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Research Papers

ADSORPTION OF CHLORPHENIRAMINE MALEATE BY MONTMORILLONITE

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SUMMARY

In an attempt to achieve sustained action in the oral administration of antihistamines, the interaction between montmorillonite and chlorpheniramine maleate (3-chlorphenyl-N,N-dimethyl-3-pyrid-2′-ylpropylamine) has been studied by adsorption isotherms, X-ray diffraction and I.R. spectroscopy.

From the adsorption studies, it may be deduced that: (1) the amount of chlorpheniramine adsorbed by sodium montmorillonite increases with the increase in the pH of the solution; (2) the reaction is rapid and there is no additional adsorption of the compound after 15 min of treatment; and (3) the maximum amount adsorbed, according to the adsorption isotherms (pH = 7 and 30 min of treatment), is very close to the cation exchange capacity of montmorillonite (80 mEq/100 g).

The results from X-ray diffraction and I.R. spectroscopy show that the organic molecules are adsorbed into interlayer space of montmorillonite, and that the cation exchange is the mechanism responsible for these interactions.

INTRODUCTION

From a biopharmaceutical point of view, the presence of clays in the gastrointestinal tract is of interest for two reasons: a decrease in the bioavailability of orally administered drugs together with the possibility of achieving a sustained action, by means of a programmed adsorption speed, thus ensuring efficient plasma levels over long periods, with obvious therapeutic advantages.

Numerous works are cited in the literature concerning applications of clay minerals in pharmacy, some of which present results on the adsorption of drugs by montmorillonite (Pinck et al., 1961; McGinity et al., 1976), but there are very few which deal with the study of the mechanisms of adsorption responsible for the interaction of drugs with clays. Outstanding in this field, is a recent study on the adsorption of clindamycin and tetracycline by montmorillonite (Porubcan et al., 1978).

Knowledge of the interaction mechanisms of clays with drugs should allow one to predict the possibility of adsorption of a given compound by a clay, as a function of the properties of the clay and the structure of the drug.

The aim of this paper is to study the interaction mechanism of montmorillonite with chlorpheniramine maleate in the future hope of achieving a sustained action in the administration of antihistamines.

Montmorillonite was chosen because it is the clay with the highest exchange capacity and largest surface area among those used in pharmaceutical systems. These two properties of the clay are directly related to the mechanisms of adsorption.

Background

The expanding layer clays are able to form definite interlayer complexes with organic compounds by means of the intercalation of the organic molecules in the interlayer space of the silicate (MacEwan, 1962; Greenland, 1965).

The formation of these complexes is influenced by the structural characteristics of the silicate and, in particular, by the interlayer bonding strength. Thus, in the case of montmorillonite, the electrostatic bonding between the layers and the cations is very weak and facilitates the entrance of organic molecules into the interlayer space with a consequent swelling in the direction of the c-axis of the crystals. There are other factors which also affect the adsorption, such as the nature of the organic molecule (chemical structure, polarity, etc.) and the nature and hydration status of the interlayer cations of the clay.

The intercalation of the organic molecule into the interlayer space may be detected by X-ray diffraction, which also allows deductions of the probable disposition adopted by the molecules within the interlayer. The amount of organic compound adsorbed may be easily determined by adsorption isotherms. I.R. spectroscopy offers an adequate method for the study of the mechanisms of adsorption, and, except in some cases in which the strong adsorption of the silicate lattice masks the results, the bands of the organic molecule adsorbed are easy to differentiate and the shifts which these bands undergo when the molecules are adsorbed by the clay present information about the adsorption mechanism.

Adsorption mechanisms include hydrogen bonding, π electrons and van der Waals forces within physical adsorption; and cation exchange, protonation and coordination in the field of chemical adsorption, (Mortland, 1970; Calvet and Chassin, 1973). In the case of molecules of a large size and complex structure, such as certain drugs, the understanding of the mechanism or mechanisms implicated in the clay–organic compound interaction presents serious difficulties.

When adsorption is of a physical nature, the organic molecules are weakly retained and their desorption is easy, while in the case of chemisorption, the greater bonding strength impedes their release to a considerable extent.

MATERIALS AND METHODS

The less than 2 μm fraction of Albagel montmorillonite was used in this study. This fraction was separated by sedimentation from an aqueous suspension of the original clay.

Its cation exchange capacity determined by the ammonium acetate method, (Gonzalez Zapatero, 1966), is 80 mEq/100 g. Sodium montmorillonite was prepared by successive treatment of the clay with neutral solutions of sodium acetate followed by washings with water and with ethanol.

The chlorpheniramine maleate used was of the standard required by B.P. and U.S.P. It is a solid white compound which is soluble in water.

Adsorption

In the studies on adsorption, 100 mg of sodium montmorillonite equilibrated in an atmosphere of 50% H_2SO_4, 50 ml in volume, and a temperature of 40°C were used in all cases. A water bath was used and the suspension was shaken continuously. All determinations were performed twice.

The influence of pH on the adsorption of the drug was studied by treating 100 mg of montmorillonite with solutions of chlorpheniramine maleate (0.2 mEq in 50 ml) adjusted to pH between 2 and 9. The suspensions were shaken in a water bath for one hour at 40°C. After the period of treatment, the suspension was centrifuged and the equilibrium concentration in the supernatant fluid was determined by U.V. spectroscopy [1] (chlorpheniramine absorption maximum at 263 nm).

The determination of adsorption as a function of the concentration in order to obtain the isotherm was carried out according to the method described for the study of the influence of pH; the amounts of chlorpheniramine maleate used being 0.050, 0.070, 0.080, 0.100, 0.120, 0.150, 0.200, 0.300, 0.350 mEq. pH was 7.0 and the time of contact was 30 min.

X-ray diffraction

For the study by X-ray diffraction [2], oriented aggregates of sodium montmorillonite were used, together with oriented aggregates of the montmorillonite–drug complexes, unwashed, or previously washed with distilled water adjusted to the pH of the solution used in the preparation of the corresponding complexes. For the preparation of these aggregates, appropriate volumes of the sample suspension was pipetted onto glass slides and air-dried. Diffractograms of the complexes, air-dried and dried under a vacuum of 0.1 mm Hg for 24 h, were obtained. In the case of the dehydrated complexes, the aggregates were previously wrapped in a film [3] of polyethylene terephthalate in order to prevent their rehydration. The corresponding diffractograms were obtained with Cu Kα radiation.

I.R. analysis

For the I.R. analysis [4], KBr discs at 0.8–1.0% of the samples of natural montmorillonite, chlorpheniramine maleate and of the complexes were prepared.

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[1] Model Beckman DB-GT.

[2] Philips PW 1010.

[3] Mylar.

[4] Model Beckman Acculab-6.

RESULTS AND DISCUSSION

Fig. 1 shows the influence of the pH on the adsorption of chlorpheniramine maleate by sodium montmorillonite. It may be seen that the adsorption increases with the rise in pH, the amount adsorbed at pH 7 being 76 mEq/100 g, very close to that necessary to satisfy the cation exchange capacity of the clay of 80 mEq/100 g.

The processes which might take place in the adsorption of chlorpheniramine maleate as a function of pH may be represented by the following equations:

$$AHM \rightleftharpoons AH^+ + M^- \qquad (I)$$

$$\text{Mont-Na} + AH^+ \rightleftharpoons \text{Mont-AH} + Na^+ \qquad (II)$$

$$\text{Mont-Na} + H^+ \rightleftharpoons \text{Mont-H} + Na^+ \qquad (III)$$

$$AHM + OH^- \rightleftharpoons A + H_2O \qquad (IV)$$

$$\text{Mont-AH} + A \rightleftharpoons \text{A-Mont-AH} \qquad (V)$$

where A is chlorpheniramine, AH^+ the chlorphenirammonium cation and M^- the maleate anion.

The chlorpheniramine maleate in solution is dissociated into chlorphenirammonium and maleate ions (I). The principal adsorption reaction must therefore be (II) in which the sodium ions of the montmorillonite are exchanged for the chlorphenirammonium ions of the solution. At low pH there must be great competition between the hydrogen and chlorphenirammonium ions, which would impede the total substitution of the sodium by the organic cation (III), thereby giving rise to low adsorption values, which decrease as the pH does. At a pH of 7.0, only reaction (II) takes place, almost all of the sodium ions being replaced by those of chlorphenirammonium. At pH higher than 7.0, adsorption is greater than the exchange capacity. At these pH values, close to the pK_a of the amine, the concentration of the chlorphenirammonium ion decreases and part of the compound must exist in a neutral form, according to reaction (IV); these neutral molecules being adsorbed additionally through van der Waals forces (V). The higher the pH,

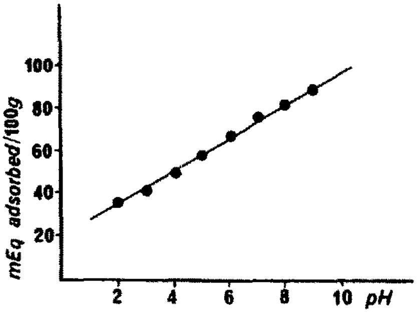

Fig. 1. Influence of the pH on the adsorption of chlorpheniramine maleate by sodium montmorillonite (0.2 mEq of chlorpheniramine maleate with 100 mg of montmorillonite in 50 ml, T = 40°C, time of treatment = 1 h).

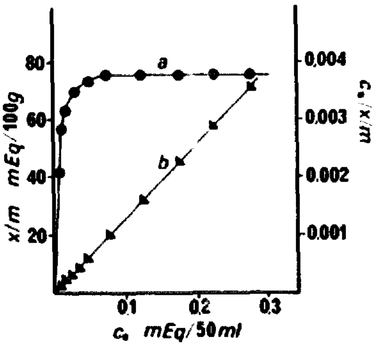

Fig. 2. Adsorption isotherm of chlorpheniramine maleate by sodium montmorillonite. a: amount adsorbed/100 g of the clay (X/m), against the equilibrium concentration (C_e) (0.050, 0.070, 0.080, 0.100, 0.120, 0.150, 0.200, 0.250, 0.300 and 0.350 mEq of chlorpheniramine maleate with 100 mg of montmorillonite in 50 ml, T = 40°C, time of treatment = 30 min). b: Langmuir plot.

the more free amine there is, and the greater the amount adsorbed. At pH values higher than 9.0, the amine released exceeds its limit of solubility in water and therefore precipitates.

It should be pointed out that at low pH, it is possible that protonation of the nitrogen of the piridinic ring takes place, the chlorphenirammonium ion thus becoming divalent, and that this might contribute to the fact that adsorption decreases at low pH.

The phenomenon of the adsorption of organic cations by montmorillonite in excess of its exchange capacity has been reported by various authors, (Grim et al., 1947; Kurilenko and Mikhalyuk, 1959; Morel and Henin, 1956), in studies on the adsorption of different amine salts by montmorillonite and they, too, attribute it to the additional adsorption by van der Waals forces.

The study of the influence of the time of contact intervals in the adsorption of chlorpheniramine by montmorillonite shows that the reaction is rapid, there being no additional adsorption of the compound after 15 min of treatment.

The adsorption isotherm of chlorpheniramine maleate by montmorillonite is shown in Fig. 2a. It shows the equilibrium concentration as a function of the amount adsorbed. Fig. 2b shows the adsorption data plotted according to the Langmuir equation. It may be seen that the maximum amount adsorbed is 76 mEq/100 g, close to the exchange capacity of the clay, and does not increase upon addition of an excess of the compound. When the adsorption data are plotted according to the Langmuir equation, a straight line is obtained. The conformity of the data to this equation implies a chemisorption mechanism. It should be noted that the data also agree with the Freunlich equation.

In order to confirm the adsorption of chlorphenirammonium ions in the interlayer space of montmorillonite and to suggest the possible disposition of the organic cations in the interlayer, X-ray diffractograms were made of sodium montmorillonite and of the same treated with solutions of chlorpheniramine maleate at different pH and with chlorpheniramine maleate solutions at different concentrations. The basal spacings, d_{001}, are included in Tables 1 and 2; and Fig. 3 shows some of the diffractograms. The results show that chlorpheniramine penetrates into the interlayer space of the montmorillonite, and

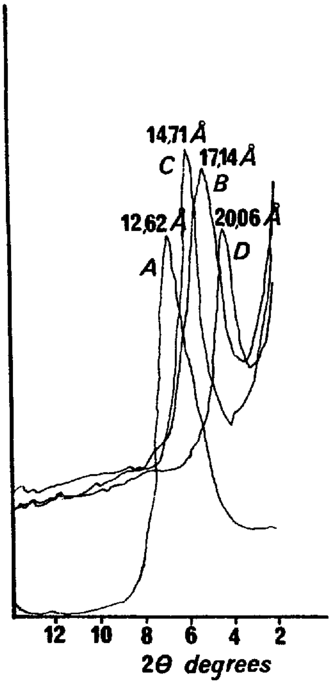

Fig. 3. X-ray diffractograms. A: sodium montmorillonite. B: montmorillonite–chlorpheniramine maleate at pH 7.0 (76 mEq/100 g). C: montmorillonite–chlorpheniramine maleate at pH 7.0 (43 mEq/100 g). D: montmorillonite–chlorpheniramine maleate at pH 9.0 (89 mEq/100 g).

are in agreement with the adsorption data as a function of the pH. Thus, upon increasing the pH, the basal spacings, d_{001}, of the clay also increase. The increases in the spacing with relation to the value of 9.6 Å of the dehydrated montmorillonite varies from 6.45 Å at a pH of 5.5 to 10.46 Å at pH 9.0. The increase which corresponds to the sample treated with solution at pH 7.0 is that of 7.54 Å; under these conditions, as has been previously indicated, adsorption is equal to the exchange capacity of the clay. If the samples treated with a solution at pH 8.0 pr 9.0 are washed several times with water, their

TABLE 1

SPACINGS, d_{001}, OF SODIUM MONTMORILLONITE TREATED WITH A SOLUTION OF CHLORPHENIRAMINE MALEATE AT DIFFERENT pHs

pH	Unwashed samples		Washed samples	
	d_{001} (Å)	ΔÅ	d_{001} (Å)	ΔÅ
5.5	16.05	6.45	15.77	6.17
7.0	17.14	7.54	17.14	7.54
8.0	19.83	10.23	17.14	7.54
9.0	20.06	10.46	17.14	7.54

TABLE 2

SPACINGS, d_{001}, OF SODIUM MONTMORILLONITE TREATED WITH SOLUTIONS OF CHLORPHENIRAMINE AT DIFFERENT CONCENTRATIONS

Amount of organic compound		Organic compound adsorbed (mEq/100 g)	d_{001} (Å)	ΔÅ
Added mEq	Adsorbed mEq			
0.050	0.043	43	14.71	5.71
0.080	0.063	63	15.77	6.17
0.100	0.071	71	16.66	7.06
0.200	0.076	76	17.14	7.54
0.350	0.076	76	17.14	7.54

basal spacing also shifts to 17.14 Å (Δ = 7.54 Å), which confirms the adsorption of the excess molecules of the exchange capacity by weak van der Waals forces.

The basal spacings of the samples treated with chlorpheniramine also increase with the concentration of the solution until a concentration necessary to saturate the exchange capacity is reached; from this concentration onwards, the spacing of 17.14 Å remains constant.

Fig. 4 shows the I.R. spectra of: (a) montmorillonite; (b) chlorpheniramine maleate; (c) montmorillonite–chlorpheniramine maleate at pH 7.0 (washed sample); and (e) montmorillonite–chlorpheniramine maleate at pH 9.0.

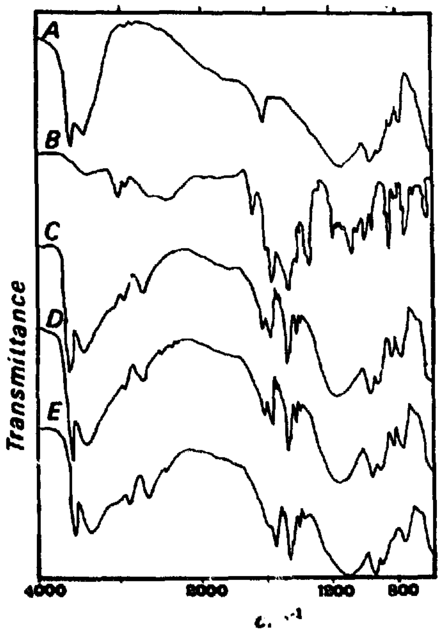

Fig. 4. I.R. spectra of: (A) sodium montmorillonite; (B) chlorpheniramine maleate; (C) montmorillonite–chlorpheniramine maleate at pH 7.0; (D) montmorillonite–chlorpheniramine maleate at pH 7.0 (washed sample); and (E) montmorillonite–chlorpheniramine maleate at pH 9.0.

The presence of the chlorpheniramine bands in the spectrum of the complex washed several times indicates the existence of the organic compound in the interlayer space of the clay. On the other hand, the disappearance of the maleate anion bands in the spectra of the complexes suggest that the compound is not adsorbed as an amine salt. The progressive displacement of the interlayer water by the organic ions gives rise to the decrease in intensity in the deformation band of the water at 1630 cm^{-1}, which almost disappears in the montmorillonite–chlorpheniramine system at pH 9.0 when the adsorption is greater (Fig. 4E), surpassing the exchange capacity, as has been reported above.

None of the bands undergo a frequency shift, which suggests the absence of another kind of bonding mechanism different from cation exchange or van der Waals forces.

Bearing in mind the molecular dimensions of chlorpheniramine and the increase in spacing which the clay undergoes during adsorption (Δ = 7.54 Å), the montmorillonite–chlorpheniramine complex at 17.14 Å must be monolayer, with the benzene rings perpendicular to the surface of the oxygen atoms. The increase is greater than the height of the molecules with this disposition (6.5 Å) and they must therefore be tilted in the interlayer with the amine group on the surface of the oxygen atoms. This orientation permits closer packing than does the parallel orientation of chlorpheniramine, and is necessary because the flat surface of the organic cation (100 $Å^2$) is larger than the surface available for the inorganic exchange cation (80 $Å^2$).

In the unwashed complexes formed with a solution of pH 8.0 and 9.0 when the adsorption exceeds the exchange capacity, with basal spacings of 19.83 Å and 20.06 Å and with increases of 10.23 Å and 10.46 Å, the presence of neutral chlorpheniramine molecules in the interlayer demands a greater packing. This gives rise to a greater tilt of the molecules in the interlayer space, with the consequent increase in spacing.

It may be concluded that by treatment of montmorillonite by an aqueous solution of chlorpheniramine maleate, the chlorphenirammonium cations are adsorbed into the interlayer space of the clay, giving rise to the formation of a definite complex with a basal spacing, d_{001}, of 17.14 Å. The adsorption mechanism is cation exchange and the maximum amount adsorbed by this mechanism is 76 mEq/100 g.

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