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The adsorption of esters of *p*-hydroxybenzoic acid by magnesium trisilicate

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Summary

The adsorption of esters of *p*-hydroxybenzoic acid to magnesium trisilicate and kaolin was examined. Adsorption isotherms at pH 8.0 for 4 esters were linear at low concentration. Adsorption increased with increasing ester chain length. Adsorption was strongly influenced by pH, since the amount of ester adsorbed decreased with increasing pH. Further studies showed that only the non-ionized compound was adsorbed, and this process was Langmuirian. In fact a Langmuirian plot of combined data from the four esters investigated showed that adsorption was independent of the molecular weight and hence the hydrophobicity of the compound. These results suggest that adsorption of the non-ionized compound is a function of the hydroxybenzoate rather than the ester side-chain. In contrast, esters of *p*-hydroxybenzoic acid were not adsorbed by kaolin.

Introduction

Formulae in the British Pharmaceutical Compendia for mixtures containing suspended solids usually include chloroform as a preservative to protect the product against microbial contamination. The inclusion of chloroform in medicines is coming under increasing criticism because of its possible toxicity and rapid loss from any preparation by evaporation (Lynch et al., 1977). The most widely used alternative preservatives for oral liquid medicines are the esters of *p*-hydroxybenzoic acid (parabens esters). However, a number of factors influence the antimicrobial activity of such compounds. Since the parabens esters are only active in the non-ionized state, and the pK_a of these compounds is 8.4, activity in alkaline conditions will be

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relatively low. Ester hydrolysis also occurs under such conditions (Blaug and Grant, 1974; Allwood et al., 1975).

The adsorption of certain drugs to suspended solids in medicines has been reported. These compounds adsorbed by magnesium trisilicate include steroids (Khalil and Iwuagwu, 1978), digoxin (Brown and Juhl, 1976) and diazepam (Naggar, 1981). The antimicrobial activity of preservatives appears to be especially reduced in the presence of magnesium trisilicate (Yousel et al., 1973), in particular benzalkonium chloride, chlorhexidine, phenylmercuric nitrate and methyl *p*-hydroxybenzoate. Kaolin severely reduces the activity of benzalkonium chloride although the activity of chlorcresol is unaffected (Bean and Dempsey, 1971). Fulayyeh et al. (1981) have reported, however, that cetylpyridinium chloride may be more active in attapulgite suspensions than in aqueous solution, despite partially reversable adsorption of the preservative. The adsorption of preservatives to suspended solids used in pharmaceutical preparations has been reported by other workers. Myburgh and McCarthy (1980) have indicated that Hyamine 10X is strongly sorbed onto many suspended solids, while bronopol, Kathon CG and Irgason are much less likely to be adsorbed. Clarke and Armstrong (1972) reported that benzoic acid is strongly adsorbed by kaolin. The degree of binding depended on the pH of the solution. Results indicated that only the ionized compound was adsorbed.

Esters of *p*-hydroxybenzoic acid are being increasingly used as preservatives to replace chloroform in alkali mixtures. The adsorption of these esters to suspensions of magnesium trisilicate and kaolin was therefore examined to determine the extent of the loss of such preservatives by adsorption and gain insight into the mechanisms responsible.

Materials and Methods

Chemicals

Esters of parahydroxybenzoic acid were obtained from BDH, Poole, Dorset. Magnesium trisilicate BP and Kaolin BP were obtained from Evans Medical, Speke, Liverpool. The buffer used was Sorensen's Borate.

pH measurement and adjustment

A type 401 E7 combined glass electrode (Pye Unicam, Cambridge) was used in conjunction with model PW 9409 digital pH meter (Pye Unicam) to measure pH. When required, pH was adjusted using hydrochloric acid (0.1 M).

Assay for parahydroxybenzoate esters

Analysis of solutions for parabens content was conducted by liquid chromatography. A μBondapak C18 reverse-phase column (Waters Associates, Hartford, Cheshire) was used in conjunction with a UV detector (model 440, Waters Associates). The solvent was methanol: 1% v/v acetic acid (70:30), at a flow rate of 1 ml/min.

Design of experiment to measure adsorption

One gram of magnesium trisilicate was placed in a 30-ml glass tube and 10 ml of a solution of the appropriate parabens in buffer added. (pH was adjusted by the addition of 0.1 M hydrochloric acid when necessary.) Suspensions were shaken for 10 min at 18°C, then centrifuged at 5000 g for 15 min; 5 ml of the supernatant solution was removed. After the addition of an internal standard (an alternative ester) 10 μl aliquots were injected into the liquid chromatograph. Control experiments indicated that the presence of the buffer salts did not influence adsorption of the esters to magnesium trisilicate.

Results

Preliminary studies indicated that esters of *p*-hydroxybenzoic acid were not adsorbed by kaolin but were strongly adsorbed by magnesium trisilicate. Isotherms for the 4 esters were therefore determined for suspensions of magnesium trisilicate in borate buffer carefully adjusted to pH 8.0 (±0.1) with hydrochloric acid. These are shown in Fig. 1. The isotherms for methyl and ethyl esters were approximately linear over the concentration range studied. The higher molecular weight esters were most strongly adsorbed and the isotherms became non-linear at high concentrations, presumably as adsorption sites on the magnesium trisilicate became saturated.

Further investigations showed that adsorption was influenced by the pH of the suspension. As shown in Fig. 2, the adsorption of the butyl ester decreased as the solution became more alkaline. This change in adsorption with pH was linear over the pH range studied (this was limited by the ability of the buffer to stabilize the pH in the presence of magnesium trisilicate below pH 7.6). Similar results were obtained with the other esters studied and it suggests that hydrogen ion concentration has a

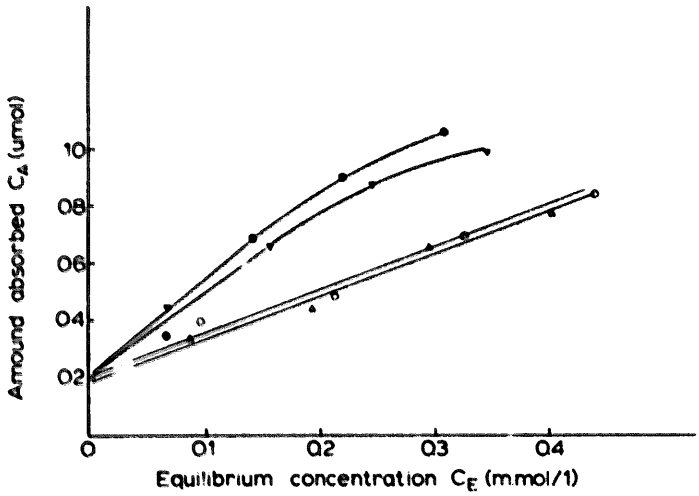

Fig. 1. Adsorption isotherms for the adsorption of different esters of *p*-hydroxybenzoic acid to magnesium trisilicate at pH 8. O, methyl; △ ethyl; ▼, propyl; ●, butyl.

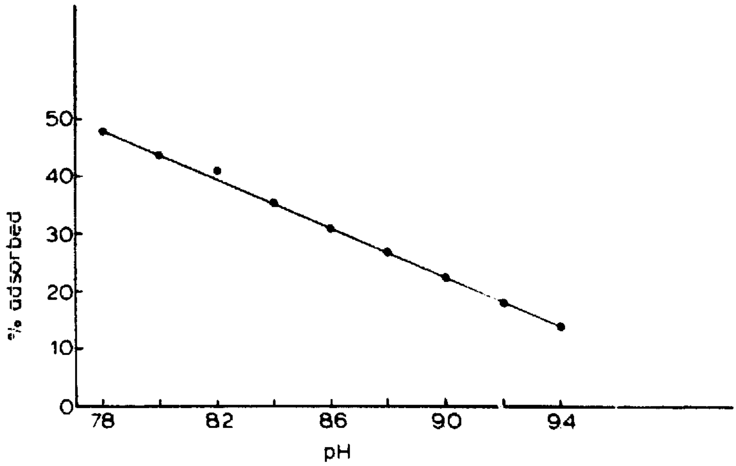

Fig. 2. The influence of pH on the adsorption of butyl p-hydroxybenzoate (0.26 mmol/l) to magnesium trisilicate.

direct influence on adsorption, presumably due to its effect on the ionisaton of the esters.

The nature of the adsorption process was further studied. It was first necessary to determine if adsorption was Langmuirian. This can be expressed (Clarke and Armstrong, 1972) as:

$$\frac{c}{x/m} = \frac{1}{ab} + \frac{1}{b} C$$

where x = weight of adsorbate (μg: μM) adsorbed by m grams of adsorbent; c = the equilibrium concentration (μg/ml; mmol/l); and a and b are constants. Therefore a plot of c/(x/m) vs C is a straight line of slope 1/b and intercept 1/ab. Adsorption of the butyl ester to magnesium trisilicate was measured over a range of concentrations at each pH studied. Plots of c/(x/m) vs C were constructed and values for the

TABLE I

THE LANGMUIRIAN CONSTANTS FOR THE ADSORPTION IN ISOTHERMS FOR ADSORPTION OF BUTYL p-HYDROXYBENZOATE TO MAGNESIUM TRISILICATE AT DIFFERENT pHs

pH	r	b	a
7.75	0.98	0.26	3.03
8.0	0.96	0.26	2.39
8.4	0.95	0.25	2.52
8.5	0.98	0.13	2.62
8.87	0.98	0.10	2.78

TABLE 2

THE LANGMURIAN CONSTANTS FOR THE COMBINED ADSORPTION ISOTHERMS FOR ADSORPTION OF ESTERS OF *p*-HYDROXYBENZOATE TO MAGNESIUM TRISILICATE, THE EQUILIBRIUM CONCENTRATION CALCULATED AS THE UNIONIZED SPECIES

Ester	*r*	b	a
Methyl	0.88	0.12	5.41
Ethyl	0.94	0.13	5.31
Propyl	0.96	0.14	5.28
Butyl	0.87	0.13	5.50

Summed data for 4 different pHs (8.0, 8.2, 8.4, 8.6) at at least 4 different concentrations/isotherm. Correlation coefficient (*r*) is calculated from the combined data from the 4 pHs.

constants a and b calculated. The data is shown is Table 1. The correlation coefficient for each line indicated that the plots were linear at each pH, confirming that adsorption was Langmuirian. Slopes of the lines were almost identical at the lower pHs studies but increased markedly under more alkaline conditions, with a corresponding reduction in values for ‘b’. Values for ‘a’ were almost constant over the pH range studied.

A major influence of pH is on the degree of ionization of the esters, with pK_a values of 8.40 (Anon, 1980). Therefore, the equilibrium concentration C was calculated as the concentration of unionized compound, and Langmuirian plots prepared from this data. The same plots were also prepared for methyl, ethyl and propyl esters. In each case, all points fell on one line and the results from the combined data are summarized in Table 2. The correlation coefficients show some greater variation, reflecting the combination of data from a series of experiments and the difficulties involved in controlling pH very precisely, especially around the pK_a where the degree of ionization of the ester is changing rapidly. The slope of the line decreases as the hydrophobicity of the molecule increases. However, when volumes of b are calculated on a molar basis, they are almost identical. Values for a are also similar for each ester.

Discussion

Some preservatives have been found to be inactivated by the addition of magnesium trisilicate (Yousef et al., 1972). However, no account was taken of the effect on pH of adding magnesium trisilicate to the suspending menstruum. Adsorption of benzoic acid by kaolin is markedly influenced by pH (Clarke and Armstrong, 1972). Only the dissociated anion was adsorbed. It was also observed that changes occurred on the kaolin surface, caused by pH, which influenced adsorption. The present study shows that esters of *p*-hydroxybenzoic acid are adsorbed onto magnesium trisilicate particles. The mechanism, however, must be very different from that operating for adsorption of similar compounds to kaolin. Firstly hydroxybenzoic acid esters are not adsorbed to kaolin. Secondly, adsorption to magnesium trisilicate decreases as pH rises, and the ester molecule becomes ionized. Adsorption is Langmuirian, and is a direct function of the concentration of the ionized species. Adsorption must be associated with non-ionic forces but may occur subsequent to the neutralization of negative charges on the adsorbent surface by hydrogen ions. The present study shows that, when the adsorption process is considered in relationship to non-ionized ester concentrations, values for the Langmuirian constants a and b are similar for the 4 esters. Adsorption must be a function of the aromatic core of the molecule, rather than the alkyl ester side-chain. Adsorption is not affected by the hydrophobicity of the molecule. Both the adsorptive capacity (indicated by b) of the adsorbent and the binding process (related to a) are unrelated to the length of the ester side-chain.

Other molecules have been shown to be strongly bound to magnesium trisilicate. Diazepam appears to be bound as the non-ionized compound (Naggar, 1981). The involvement of surface interaction through Van der Waal's or other types of forces was implicated, as well as ion dipole interaction, since unionized diazepam possesses a dipole moment. Steroids also appear to be adsorbed as non-ionized molecule (Khalil and Iwagwa, 1978). Therefore, the tendency of magnesium trisilicate to adsorb non-ionized molecules has been further established. In the case of parabens esters, this process is independent of the hydrophobicity of the parent molecule. Despite the significant binding of the parabens esters to magnesium trisilicate, preliminary studies suggest that the preservative activity in suspension is almost unaffected. A similar observation has been reported by Fulayyeh et al. (1981) in which adsorption of quaternary ammonium compounds to attapulgite has not led to loss of antibacterial activity. Factors other than the aqueous concentration of preservatives have a marked effect on the survivial of micro-organisms, such as the high pH and adsorption of organisms onto the suspended solid. Thus, this complex system requires further microbiological study to elucidate the significance of adsorption to the preservative capacity of the parabens in magnesium trisilicate mixtures.

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