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Interaction of monovalent cationic drugs with montmorillonite

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Abstract The aim of this study was to compare the adsorption of various organic drugs and a well-studied surfactant. The organic drugs used were promethazine chloride [10-(2-dimethylammonium) propylfenothiazine chloride] and buformin hydrochloride (1-butylbiguanidine chloride). The surfactant was benzalkonium chloride (*N*-tridecyl-*N*-benzyl-*N*,*N*-dimethylammonium chloride). Different amounts of drug solutions were added to montmorillonite suspensions, either separately (simple system) or in combination (competitive system) under the same conditions, and the organocomplexes formed were investigated. The organic molecule with the short alkyl chain adsorbed to yield monolayer coverage, whereas the aromatic molecule and the surfactant formed a pseudotrimolecular arrangement. In the competitive system, the larger organic molecules (having the same charge) displaced the smaller one from the interlayer space. The intercalation of molecules in the interlayer space was investigated by X-ray diffraction measurements.

Keywords Montmorillonite · Clay–mineral organocomplexes · X-ray diffraction measurements · Competitive adsorption · Drug intercalation

Introduction

The interactions of organic molecules (surfactants, dyes and drugs) with swelling clay minerals have been studied since the 1960s. The possibility of their wide-ranging application in environmental science (ecology), soil chemistry and pharmacy (because of their high cation-exchange capacity (CEC) and large specific surface) attracted considerable interest.

The study of the multilevel process of adsorption of surfactant molecules on the surface of clay minerals has been widely reported in the literature [1–3]. The first step in the adsorption of organic surfactants (which depends on the nature of the adsorbent surface) is the individual adsorption of the molecules or ions, which proceeds via direct adsorption or cation exchange. The second step involves the hydrophobic interactions between the organic molecules or ions already bound on the clay surface and the newly adsorbed molecules. In the presence of certain molecules regarded as impurities, qualitative (mechanism of adsorption) and quantitative change can occur during the adsorption process [4]. One important factor which influences the adsorption process is the structure of the adsorbed molecule or ion and especially the length of its alkyl chain. Surfactants with a linear structure and fewer than nine carbon atoms in the chain usually take up a more perpendicular position on the surface, while molecules with chains longer than nine carbon atoms prefer a flat distribution [5]. Lagaly [6] studied and described the physicochemical factors which govern and influence the adsorption process. He distinguished between physical adsorption, ion-exchange adsorption and intercalation.

Of the factors which determine the adsorption process (nature of the clay mineral, crystallographic and hydration conditions), Lagaly focused on the influence of the size and arrangement of the clay mineral layers [7].

Margulies et al. [8] utilized an adsorption model that combines specific bonding and electrostatic interactions. The adsorption of organic cations on negatively charged clay minerals is described by two binding coefficients. The first relates to the formation of a neutral complex between one organic cation and one clay mineral site, and the second to the binding of an organic cation and the neutral complex [9]. The influences of molecular aggregations on the adsorption process were studied by Spencer and Sutter [10] and Cenens and Shoonheydt [11]. The process of aggregation of surfactant molecules becomes important at concentrations just in excess of the CEC of the surfactant; at lower concentrations, all the molecules are adsorbed. For organic molecules with a short alkyl chain, the amount adsorbed does not exceed the value corresponding to the total exchange capacity [12].

Adsorption phenomena were first made use of in pharmacy by Rupprecht et al. [14], and later by Carstensen and Su and [15] and McGinity and Hill [16], who studied the adsorption of diazepam and neomycin sulfate on montmorillonite and attapulgite. Diazepam binds only on the external surface. Neomycin strongly binds into the interlayer spaces of montmorillonite and decreases the bioavailability. The difference in behaviour of drug molecules in the process of adsorption on clay minerals posed a challenge for scientists, and such investigations continued in the 1980s and 1990s.

Sanchez-Camazano et al. [17] and Vincente et al. [18] studied the binding of chlorpheniramin maleate and found that the greatest adsorbed quantity of drug was equal to the total exchange capacity of the montmorillonite. Porubcan and coworkers studied the adsorption of digoxin [19], clindamycin and tetracycline [20]. Digoxin was reversibly adsorbed at pH 2–6 on montmorillonite. Interaction of digoxin with montmorillonite was possible since many neutral molecules are known to interact with clays by physical adsorption and hydrogen bonding. Clindamycin and tetracyclin were adsorbed by cation exchange.

The aim of the present work relates to the development of long-release products, involving montmorillonite as a drug carrier. For this reason, we studied the interactions between montmorillonite and the monovalent organic molecules buformin hydrochloride, promethazine chloride and benzalkonium chloride. In the first step, we focused on the differences between the adsorption processes of these molecules. These drugs differ in structure, size and chemical behaviour. We included a surfactant (also utilized in pharmacy) for comparison with the drug molecules.

Materials and methods

Materials

Wyoming montmorillonite with a CEC of 0.82 mEq/g was used. The CEC of the purified montmorillonite was determined by the ammonium saturation method [21]. A 2-μm fraction was separated by sedimentation from a 1.4% w/w aqueous suspension of the original bentonite [21]. After separation, the suspension was spray-dried with a Niro Minor atomizer (Copenhagen, Denmark); temperature of inlet air: 110 °C, temperature of outlet air: 75 °C, pressure: 3 atm, atomizer rotation rate: 25,000 rpm. We prepared a 1% suspension by dispersing 2 g of this montmorillonite in 200 ml distilled water.

Promethazine chloride, buformin hydrochloride (Egis Pharmaceuticals, Budapest, Hungary) and benzalkonium chloride (CHINOIN-Sanofi Chemical and Pharmaceutical Works, Budapest, Hungary) were used as received, without further treatment or purification. Their structures are shown in Fig. 1.

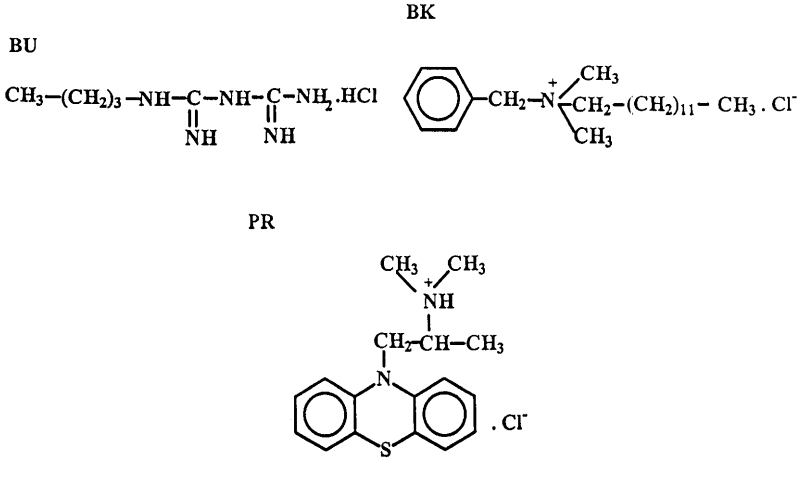

Fig. 1 Molecular structures of buformin hydrochloride (*BU*), benzalkonium chloride (*BK*) and promethazine chloride (*PR*)

Determination of adsorption isotherms

Different amounts of drug solutions (Table 1) were added to 20 ml 1% montmorillonite suspension in conical flasks. The dispersions were shaken for 1 h at constant room temperature and were left to equilibrate for 48 h. The pH was between 6.02 and 7.54. The suspension was then centrifuged for 20 min at 5000 rpm, using a Janetzki K-23 (Engelsdorf/Leipzig, Germany) centrifuge. After 48 h, the suspension was filtered and analysed. The different amounts of drugs/surfactant added to each sample are presented in Tables 1 and 2.

The organic cation concentration in each of the filtrates was determined by measuring the absorption at 250 nm (promethazine), 234 nm (buformin) and 262 nm (benzalkonium) with a ATI-Unicam UV2 UV–vis spectrophotometer. The amount of drug adsorbed was calculated from the difference in the concentrations of the solutions before and after adsorption. The number (n^s) of monovalent cations adsorbed was calculated from the equation

$$n^s = V(c_o - c_e)/m \,, \quad (1)$$

where V is the total volume of suspension and added drug solution, c_o and c_e are the initial and equilibrium concentrations, respectively, and m is the mass of adsorbent.

To evaluate the competitive adsorption between these two monovalent cationic drugs, equal molar quantities of each cationic drug in aqueous solution were added simultaneously to a 1% w/w montmorillonite suspension. The concentrations of the aqueous solutions of the drugs were varied (Table 2). The flasks were shaken for 1 h and then kept at room temperature. Separation and spectrometric measurements were performed after 48 h, in the same way as for the simple systems. Subtraction of the spectrum of one organic cation from the measured spectrum yielded a spectrum that correlated closely with that of the second cation, and vice versa. This led to the conclusion that there was no chemical interaction between the two organic cations in solution that affected their spectra.

X-ray diffraction experiments

For air-dried samples, the suspensions were placed on glass plates and allowed to dry under atmospheric conditions. For wet samples, the initial suspensions were centrifuged and the residue was used in paste form in a sample support, covered by Mylar foil (25 μm). To prevent evaporation of the dispersion, the sample was immediately subjected to X-ray measurements. The basal

Table 1 Composition of the simple systems containing buformin hydrochloride (*BU*), benzalkonium chloride (*BK*) and promethazine chloride (*PR*). System 1: buformin–montmorillonite–water. System 2: promethazine–montmorillonite–water. System 3: benzalkonium–montmorillonite–water. n_{add} is the quantity (mmol) of drug or surfactant added to each sample relative to 1 g montmorillonite. V_{total} is the total volume of the suspension

System		Sample										
		1	2	3	4	5	6	7	8	9	10	11
1	n_{add} (mmol BU/g)	0.057	0.129	0.241	0.457	0.920	1.120	1.466	1.683	1.913	2.132	2.961
2	n_{add} (mmol PR/g)	0.058	0.115	0.225	0.439	0.897	1.135	1.449	1.675	1.899	2.127	2.944
3	n_{add} (mmol BK/g)	0.060	0.120	0.214	0.444	0.911	1.129	1.479	1.657	1.964	2.133	2.899
	V_{total} (cm^3)	25	25	25	25	25	25	25	25	25	25	25

Table 2 Composition of the competitive system: promethazine–buformin–montmorillonite–water. n_{add} is the quantity (mmol) of drug added to each sample relative to 1 g montmorillonite. V_{total} is the total volume of one sample

Drug	Sample							
	4	5	6	7	8	9	10	11
n_{add} (mol BU/g)	0.225	0.459	0.565	0.733	0.849	0.955	1.069	1.477
n_{add} (mmol PR/g)	0.226	0.453	0.562	0.729	0.840	0.951	1.064	1.477
V_{total} (cm^3)	30	30	30	30	30	30	30	30

Table 3 System parameters for the simple and competitive systems. System 1: buformin–montmorillonite–water. System 2: promethazine–montmorillonite–water. System 3: benzalkonium–montmorillonite–water. System 4: promethazine–buformin–montmorillonite–water referring to buformin. System 5: promethazine–buformin–montmorillonite-water referring to promethazine. $n^s_{m,calc}$ is the calculated quantity of drug necessary for monolayer coverage calculated by the Langmuir equation. n^s_{max} is the experimentally determined maximal adsorbed quantity of drug or surfactant. $d_{L,m,calc}$ is the calculated basal distance, d_{001}, for monolayer coverage, $d_{L,m,measured}$ is the measured basal distance for monolayer coverage. d_{Lmax} is the determined maximal basal distance

System	$n^s_{m,calc}$(mmol/g)	$d_{L,m,calc}$ (nm)	$d_{L,measured}$ (nm)	$d_{L,max}$ (nm)	n^s_{max}(mmol/g)
1	1.31	1.41	1.37	1.37	0.75
2	0.73	1.50	1.59	2.10	1.61
3	0.52	1.41	1.45	2.71	1.68
4	–	–	–	2.02	0.17
5	–	–	–	2.02	1.17

spacings (d_L values) were determined with a Philips PW-1830 diffractometer (Cu Kα radiation, $\lambda = 1.54$ nm) in the 2Θ range 1–15°.

Results and discussion

First, we present the adsorption of the surfactant-like benzalkonium chloride, also used in pharmacy, on montmorillonite. The adsorption isotherm obtained for surfactant molecule (Fig. 2) shows that at low concentrations of benzalkonium chloride solution the total quantity added was adsorbed. This section of the isotherm corresponds to the ion-exchange process on sodium montmorillonite. On increasing the concentration of the surfactant solution, we obtained the increasing part of the adsorption isotherm. From the concentration of the organic cations, $n_{add} = 0.444$ mmol/g, just a part of the added amount of benzalkonium was adsorbed. For a concentration of $n_{add} = 1.658$ mmol/g, the isotherm reached the plateau, and just a slight increase in the number of cations adsorbed was observed.

For the monolayer coverage, the basal spacing of $d_{001} = 1.44$–1.75 nm indicated the organic cations lying flat on the surface (Fig. 3). On increasing the number of organic cations added, their arrangement became more compact, and then a bilayer structure with tilted cations [22] started to develop. The monolayer coverage determined from the reciprocal Langmuir equation was 0.514 mmol/g. When this quantity was adsorbed, the formation of the bilayer structure began by physical adsorption. When the concentration of the added surfactant solution was 2.4 × CEC, the 001 reflection shifted to smaller angles and a new reflex indicated the development of a second phase. With increasing concentration of benzalkonium chloride, the intensity of this reflection increased and on approaching a d value of 3.32 nm separated from the first peak. This process indicates the ordering of the new structure under the influence of further adsorbed cations. The basal spacing is shown as a function of the quantity of surfactant molecules adsorbed in Fig. 4.

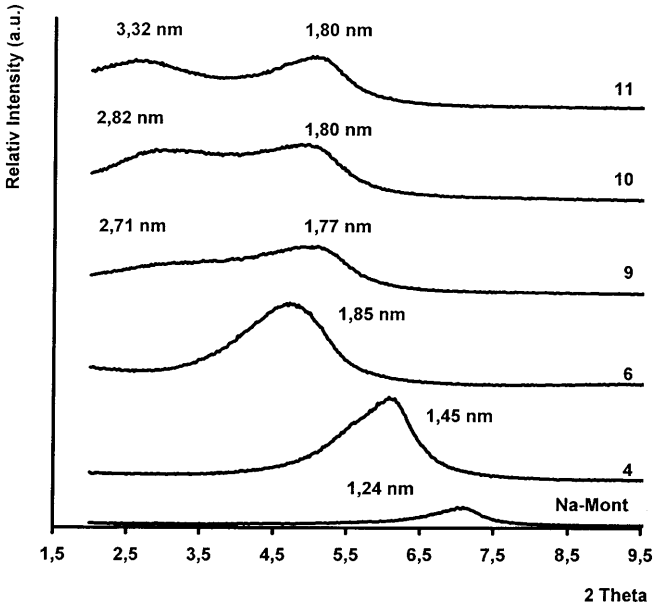

Fig. 3 X-ray diffractograms of benzalkonium–montmorillonite (samples 4, 6, 9, 10 and 11) and sodium montmorillonite

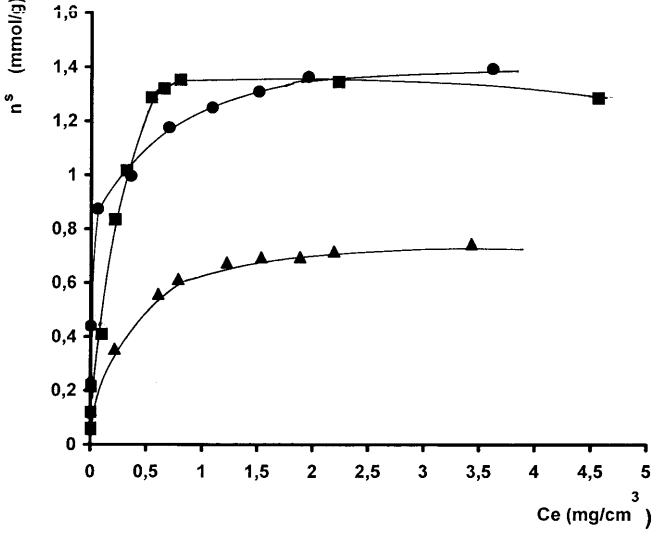

Fig. 2 Adsorption isotherms of BU (*triangles*), BK (*squares*) and PR (*circles*) on montmorillonite

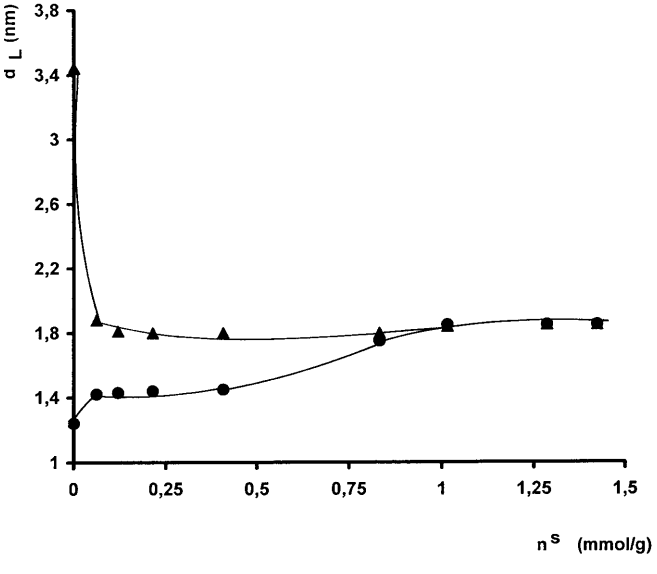

Fig. 4 Basal spacing, d_{001}, of benzalkonium–montmorillonite in suspension (*triangles*) and after drying (*circles*)

The adsorption of buformin hydrochloride, a simple monovalent organic cation with a short alkyl chain and a quaternary ammonium head group, is described by a monolayer Langmuir isotherm (Fig. 2). At low concentrations of buformin, the added cations were totally adsorbed on the surface of the montmorillonite. When the monolayer structure was formed, the isotherm reached the plateau. At cation concentrations equivalent to $2 \times$ CEC and $3 \times$ CEC, no changes in the amount adsorbed were observed. Thus, further organic molecules were not adsorbed.

From the reciprocal of the Langmuir equation,

$$1/n^{s} = 1/n^{s}_{m} + 1/n^{s}_{m}bc \ , \qquad (2)$$

where n^{s} is the surface concentration, n^{s}_{m} is the surface concentration at monolayer coverage, b is the Langmuir equilibrium constant and c is the equilibrium concentration, the monolayer adsorption capacity was found to be 1.31 mmol/g (Fig. 5). Comparing the value obtained from Eq. (2) and the value of the plateau of 0.745 mmol/g (Fig. 2), we conclude that a complete monolayer structure cannot be attained up to the maximum buformin concentration (1.48 mmol/g). From the maximal quantity of buformin adsorbed of 0.745 mmol/g, we presume that this system mainly involves cation exchange. The basal spacing (Fig. 6) of the buformin derivative (in suspension 1.45 nm, dried 1.37 nm) indicates that even small numbers of buformin cations were adsorbed; they displaced the interlayer water molecules. For this reason, the measured basal distances have the same values for the suspension and the dried samples (Fig. 7). During adsorption of the organic cations, the intensity of the 001 reflection decreased strongly. The reflections at low concentration (e.g. sample 3) have a well-determined shape but are flattened and weak at higher concentration (e.g. samples 9 and 11). The adsorbed buformin molecules are situated parallel to the surface of the montmorillonite.

The adsorption isotherm of promethazine chloride on montmorillonite is presented in Fig. 2. The total quantity of promethazine, as for the other two systems, was bound at low concentrations by a cation-exchange process. At higher concentrations, up to monolayer

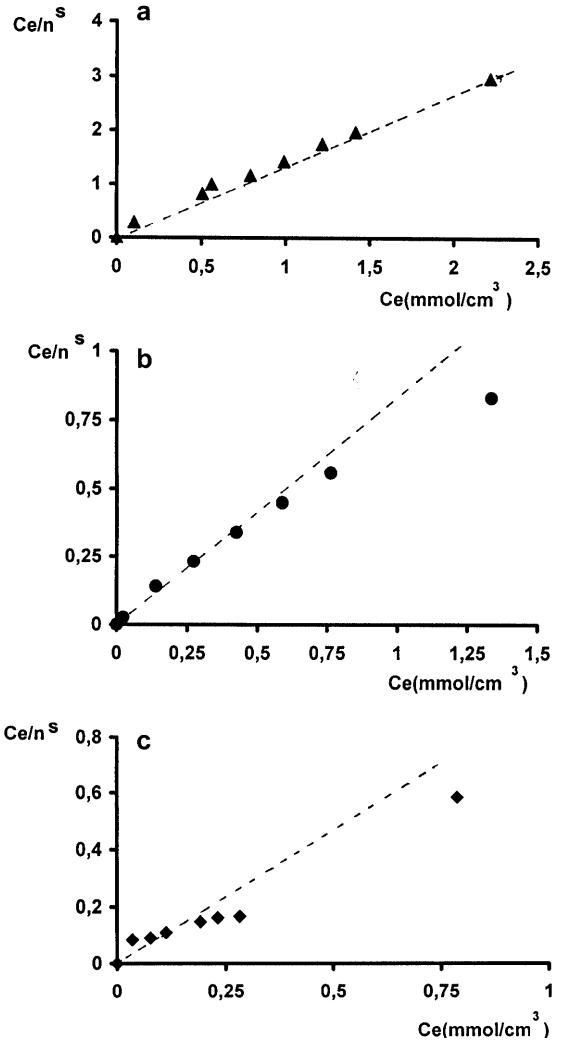

Fig. 5a–c Reciprocal representation of Langmuir isotherms. **a** Buformin–montmorillonite–water. **b** Promethazine–montmorillonite–water. **c** benzalkonium–montmorillonite–water

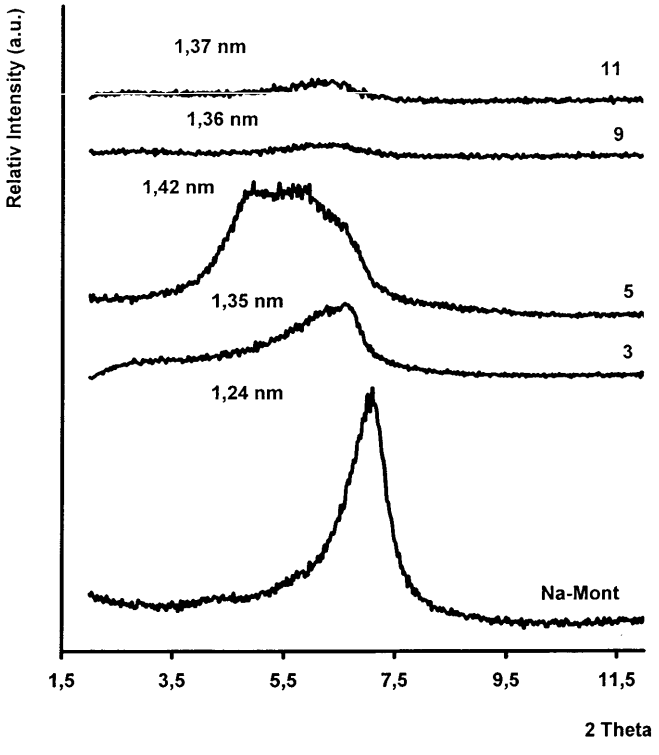

Fig. 6 X-ray diffractograms of buformin-montmorillonite (samples 3, 5, 9 and 11) and sodium montmorillonite

coverage, the adsorption isotherm increases. The reciprocal of the Langmuir equation for this system (Fig. 5b) shows that the determined points diverge from linearity.

The maximal coverage ($n^s_{max} = 1.608$ mmol/g) corresponds to the formation of a pseudotrilayer structure with a spacing of $d_L = 2.08$ nm. The monolayer coverage determined from the reciprocal Langmuir equation corresponds to $n^s_m = 0.794$ mmol/g (Fig. 5b). The basal spacing of sodium montmorillonite decreased when the organic cations were adsorbed (Fig. 8), even at low concentrations and the spaces of the wet and dried samples became identical. On increasing the concentration, the interlayer molecules are increasingly ordered (Fig. 9). At higher concentrations, the reflections broadened again (Fig. 9, sample 8), because disorder appears

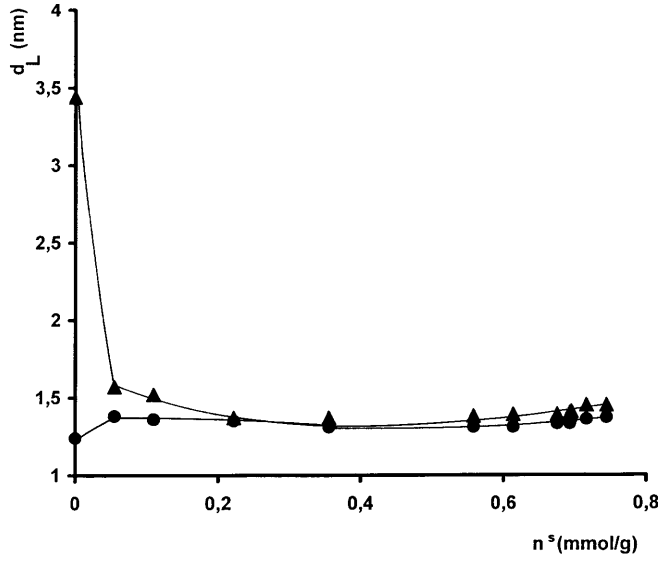

Fig. 7 Basal spacing d_{001} of buformin–montmorillonite in suspension (*triangles*) and after drying (*squares*)

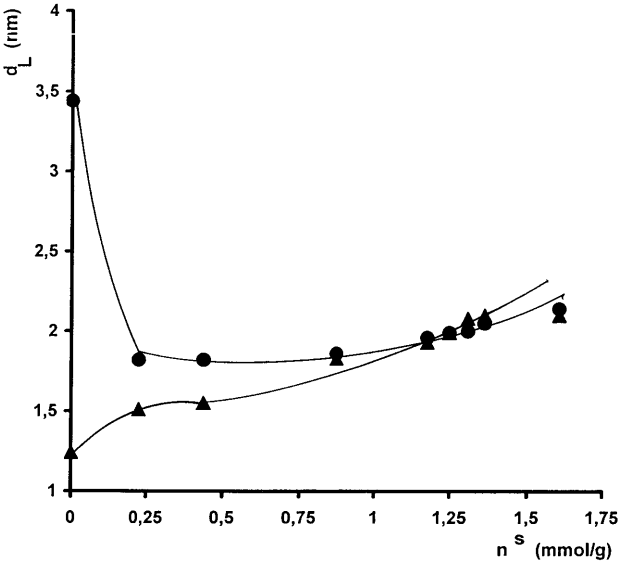

Fig. 9 d_{001} of promethazine–montmorillonite in suspension (*triangles*) and after drying (*circles*)

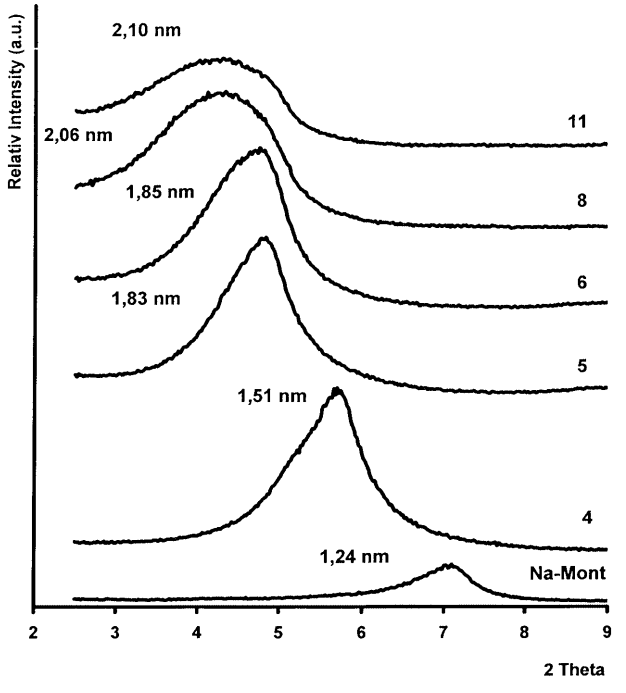

Fig. 8 X-ray diffractograms of promethazine–montmorillonite (samples 4, 5, 6, 8 and 11) and sodium montmorillonite

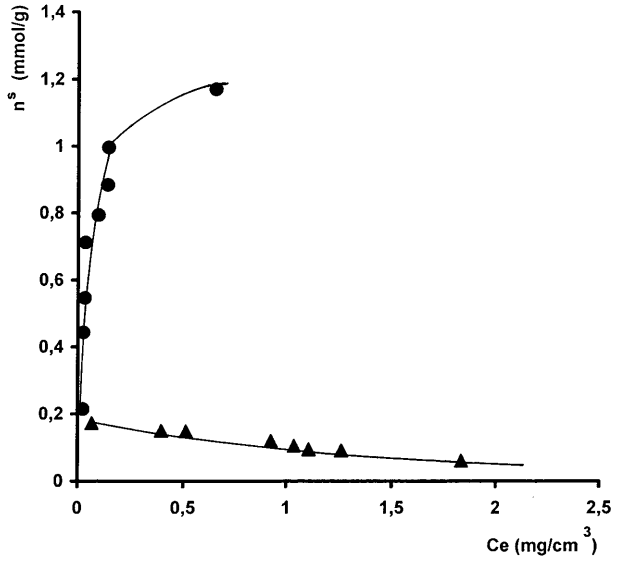

Fig. 10 Adsorption isotherm of buformin–montmorillonite (*triangles*) and promethazine–montmorillonite (*circles*) from equimolar mixtures

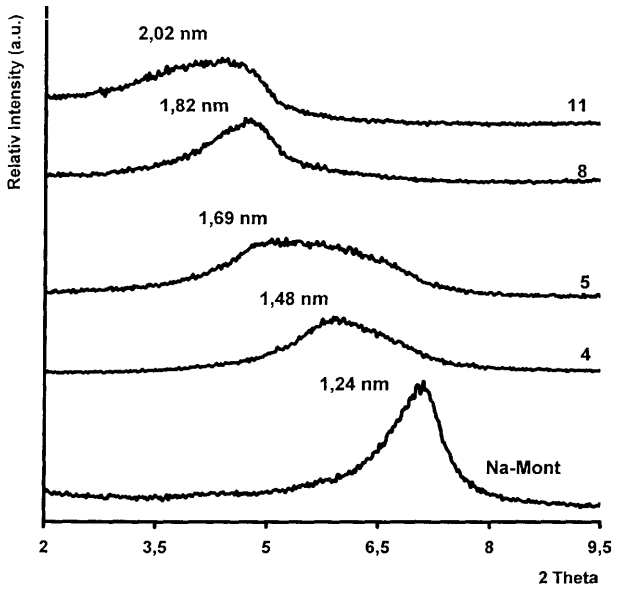

Fig. 11 X-ray diffractograms of buformin–promethazine–montmorillonite (samples 4, 5, 8 and 11) and sodium montmorillonite

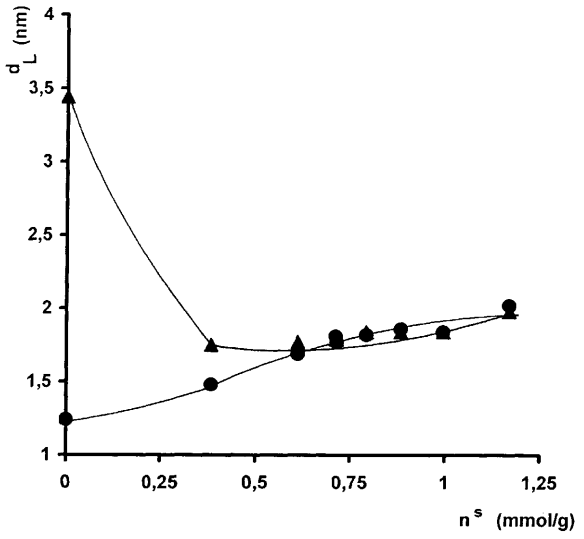

Fig. 12 d_{001} of buformin–promethazine–montmorillonite in suspension (*triangles*) and after drying (*circles*)

during multilayer adsorption. Samples 5 and 6 correspond to a bilayer ($d_L = 1.83$ nm and $d_L = 1.85$ nm) and samples 8 and 11 to a pseudotrilayer structure ($d_L = 2.06$ nm and $d_L = 2.08$ nm).

The competition between buformin hydrochloride and promethazine chloride was studied for solutions containing equimolecular amounts of both cations (Table 2). The individual adsorption isotherms of the molecules are depicted in Fig. 10. On increasing the equimolar concentrations of both cations, the smaller buformin cation is progressively displaced by the larger promethazine. The highest amount of buformin adsorbed is $n^s_{max} = 0.17$ mmol/g and that of promethazine is $n^s_{max} = 1.17$ mmol/g. The basal spacing changes during the adsorption (Fig. 11) and is similar to that of the pure cations (Figs. 4, 8). The X-ray diffractograms of the competitive system (Fig. 12) also reveal the shift of the peaks to smaller angles, as in the other systems; however, the intensities and the shapes of the diffractograms of competitive system differ from those for the simple systems. At low concentrations of the added organic molecules, flattening and broadening of the reflections occurred. It seems that the disorder is more pronounced. At higher concentrations of organic cations, when the displacement of the smaller cation by the larger molecule dominates, a slightly higher order, at least for sample 8, may be obtained.

Conclusions

In the montmorillonite–benzalkonium chloride system, the surfactant molecules are bound on the montmorillonite mainly by ion exchange. The highest quantity of surfactant adsorbed corresponds to a pseudotrilayer structure. At additions above 1.964 mmol/g benzalkonium chloride, a second phase developed.

The amount of buformin adsorbed is less than required for monolayer coverage even at the highest concentration of the added buformin, 2.961 mmol/g. The molecules are probably bound by cation exchange. X-ray diffraction measurements show no shifts of the characteristic peaks during the increasing of the concentration of buformin. The recorded basal spacings have the same values for the suspension and the dried samples.

Promethazine molecules at low concentrations are bound by ion exchange. The maximal coverage corresponds to the formation of a pseudotrilayer structure. In the presence of promethazine chloride and buformin hydrochloride, the smaller molecules are continuously displaced by the larger ones when the concentration of both cations is increased. The system already presents a certain degree of disorder at intermediate concentration.

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