Colloid Polym Sci 279:1177–1182 (2001)

ORIGINAL CONTRIBUTION

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Release of cationic drugs from loaded clay minerals

Received: 20 January 2001
Accepted: 8 March 2001

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Abstract The adsorption of promethazine chloride [10-(2-dimethylammonium propyl) fenothiazine chloride] and buformin hydrochloride (1-butylbiguanidine chloride) on montmorillonite was studied in previous work. The present article focuses on the desorption of these molecules from their organocomplexes in a medium of artificial intestinal juice (pH 7.0 ± 0.1) at the temperature of the human body (37 ± 0.5 °C). The desorption was investigated by kinetic studies, basal spacing measurements and Fourier transform IR studies. Important quantitative differences were observed: buformin, which adsorbed in a monolayer coverage, exhibited a very high desorption rate, whereas promethazine formed a pseudotrilayer arrangement and showed a lower dissolution rate.

Key words Montmorillonite · Promethazine chloride · X-ray diffraction measurements · Desorption · Drug intercalation

Introduction

The adsorption and desorption of organic molecules and surfactants on various solids were studied extensively because of their great importance in many industrial fields.

Such solids include natural clays, for example, montmorillonite, kaolinite, bentonite and illite; carbon or graphite, and synthetic alumina. The adsorbed compounds include simple surfactants, mixed surfactants and organic molecules such as drugs and copolymers.

Malik et al. [1] studied the adsorption and desorption of three surfactant molecules on bentonite, kaolinite and illite. They concluded that the increase in the extent of adsorption with the size of the organic cation was due to an increase in the van der Waals forces between the clay mineral and the surfactant. They also observed that the larger ions desorbed to a lower extent, in consequence of the poor solubility and the larger contribution of dispersion forces.

Maheshwari et al. [2] investigated the possibility of obtaining sustained release formulations, involving the bentonite–phenformin complex. They studied retardation in vivo and in vitro conditions. They concluded that the interactions between the cationic drug and montmorillonite should successfully prolong the action of phenformin hydrochloride.

The adsorption and desorption behaviour of anionic molecules on clay mineral was studied by Blockhaus et al. [3]. They used an acrylic–maleic acid copolymer adsorbed on the clay mineral as adsorbent. Monophos-

phate and tripolyphosphate displaced the adsorbed copolymer. The authors concluded that the desorption process resulted from the competition between the copolymer and phosphate compounds for the same binding sites on the kaolin surface.

Huang et al. [4] examined the desorption process of surfactant mixtures from an alumina–water interface at an ionic strength of 0.03 M NaCl at pH 10. They found that the equilibrium time for the desorption process was the same as for the adsorption process; however, the results obtained for the desorption of a single surfactant indicated that the adsorption/desorption was not completely reversible, and nonequilibrium effects due to changes in the system variables, such as pH, ionic strength and dissolved mineral species, made the adsorption/desorption process more complex.

In the present article, we focus on desorption of drug–montmorillonite complexes in artificial intestinal juice.

Materials and methods

Materials

Wyoming montmorillonite with a cation-exchange capacity of 0.82 mEq/g was used. The cation-exchange capacity of the purified montmorillonite was determined by the ammonium saturation method [5]. The fraction smaller than 2 μm was separated by sedimentation from a 1.4% w/w aqueous suspension of the original bentonite. 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.

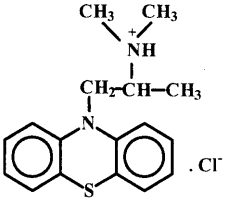
We prepared a 1% suspension by dispersing 2 g of this montmorillonite in 200 ml distilled water.

Promethazine chloride and buformin hydrochloride (Egis Pharmaceuticals, Budapest, Hungary) were used as received, without further treatment or purification. Their structure is shown in Fig. 1.

Desorption experiments

The rate of dissolution of the pure drugs as a blank experiment and their mineral complexes at 37 ± 0.5 °C was determined using a Vibrotherm shaker bath of type 609/a (MTA Kutesz, Budapest, Hungary) at frequencies of 50 min^{-1} medium intensity. Samples containing 5 mg pure drug or organocomplexes involving 5 mg drug were placed progressively into new bottles containing 50 ml artificial intestinal juice. To avoid the passage of small clay particles into the dissolution medium, the samples were placed in dialysis membrane bags (44120 Visking dialysis tube 36/32 from Serva Biochemicals). After 5, 15, 30, 60, 120, 240 and 360 min, the dialysis bags with the samples were placed in a new bottle containing pure dissolution medium under the same conditions. The quantity of dissolved drug in each bottle was determined spectrophotometrically at 234 nm for buformin hydrochloride and at 250 nm for promethazine chloride (Unicam UV/vis spectrometer). The composition of the artificial intestinal juice used was 14.40 g $Na_2HPO_4 \cdot 2H_2O$ and 7.10 g KH_2PO_4 dissolved in 1000 cm^3 distilled water.

PROMETHAZINE CHLORIDE



BUFORMIN HYDROCHLORIDE

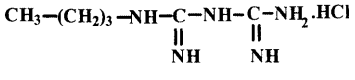


Fig. 1 Molecular structure of promethazine chloride and buformin hydrochloride

Fourier transform IR measurements

IR spectra of all the solid samples were recorded using a Bio-Rad Digilab Division FTS-65A/896 Fourier transform IR spectrometer with a deutered triglyceryl sulfate detector in KBr pellets in the range 4000–400 cm^{-1}. Each pellet contained 147 mg KBr and 3 mg dried sample. The optical resolution was 4 cm^{-1}, and 128 scans were averaged to gain a good signal-to-noise ratio.

X-ray diffraction experiments

The suspensions were placed on glass plates and allowed to dry under atmospheric conditions. The basal spacing (d_L) of the dried sample was determined with a Philips PW-1830 diffractometer (Cu Kα radiation, $\lambda = 1.54$ nm).

Results and discussion

The release of buformin from the buformin–montmorillonite complexes in artificial intestinal juice over 360 min is presented in Fig. 2 together with the dissolution of pure buformin hydrochloride under the same conditions. The compositions of the samples of buformin–montmorillonite are shown in Table 1. The curves reveal a very high desorption rate of the monolayer organocomplexe at pH 7.0 ± 0.1. As an example, sample C, which had the highest initial content of organic molecules ($n^s = 0.696$ mmol/g), released 70%, $c = 0.488$ mmol/g, of the adsorbed molecules over 360 min. The samples containing lower amounts of adsorbed buformin also displayed good dissolution rates. Sample B, with $n^s = 0.676$ mmol/g, reached 61% desorption, corresponding to $c = 0.416$ mmol/g. For sample A, with $n^s = 0.558$ mmol/g, the desorption is 43% ($c = 0.239$ mmol/g). Compared with the dissolution of pure buformin hydrochloride the organocomplexes exhibited a lower, but still appreciable, rate of desorption. Over a 360-min period of dissolution virtually all the buformin hydrochloride dissolved into the intestinal juice. The time for the dissolution of half the quantity of previously adsorbed buformin was 60 min for sample 5 and 30 min for samples B and C. There was no variation in the d_{001} basal spacing of the dried samples before and after desorption (Table 1).

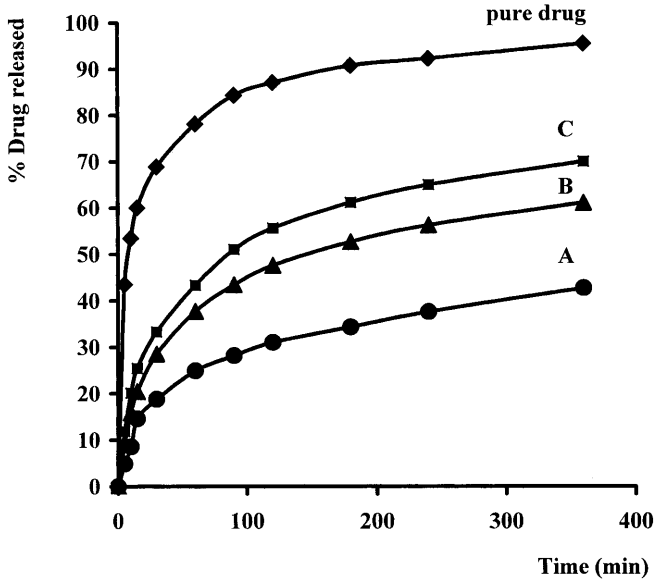


Fig. 2 Rate of desorption of buformin from the montmorillonite complexes in artificial intestinal juice:sample A (●), sample B (◆), sample C (■), buformin hydrochloride (◆)

Table 1 Adsorption/desorption of buformin on montmorillonite. Maximal adsorbed amount of buformin: n_1^s; amount of buformin remaining in the complex after 360 min release in artificial intestinal juice n_2^s; basal spacing of the dried buformin–montmorillonite complexes before desorption: d_{L1}; basal spacing of the dried buformin–montmorillonite complexes after 360 min release in artificial intestinal juice: d_{L2}

Samples	A	B	C
n_1^s (mmol/g)	0.558	0.676	0.696
n_2^s (mmol/g)	0.319	0.260	0.208
d_{L1} (nm)	1.30	1.33	1.36
d_{L2} (nm)	1.30	1.33	1.30

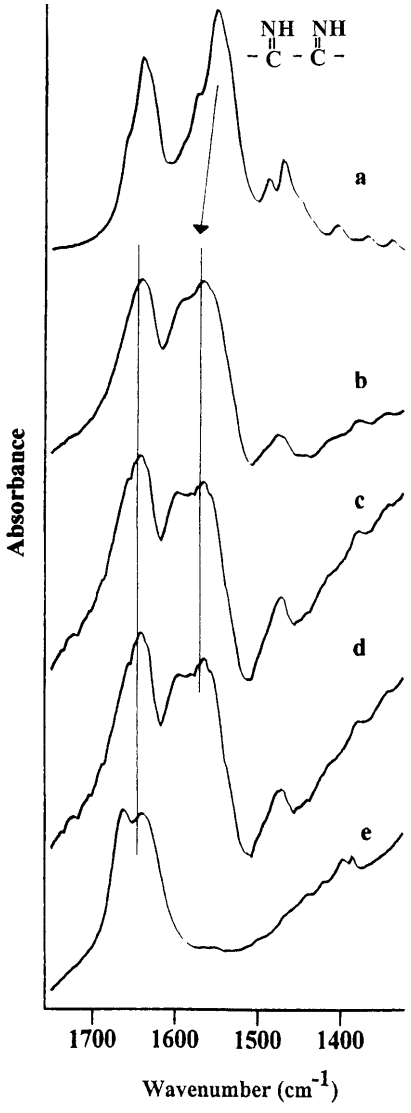


Fig. 3 IR spectra of buformin hydrochloride, montmorillonite and buformin–montmorillonite complex, sample C, released in artificial intestinal juice:*a* buformin hydrochloride, *b* complex before release, *c* complex after 5 min, *d* after 360 min of release and *e* montmorillonite

An IR study of the released complexes was undertaken in the hope that it might be possible to observe a perturbing effect of the dissolution process on the NH_2 groups of the organic molecules adsorbed on montmorillonite. The IR spectra of pure buformin and the buformin–montmorillonite complexes (Figs. 3, 4) indicated two regions with the bands shifted to higher wavenumbers. The bands at 3373 and 3316 cm^{-1} were assigned as the N–H stretching of the C = NH groups, while those at 3207 and 3146 cm^{-1} were the antisymmetric and the symmetric stretching modes of the NH_3^+ group, respectively (Fig. 4, spectrum a). All these bands were shifted to higher wavenumbers, indicating that the adsorption influenced the electron distribution of all three groups. The C = NH shifts were larger, from 3316 to 3387 cm^{-1} and from 3373 to 3437 cm^{-1}, while the NH_3^+ bands (3146 and 3207 cm^{-1}) shifted and broadened into a strong shoulder at 3229 cm^{-1}. Desorption affected only the intensities of the bands; there was no further shift in their position (Fig. 4, spectra b, c, d). The region between 1700 and 1500 cm^{-1} also featured characteristic changes. The strong doublet at 1638 and 1549 cm^{-1} belongs to the symmetric and the antisymmetric C = N stretching modes of the HN = C-C = NH moiety (Fig. 3, spectrum a). These bands overlapped with the bending modes of all N–H containing groups. The shifts of the two C = N modes to 1640 and 1565 cm^{-1} verified that these groups were influenced by the adsorption. Unfortunately, the band at higher wavenumber overlaps with the strong OH bending band of montmorillonite. The weak shoulder

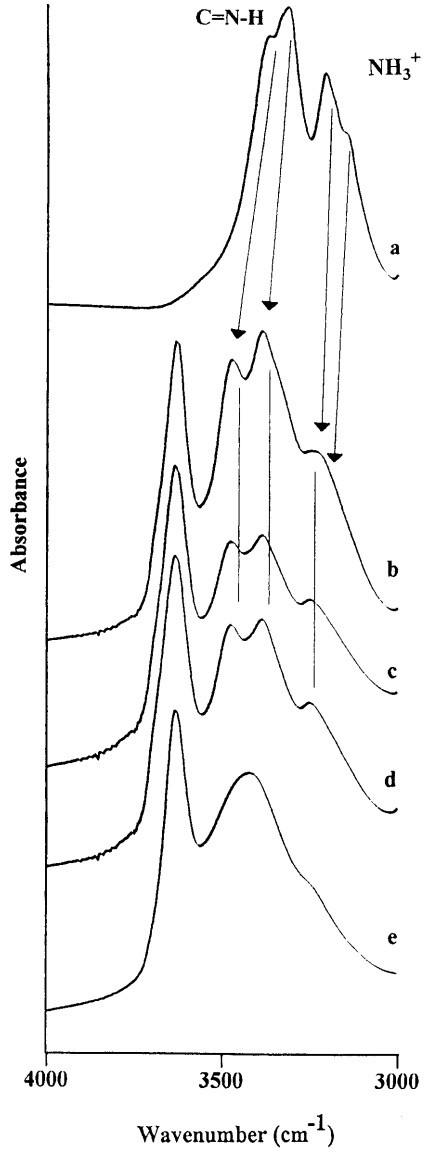


Fig. 4 IR spectra of buformin hydrochloride, montmorillonite and the buformin–montmorillonite complex, sample C, released in artificial intestinal juice: *a* buformin hydrochloride, *b* complex before release, *c* complex after 5 min, *d* complex after 360 min of release, *e* montmorillonite

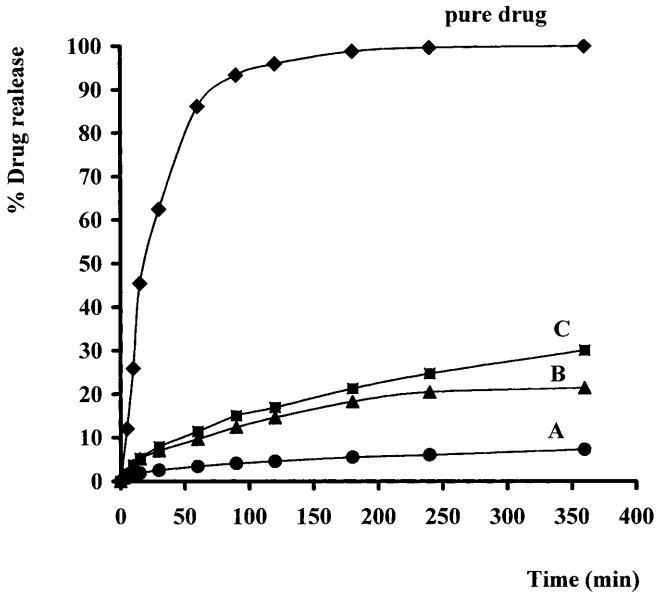


Fig. 5 Rate of desorption of promethazine from the montmorillonite complexes in artificial intestinal juice: sample A (●), sample B (◆), sample C (■), promethazine chloride (◆)

Table 2 Adsorption/desorption of promethazine on montmorillonite. Maximal adsorbed amount of promethazine: n_1^s; amount of promethazine remaining in complex after 360 min release in artificial intestinal juice: n_2^s; basal distance of the dried promethazine–montmorillonite complexes before desorption: d_{L1}; basal distance of the dried promethazine–montmorillonite complexes after 360 min release in artificial intestinal juice: d_{L2}

Samples	A	B	C
n_1^s (mmol/g)	0.439	1.250	1.310
n_2^s (mmol/g)	0.407	0.920	0.916
d_{L1} (nm)	1.55	2.10	2.10
d_{L2} (nm)	1.70	1.96	1.97

at 1570 cm^{-1} in spectrum also shifted to 1593 cm^{-1} and became more pronounced. Neither of these bands underwent any further shift on desorption. The constant positions of the peaks during desorption indicated different bonding sites of buformin on the surface of the montmorillonite.

The promethazine desorption from the promethazine–montmorillonite complexes in artificial intestinal juice is presented in Fig. 5 and Table 2. For promethazine the extent of desorption was lower. For sample C, with the highest content of promethazine, 30% of the initial content was desorbed compared with 26% for sample B and 7% for sample A (Table 2). For pure promethazine chloride under the same conditions, 100% dissolved over 360 min. For sample A, half the amount desorbed within 60 min, while for samples B and C 120 min was required. In the first 15 min, the rate of desorption was very high (sample A: 0.7% after 5 min, 1,9% after 15 min and 2.54% after 30 min). After 30 min, the rate of desorption began to decrease. Sample C released 1.72% after 5 min, 5.20% after 15 min and 7% after 30 min.

The variation in the d_{001} basal spacing of the promethazine–montmorillonite complexes was noteworthy (Table 2, Fig. 6). For samples B and C, the basal spacing decreased in the first 10 min, then remained constant at $d_{001} = 1.96$ nm, which corresponds to a bilayer system. During the desorption the pseudotrilayer arrangement of sample C changed into a bilayer one.

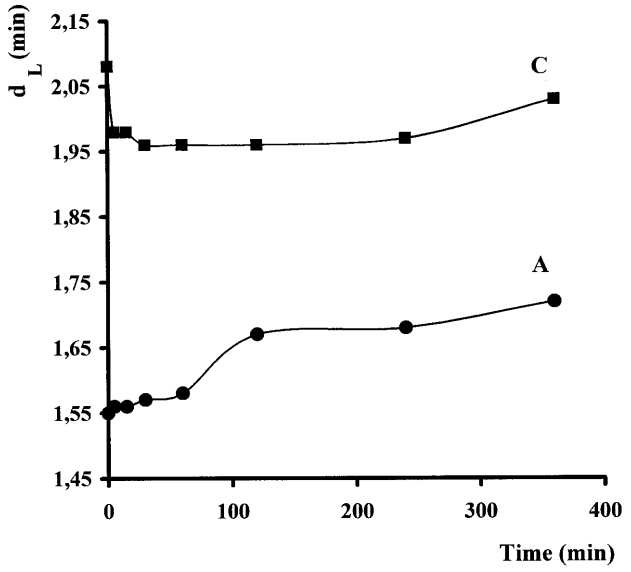


Fig. 6 d_{001} basal spacing of the dried promethazine–montmorillonite complexes at different desorption times: sample A (●), sample C (■)

The basal spacing of the dried sample A after desorption increased as a function of the time of desorption (Fig. 6).

IR spectra of the promethazine–montmorillonite complex and the released complexes are depicted in Fig. 7. The spectrum of pure promethazine chloride has an intensive and broad band at around 2370 cm^{-1}, assigned to the N–H stretching mode of the quaternary ammonium group in the molecule (Fig. 7, spectrum a). This band shifted considerably during the adsorption, yielding a broad band with a maximum at 2667 cm^{-1} (Fig. 7, spectrum b). The maximum of this broad band shifted further, to 2730 cm^{-1}, on desorption, showing that the process removed only the less strongly bonded molecules from the surface. In contrast, the bands characteristic of the skeletal vibrations of the aromatic ring, below 1600 cm^{-1}, shifted only slightly.

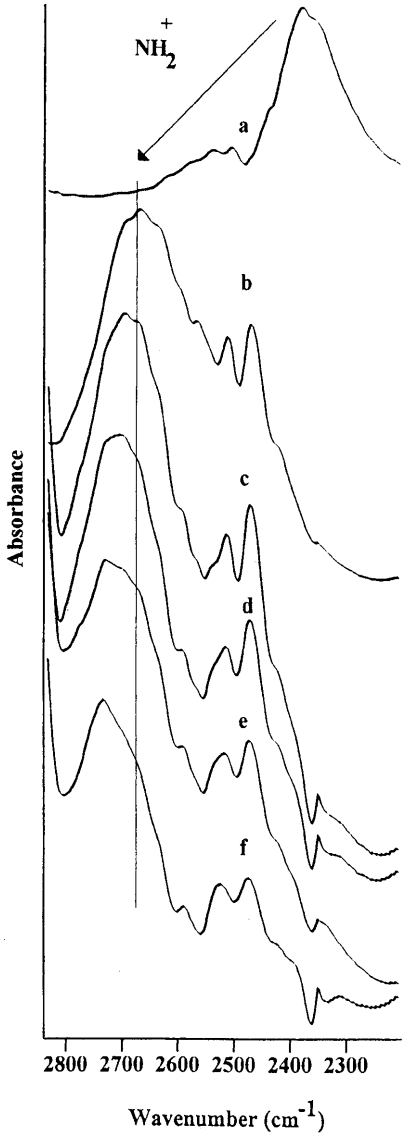


Fig. 7 IR spectra of promethazine chloride and the promethazine–montmorillonite complex, sample C, released in artificial intestinal juice: *a* promethazine chloride, *b* complex before release, *c* complex after 5 min, *d* after 30 min, *e* after 120 min, *f* after 360 min of release

Conclusions

The desorption of buformin from its montmorillonite complex attains 70% without any change in the basal spacing. The desorption rate is very high in the first 15 min, but decreases subsequently. The high rate of dissolution of buformin from its montmorillonite complexes is due to the desorption of molecules bonded to montmorillonite by very weak forces. Desorption of these molecules does not change the IR spectra of the complexes.

In the promethazine–montmorillonite system, the desorption rate is lower. A variation in the d_{001} basal spacing is observed only in the first 10 min of desorption. The IR spectra of pure and adsorbed promethazine chloride at various stages of desorption proved that the bonding sites for promethazine vary in strength. The bonding of promethazin on montmorillonite involves cation-exchange and hydrogen bonds, and a few free promethazine molecules are very weakly bonded. We can conclude that both the adsorption and desorption of the small organic molecules (containing fewer than eight carbon atoms) differ from those of the larger molecules.

Acknowledgement This study was supported by the Hungarian National Scientific Research Foundation (OTKA), project number: T 026579.

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