Properties of Bentonite and Local Anesthetics Composition

Sh. N. Zhumagalieva, B. M. Kudaibergenova, M. K. Beisebekov, Zh. A. Abilov

Chemistry Department, The Al-Farabi Kazakh National University, Almaty, Kazakhstan

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ABSTRACT: The interaction of the bentonite of the Manrak deposit of the East-Kazakhstan region with the AK-29 and richlokain local anesthetics has been studied to synthesize the new prolonged medical compounds. The methods of equilibrium swelling, sedimentation, electrophoresis, rotational viscosimetry, and IR spectroscopy have been used. The comparative analysis of interaction of bentonite clay with medical compounds has been carried out. The dependence of interaction nature on an anesthetic structure has been observed. Results of anesthetic release from polymer show a high degree of their fixation and prolongation. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 1601–1605, 2007

Key words: bentonite clay; richlokain; AK-29; sedimentation; medical compounds; immobilization; rheology; sorption; desorption

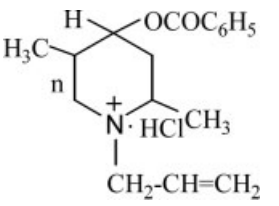
INTRODUCTION

Bentonite clays are the natural inorganic polymers and have an importance as adjutants and supports for the technology of medical products.[1,2] They have a number of useful physicochemical, mechanical, and biological properties such as absence of toxicity, indifference to other raw material, sorption, swelling, and complex formation properties, capacity to form a stable uniform dispersed system (suspense, gels, paste) making them as an ideal support. It has been noted that synthetic and natural polymers able to form gels have advantages at immobilization of medical compounds.[3,4] Unlike the organic analogues, the bentonite clays having a power to thixotropic gel formation are distinguished by a resistance to microbial decay.[1] Besides, the bentonite clays are available and economically sound raw material. It meets the basic requirements for polymer-supports.[5]

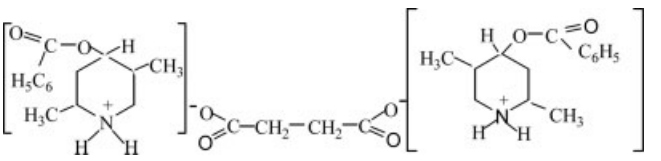
With purpose of using the bentonite clays from the Manrak deposit of the East-Kazakhstan region as a possible support for the medical anesthetic products: hydrochloride of benzoic ether α-isomer of 1-allyl-2,5-dimetylpiperidol-4 (richlokain), succinate of benzoic ether of 2,5-dimetylppiperidol-4 (AK-29), their properties have been studied. For production of medical compounds with required quality it is necessary to know, firstly, the rules of interaction of all the medicine components, and, secondly the interaction of a medicine with organism.[6] Based on all these factors it is possible to select the optimal conditions for a medicine production, where the support would be an active component providing a medicinal effect. For this reason, the sedimentation, swelling, electrophoresis, sorption-desorption, and other properties of clay composition of medical compounds have been studied.

EXPERIMENTAL

Hydrochloride of benzoic ether of α-isomer of 1-allyl-2,5-dimetylpiperidol-4 (richlokain)- $C_{17}H_{27}NO_2HCl$ (the commercial product of Asfarma, Russia) have been multiply crystallized from ethanol, dried in vacuum at T_r till the constant weight (T_m = 490 K).



Succinate of benzoic ether of 2,5-dimethylpiperidol-4 (AK-29) has been synthesized at the Faculty of organic chemistry and chemistry of natural compounds of the Kazakh National University and used without additional purification (T_m = 423–424 K).



Correspondence to: Zh. A. Abilov (abilov@kazsu.kz).

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TABLE I
Chemical Composition of Natural and Purified Clays

Clay samples	Content of components (%)								
	SiO_2	Al_2O_3	Fe_2O_3	CaO	MgO	Na_2O	K_2O	H_2O	Weight loss[a]
Natural	65	13	1	0.5	1.5	1.5	0.5	11	6.5
Purified	60	9	0.5	0.5	1	0.8	0.5	7	20.3

[a] Weight loss after calcinations.

Purification of bentonite clay has been carried out by repeated elutriation in distilled water according to Salo's method.[7]

Chemical composition of natural and purified bentonite clays determined by the diffraction spectral analysis (DFS-13, Russia) is presented in Table I.

By X-ray analysis (DRON-4-07, Russia) the following three phases have been observed in the studied bentonite clay: α-quartz – SiO_2, montmorillonite-$Al_2[OH]_2\{Si_4O_{10}\}m\ H_2O$, and amorphous phase.

Concentration of AK-29 has been determined by UV-spectroscopy. UV spectra have been registered by spectrophotometer ''SF-26'' (Russia) by using a quartz cell with thickness of 1 cm. For calibration plotting, UV-spectra of anesthetic solutions with concentration within 10^{-5}–10^{-4} mol/L have been determined, richlokain concentration has been defined according to the optical density of solution at $\lambda = 232$ and $\lambda = 274$ nm (10^{-5}–10^{-3} mol/L), which are characteristics for pyridine ring and carbonyl groups.

Degree of swelling was determined by the method of equilibrium swelling and calculated as a ratio of volume of swelled sample to volume of dry sample according to a formula:

$$\alpha = \frac{V - V_0}{V_0} \tag{1}$$

where V-volume of swelled sample, V_0-volume of dry sample.

Electrokinetic potential of mix of clay and medical compound was measured by the moving boundary method with using the modified Rabinovich and Fodiman unit.[8] Electrical conduction of mixes and lateral liquid were defined by using the P-356 apparatus (Russia) at constant temperature (298 K). Value of electrokinetic potential was calculated according to the Smolukhovskii's formula:

$$\xi = \frac{4\pi\eta}{H\varepsilon} \times U \times 300^2 \times B \tag{2}$$

where, η–viscosity of medium; H–potential gradient, V/cm; ε-dielectric permeability; U-electrophoresis velocity.

Sedimentation analysis of bentonite clay has been carried out by the Figurovskii's method.[9]

Plastic viscosity of clay and its mixes with medical compounds were measured by using the Haake RV-20 rotary viscosimeter (Japan) with a cone-plate system, and calculated according to formula:

$$\eta = G \times S \times n_d \tag{3}$$

where G-coefficient of set is equal 12.67; S-moment of rotation; n_d-velocity of cone rotation is equal 54.14 min^{-1}.

FTIR spectra were determined by using the KBr tablet at the ''Satellite'' FTIR ''Mattson'' (USA). The method of subtraction with using the bentonite clay as a background has been used.

RESULTS AND DISCUSSION

Study of clay swelling capacity in aqueous solutions showed that introducing richlokain into clay suspense decreases the degree of swelling (Fig. 1). It can be caused by the formation of richlokain clayey complexes because of the electrostatic attractive power between the negative particles of clay and cations of richlokain and hydrogen bonds. Compacting of clayey particles is strengthened with increasing richlokain concentration. Comparison of kinetic curves in water and solutions of richlokain shows that the extreme swelling values in richlokain solutions are reached faster than in water. It indicates that the compact structure of clay-richlokain complexes effects on swelling equilibrium.

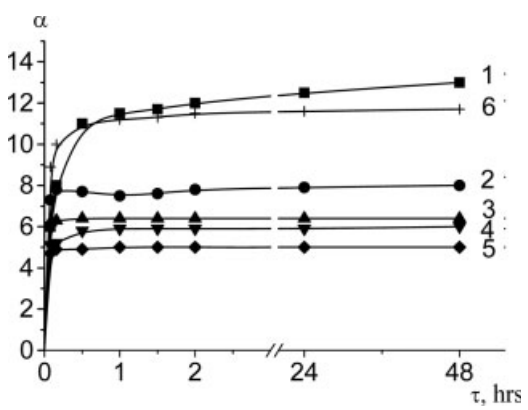

Figure 1 Kinetic of clay swelling. Water (1); [RH] = 5×10^{-5}(2); 1×10^{-4}(3); 1×10^{-3}(4); 1×10^{-2}(5); M; [NaCl] = $1 \times 10^{-2}M$ (6); [Clay] = 2%.

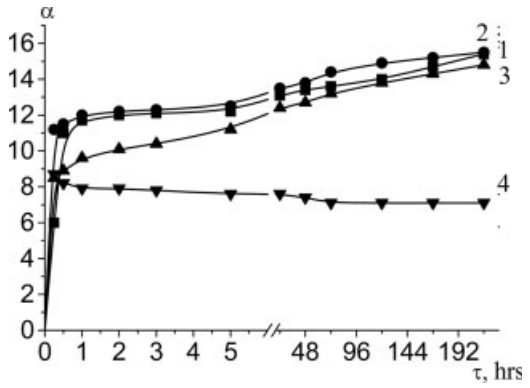

Figure 2 Kinetic of clay swelling in AK-29 solutions. Water (1); [AK-29] = 5×10^{-5} (2); 1×10^{-4} (3); 1×10^{-2} (4)*M*.

Some difference is observed in solutions of AK--29 (Fig. 2). At low concentration of AK-29 ($5 \times 10^{-5}M$), the clay swell is slightly increased. At following grow of the anesthetic concentration, degree of clay swelling is decreased by almost 2 times at concentration of AK-29 = $1 \times 10^{-2}M$. At low concentrations, probably, molecules of succinate are bounded with clayey particles surface by hydrogen bonds, which leads to appearance of hydrophilic particles causing the loosening and additional swelling of clay. The higher susceptibility of AK-29 to form the hydrogen bonds in comparison with richlokain is caused, obviously, with more proton-acceptor character of two carboxyl groups in structure of AK-29 than hydrochloride of richlokain. At increasing concentration, the molecules of AK-29 permeate into interpacked clay volume and complex formation is occurred inside of a particle. In this case, molecules of succinate can participate as a crosslinking agent between dioctahedral layers of bentonite and make them closer that result in a packing of lattice. It is interesting that there are no differences between swelling behavior of bentonite in the physiologic saline of richlokain and succinate unlike the aqueous solutions. This reminds the effect of AK-29 concentration on clay swelling capacity. It can be explained by suppression of anesthetic dissociation because of the high ionic force in the physiological solution.

Results of study of the medium pH effect on the bentonite swelling capacity in water and richlokain solutions (Fig. 3) indicate that the volume of clayey phase in water is sharply increased at changing pH from acidic to alkaline values. This can be explained by changing a character of double electric layer on the basic surfaces and lateral chips of clayey particles. In acidic medium, decreasing the swelling degree occurs owing to charges neutralization. At growing pH of medium, the whole of diffuse layer reaches the same charge, which probably leads to strengthening the swelling capacity. The same behavior of the clay was observed in richlokain solution within pH < 7. In this area, the richlokain cations, probably, interact with anions of diffuse layer of dispersed phase. As a consequence the positive charge is increased that promotes the clay swelling. At growing pH (pH > 7), the cation exchange is occurred: richlokain cations are exchanged for exchanging cations of montmorillonite that neutralizes the negative charge of clay particles. It is a reason of decreasing the swelling capacity. Analogous dependence is observed in succinate solution, the curve 3 (Fig. 3) is almost parallel to the curve for clay that can be caused by the prevailed nonelectrostatic nature of binding between AK-29 and clay, which does not depend on the clay charge.

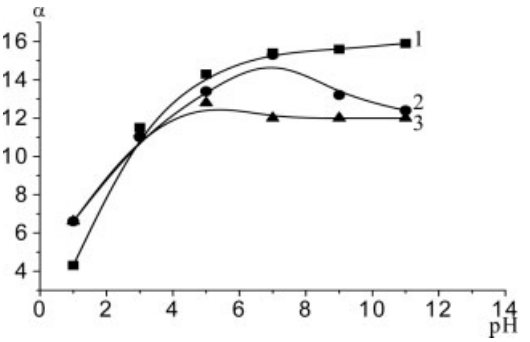

Figure 3 Dependence of clay swelling on pH of a medium. Water (1); solutions of-richlokain (2) and AK-29; (3) [MC] = $1 \times 10^{-3}M$; [clay] = 2%.

Data of electrophoresis (Fig. 4) adequately confirm the above proposed mechanisms of binding of richlokain and AK-29 with clay. Introducing richlokain into the clay suspense leads to decreasing a negative ζ-potential of clay up to complete charge neutralization at $n = 2.3 \times 10^{-4}$ mol/g. It is an evidence of electrostatic binding of richlokain cations with clayey particles. Further increase of *n* leads to inversion of ζ-potential sign because of binding of positively charged ions of richlokain. For succinate, at first the ζ-potential of suspense is slightly decreased and then, at higher *n*, gets the values that

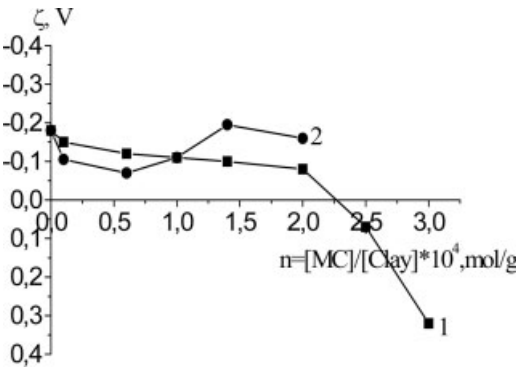

Figure 4 Dependence of electrokinetic potential of clay-richlokain and AK-29 mixes on *n*. [clay] = 0.5%, richlokain (1) and AK-29 (2).

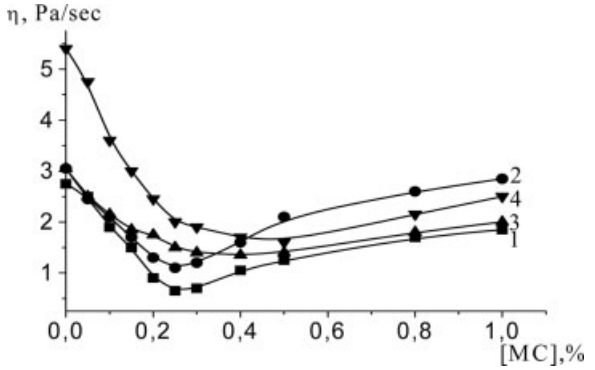

Figure 5 Dependence of plastic viscosity of mix of bentonite clay with AK-29 and RH on concentration of medical compounds. [clay] = 15(1); 20(2,3); 25(4); AK-29 (1,2); RH (3,4).

are standard for initial clay. As a whole, the negative charge of clay is not significantly changed. It is the basic distinction between succinate and richlokain solutions.

According to the sedimentation analysis, both solutions of bentonite clay in water and anesthetic are close to the mono-dispersed system and contain of particles with size of 10^{-6}–10^{-5} m. Average particle radius is 0.22×10^{-5} m in water and 0.24×10^{-5} and 2.4×10^{-5} m in richlokain solutions with concentration of 1×10^{-4} and $5 \times 10^{-3}M$ respectively. Agglomeration of particles at interaction with richlokain can be explained by adhesion of clay particles because of losing the electrostatic stability factor. In succinate solutions, at the beginning the clay dispersion is observed ($5 \times 10^{-5}M$) and then, at increasing AK-29 concentration, rather essential agglomeration of particles is occurred.

Data of rheology study (Fig. 5) demonstrate that introducing the certain anesthetic concentrations into a composition of clayey gels leads to sharp decreasing of plastic viscosity. Further increasing concentration of the medical compound leads to change of viscosity: it grows significantly in succinate and slowly in richlokain. Decreasing the plastic viscosity at low concentration of anesthetics is caused by the individual interactions of medical compounds molecules with bentonite particles leading to hydrophobicity and compacting clay. Following hydrophobicity of clay particles at increasing MC concentration can initiate the intermolecular micelle formation like the colloidal SAM and promote structuring the dispersed system.

IR-study confirms the formation of clay-medical compound complexes. According to the spectra, the OH-groups of tetrahedral silicon-oxygen lattice are significantly changed. It is an evidence of their active participation in binding of medical compounds. It needs to note that hypsochromic shift is much higher in case of succinate complexes than in richlokain that corresponds to the suggested mechanism of binding of AK-29 with clay basically because of hydrogen bonds.

To evaluate the quantitative characteristics of binding, kinetic of sorption of richlokain and AK-29 over bentonite clay has been studied. Sorption of anesthetic sorption is proportionately grown to their concentration in solutions and reaches 50–90% for 1–2 days (Fig. 6a,b). These high values of sorption provide evidence of high affinity of bentonite concerning richlokain and AK-29. The graduated kinetic curves indicate that a character of sorption is polymolecular, especially in case of sorption of richlokain at increasing the medical compound concentration.

According to the data of sorption and on a base of the crystal chemical formula of the Manrack bentonite clay $Na_{0.84}Ca_{0.07}Mg_{0.11}(Al_{3.16}Fe^{3+}_{0.08}Mg_{0.18})[Si_{7.73}Al_{0.27}]O_2(OH)_4$ established by Academician Battalova[10], the molar composition of clay-richlokain complexes has been calculated (Table II). It is shown that equilibrium molar complex composition depends on concentration of richlokain in solution and is reached during about 2 days. Thus, there are 74, 160 and 481 richlokain molecules/100 elementary bentonite cells in complex with concentration of

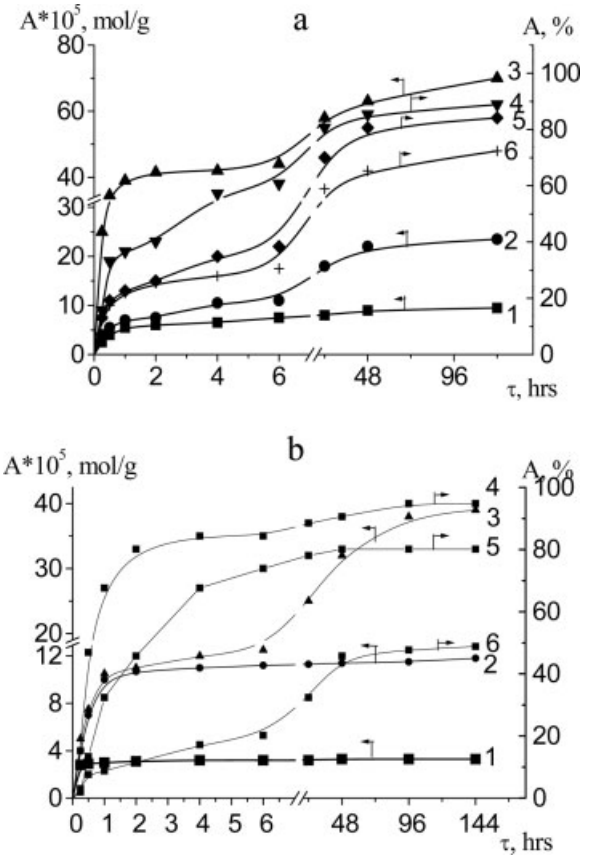

Figure 6 Sorption of richlokain (a) and AK-29 (b) over bentonite clay. [clay] = 0.5%; [MC] = 5×10^{-4} (1,4); 1×10^{-3} (2,5); $1 \times 10^{-2}M$ (3,6); sorption expressed by mol/g (1–3) and % (4–6).

TABLE II
Molar Composition of Bentonite-Richlokain Complexes ([RH]/[Bentonite], Mol/Mol)

	Duration (h)								
[RH], *M*	0.25	0.5	1	2	4	6	24	48	120
5×10^{-4}	0.018	0.029	0.037	0.044	0.051	0.059	0.066	0.074	0.074
1×10^{-3}	0.03	0.04	0.05	0.06	0.07	0.08	0.13	0.16	0.17
1×10^{-2}	0.185	0.259	0.296	0.303	0.303	0.303	0.444	0.481	0.519

richlokain is 5×10^{-4}, 1×10^{-3}, and $1 \times 10^{-2}M$ respectively, (for 2 days).

To evaluate an efficiency of binding and prolongation of anesthetics, desorption of anesthetics from the bentonite compositions has been studied. It has been shown that medical compounds are not significantly released: 1–2% into water and 3–5% into physiologic saline. It is evidence of bonding strength between clay and anesthetics. The formation of such stable complex of organic cations is caused by their binding with surface of monmorillonite not only due to electrostatic but also thanks to additional forces (hydrogen bonds, Van-Der-Vaals forces, stabilization of complexes by hydrophobic interactions). Such strong binding of medical compound with support undoubtedly should significantly increase the prolongation capacity.

CONCLUSIONS

Comparative study of interaction between richlokain and AK-29 with bentonite clay shows that richlokain forms a complex according to the mechanism of cation exchange and because of hydrogen bonds, while the complex formation by AK-29 occurs as a result of hydrogen bonds only. In last case the complex is stabilized by hydrophobic interactions of hydrocarbon radicals of anesthetic complexes. The formation of clay-anesthetic complex is accompanied by the agglomeration of dispersed phase at keeping the stability of a system. Results of sorption demonstrate that anesthetics have a high degree of affinity to the clay. Fifty to ninety percentage of medical compound are absorbed during 1–2 days. Based onsorption data, the molecular composition has been calculated. Data on anesthetic release show the high degree of prolongation: release is less than 5% for 3–5 days. The physicochemical and sorption-desorption properties allow to conclude that the bentonite clay is prospective material as a prolonged support for medical compound.

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