride. Sodium ion, as well as other electrolyte species, would be expected to compete with the protonated amine for anionic sites on the particle surface or for positions in the electrical double layer around the particles. Hence, addition of large amounts of sodium ion might be expected to decrease the extent of adsorption of the protonated species of the amine if ion-exchange mechanisms were responsible for adsorption (12, 13). Failure of sodium ion to displace the organic cation suggests that adsorption of the phenothiazine derivative is mediated through other than simple ion-exchange mechanisms alone or that even in great excess, sodium ion cannot displace the amine from the adsorption sites. The fact that adsorption of the phenothiazine derivative is actually increased by the sodium ion supports the idea that ion-exchange is not the sole mechanism for adsorption. Even if the sodium ion could not displace the solute, it should not increase adsorption if ion-exchange was solely responsible for adsorption of the phenothiazine derivative. Sodium chloride may be exerting its action through effects on solubility and other physical properties of the phenothiazine derivative. The apparent result is an increasing tendency of the phenothiazine derivative to accumulate at the solution–solid interface. Electrolyte may affect physical properties of the adsorbent as well.

The effect of 0.01 *N* sodium chloride on adsorption of promazine hydrochloride by kaolin is of interest. It may be possible to explain this effect on the basis that at low promazine hydrochloride concentrations, there is competition for exchange sites which leads to decreased adsorption. At higher promazine hydrochloride concentrations, the sodium ion is displaced. Increased adsorption at high concentrations of promazine hydrochloride may be due to effects of

[9] It may be noted that data presented in Figs. 6, 7, and 8 differ from Table IV. These experiments were carried out at a later date using different adsorbent to solvent ratios. It has been pointed out (10) that limiting adsorptive capacities may vary somewhat when measured at different adsorbent–solvent ratios. Data presented in Figs. 6, 7, and 8 should be considered separately from Table IV.

TABLE V.—pH OF VARIOUS UNBUFFERED ADSORBENT–SOLUTE MIXTURES[a]

Adsorbent–Solute System	pH of System at Max. Equilibrium Concn. of Solute	pH of System at Min. Equilibrium Concn. of Solute
Kaolin–promazine	4.6	5.0
Talc–promazine	7.6	8.6
Charcoal–promazine	4.0	4.2
Kaolin–fluphenazine	3.6	4.2
Talc–fluphenazine	4.1	7.8
Charcoal–fluphenazine	3.3	3.4

[a] The pH values for adsorbent suspensions containing no solute were kaolin, 4.3; talc, 8.4; and charcoal, 5.9.

sodium chloride on solubility, etc., as discussed. On the basis of present data, it does not appear possible to either prove or disprove ion-exchange as an important mechanism in adsorption of the phenothiazine derivative by kaolin and talc.

Results of adsorption studies at constant pH are presented in Figs. 9, 10, and 11. In all cases, adsorption is seen to be greater at pH 6.5 than at pH 2.5. A possible explanation for this pH effect could be involved with changes which occur in the relative amounts of protonated and nonprotonated amine present as pH increases. If the nonprotonated form of the phenothiazine derivative is better adsorbed as is often the case for systems of this type (10, 12), then adsorption would be expected to be greater at the higher pH. Inspection of pKa values in Table III shows that even at pH 6.5, only a relatively small portion of the total amine is in the nonprotonated form since this pH is several units below the apparent pKa. It is difficult to conceive that there would be enough free base present at pH 6.5 to exert a significantly greater driving force for adsorption as compared to lower pH levels. On the other hand, the equilibrium between protonated and nonprotonated forms is dynamic. As free base is removed by adsorption, it will be replaced from the large reservoir of protonated material. Adsorption could thus continue until equilibrium is established between the adsorbent surface and the free base in solution. The free base concentration is indeed many times greater at pH 6.5 than at the lower pH. It is not impossible that this difference may account for the greater adsorption at higher pH values.

A second possible explanation for the effect of pH might lie in the possibility that hydrogen ions and the protonated amine may compete for anionic sites on the adsorbent surface of, for positions in, the electrical double layer existing around the adsorbent particles.

As compared to kaolin and talc, adsorption of phenothiazine derivatives by charcoal is less strongly influenced by hydrogen-ion concentration, although some charcoals have a moderate electrostatic charge and some affinity for hydrogen ions (10). It is probable that the observed pH effects for charcoal result from increases in the amount of nonprotonated form of the phenothiazine derivative present at the higher pH levels. The nonprotonated forms of the phenothiazine derivatives have low water solubility and hence would have a greater tendency to accumulate at the solid–solution interface than would the protonated form.

Adsorption of solute by talc is further illustrative of pH effects on adsorption. Adsorption of promazine by talc is greatest from unbuffered solution. The reason for this becomes apparent if one considers the pH of the unbuffered systems containing talc (Table V). The pH of unbuffered suspensions containing talc is usually greater than pH 6.5, and, hence, it is not surprising that absorption from unbuffered media is even greater than from the pH 6.5 system. When Figs. 9 and 10 are compared, it is seen that under conditions of controlled pH, kaolin is actually a better adsorbent than is talc. Data in Table IV, which show talc to be a stronger adsorbent in unbuffered media, are primarily a result of the more alkaline pH of the talc systems. It appears that at a given fixed pH, there is actually not much difference between talc and kaolin with respect to adsorbent capacity.

The talc–fluphenazine dihydrochloride system shows interesting pH effects (Fig. 12). In unbuffered solutions, the more acidic proton on the fluphenazine, pKa 3.90, causes production of a relatively low pH at higher solute concentrations, and the fluphenazine is adsorbed less strongly as a result. In fact, in systems containing talc, adsorption of fluphenazine from unbuffered solutions at the higher concentration ranges is very nearly identical to adsorption from buffered solution at pH 2.5. Due to the pH effect, isotherms for fluphenazine in unbuffered talc systems, as well as for other dibasic phenothiazine derivatives, pass through a maximum with increasing solute concentration (Fig. 13). Monobasic phenothiazine derivatives such as promazine, pKa 9.38, are unable to lower the pH of talc systems to an extent that similar pH effects are observed in unbuffered media.

The fact that the ionic charge on the fluphenazine molecule is approximately doubled at pH 2.5, as compared to pH 6.5, must also be considered when explaining pH effects on adsorption of the dibasic compounds. If ionic interactions are responsible for

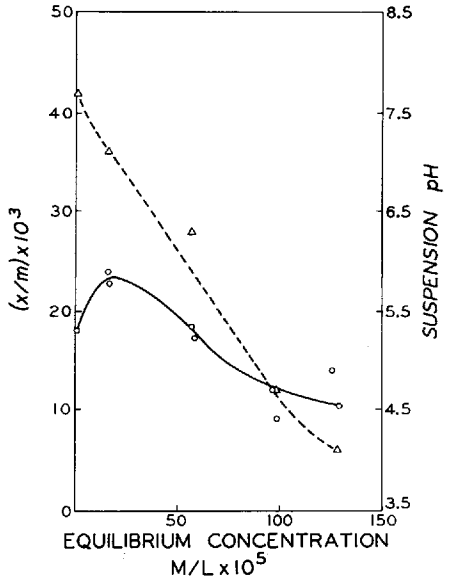


Fig. 12.—Relationship between the extent of adsorption of fluphenazine dihydrochloride by talc (O) and suspension pH (△).

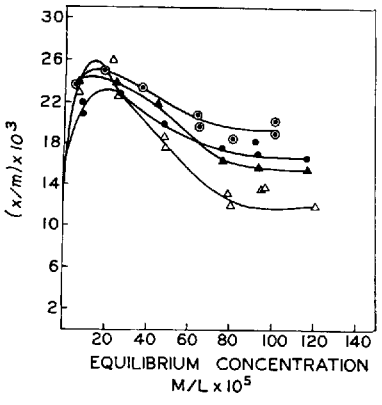


Fig. 13.—Isotherms for adsorption by talc in unbuffered media. Key: ⊙, prochlorperazine dihydrochloride; ●, trifluoperazine dihydrochloride; ▲, fluphenazine dihydrochloride; △, thiopropazate dihydrochloride.

adsorption, the compounds could potentially neutralize twice as many sites on the adsorbent surface at the lower pH and hence adsorption would be reduced to about 0.5 its value at the higher pH range. Inspection of the data shows that adsorption is decreased by a much greater factor at the lower pH. The adsorption of monobasic compounds is also decreased at low pH, even though there could be no change in the charge of the solute molecule. Thus, changes in total charge on the solute molecule do not appear to cause the observed pH effect on adsorption.

The relationship between pH and the extent of adsorption by talc lends support to the idea that the pH effect is due to changes in the amount of free base present. At pH 8.0, the midrange of the talc systems, 4% of the total amine content is in the base form. At pH 6.5, only about 0.13% exists in this form.

If adsorption is strongly influenced by the amount of free base present in the system, a correlation might be expected to exist betwen pKa and adsorption. Plots of apparent pKa *versus* the Langmuir constant, k_2, failed to show any correlation between these parameters. Likewise, apparent pKa and values for k_1k_2 could not be correlated. The lack of correlation is not surprising in view of the relatively slight differences between apparent pKa values for the compounds tested (Table III).

It is not possible to state on the basis of information obtained from these pH studies whether the observed effects are due to one specific certain mechanism. The fact that considerable adsorption occurs at pH 2.5 supports the hypothesis that adsorption of the protonated form also occurs to a considerable extent. Adsorption of solute by kaolin and talc is probably mediated through a combination of mechanisms.

Increasing temperature generally decreases the extent of adsorption. However, it is not uncommon to find that adsorption increases with temperature in certain systems (11, 12). Temperature can affect several properties of the solute molecules and the adsorbent (Table VI), as well as the adsorption interaction *per se*. The mechanism by which temperature increases adsorption in the systems under study is not known. Further investigations of the temperature effects are planned.

The effect of electrolyte and hydrogen-ion concentration is interesting with respect to potential implications regarding the effect of adsorption on the availability of certain drugs for absorption from the gastrointestinal tract. It has already been established (2) for a similar clay-type adsorbent and activated charcoal that adsorbents may alter the availability of promazine for absorption from the gastrointestinal tract. Within the stomach, the presence of hydrogen ion may cause desorption, thus favoring absorption of the drug. The electrolyte environment existing throughout the gastrointestinal tract would probably favor absorption and retard release of adsorbed drug to the fluids at the absorption site. It should be noted that the effect of electrolyte on promazine adsorption was predicted incorrectly (2). While this does not alter the validity of the research, statements made previously regarding the probable effect of electrolyte on release of promazine should be reconsidered.

It is also important that electrolyte not only changes the maximum amount of drug which can be adsorbed, but also increases the amount adsorbed at any given concentration below that which achieves surface saturation. Thus, for talc and activated charcoal, the plateau region corresponding to surface saturation is achieved at a much lower solute concentration. In terms of potential *in vivo* effects, this may be quite important. According to hypotheses presented previously (2), the amount of drug which can exist free in equilibrium with a given amount of adsorbate may be a determinant factor in modifying drug uptake from the gastrointestinal tract when adsorbents are present. These effects will bear further investigation. The reader should refer to *Reference 2* for additional discussions concerning the effects of adsorption on drug availability.

SUMMARY

It can be stated that the adsorption interaction between medicinally active phenothiazine derivatives and charcoal occurs to a significant extent in all cases studied. The mechanisms of the interaction cannot be completely defined from data obtained in experiments described in this paper. Adsorption

Table VI.—Effect of Temperature on Adsorption of Chlorpromazine Hydrochloride and Thiopropazate Dihydrochloride

	Limiting Adsorption Capacity of Adsorbent mM × 10³					
	Kaolin		Talc		Activated Charcoal	
Compd.	20°	37°	20°	37°	20°	37°
Chlorpromazine hydrochloride	24.0	27.1	51.8	70.4	102	110
Thiopropazate dihydrochloride	14.1	33.9	...[a]	...[a]	58.5	80.0

[a] The Langmuir plots for adsorption of thiopropazate dihydrochloride by talc were nonlinear and hence a limiting adsorptive capacity could not be calculated. The effect of temperature appeared to be negligible in this case, however, and the two isotherms were virtually identical.

by charcoal appears to be mediated primarily by physical forces and probably occurs as a result of the tendency of the solute to accumulate at solution–solid interfaces. This tendency to accumulate at the solution–solid interface is similar to the demonstrated surface tension lowering effects of the phenothiazine derivatives.

Adsorption of phenothiazine derivatives by clay-type materials such as kaolin and talc is more complex in nature and is probably mediated through several different mechanisms simultaneously. Mechanisms based on simple electrostatic charge interactions cannot alone explain the process. Molecular size and interfacial properties of the solute do not appear to correlate with adsorption in systems containing kaolin or talc in simple aqueous media.

The results of this experiment show that adsorption of phenothiazine derivatives is dependent upon both hydrogen-ion and electrolyte concentration. Hydrogen-ion concentration is inversely related to the extent of adsorption. The effect of hydrogen-ion may be either to determine the amount of nonprotonated form which is present or to compete with the protonated form for adsorption sites. It is probable that adsorption of phenothiazine derivatives by talc and kaolin is subject to both of these effects. The presence of sodium chloride generally increases adsorption. This is probably due to effects on various physical properties of the solute which increase its tendency to accumulate at the solution–solid interface. The failure of sodium chloride to depress adsorption tends to discount simple ion-exchange as a major mechanism of adsorption.

The effects of pH and electrolyte concentration have important implications with respect to the effect of adsorbents in altering availability of promazine for absorption from the gastrointestinal tract.

The results of these experiments will be useful in further studies of the effect of adsorbents on drug availability. They should also be of use in interpretation of drug–adsorbent interactions in general.

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Inositol N.F.

New Excipient for Chewable Tablets

By S. S. NASIR and L. O. WILKEN, JR.

An investigation of the suitability of inositol as a base for chewable tablets has been conducted by studying and comparing pertinent properties of inositol, mannitol, lactose, and a lactose–sucrose mixture (9:1). The amounts of moisture absorbed by the finely powdered materials, granulations made from these powders with the aid of selected binders, and tablets compressed from some of the granulations were determined (Karl Fischer method or difference in weight) before and after storage at selected relative humidities for specified periods of time. Tablets of similar weights and volumes were prepared from inositol as well as mannitol granulations and evaluated for hardness and dissolution times before and after aging and compared. Representative chewable tablets utilizing mannitol and inositol as bases were prepared for vitamins, antacids, and for acetylsalicylic acid and evaluated for compressability, hardness, dissolution, taste, and appearance. The experimental data indicate that inositol, due to its nonhygroscopic nature, chemical inertness, nontoxicity, physical stability, superior mouthfeel, and texture can be beneficially employed as the base for the formulation of chewable tablets.

ONE OF the recent modifications in tablet dosage forms has led to the development of the chewable tablet, a compressed dosage form, conveniently carried and self-administered, which can be chewed or sucked without the aid of external liquid (1, 2). Daoust and Lynch (1) state that the ideal chewable tablet must be nonhygroscopic and chemically stable, that it

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