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ORIGINAL ARTICLE

Cationic surfactants-modified natural zeolites: improvement of the excipients functionality

Danina Krajišnik[1], Maja Milojević[2], Anđelija Malenović[3], Aleksandra Daković[4], Svetlana Ibrić[1], Snežana Savić[1], Vera Dondur[2], Srđan Matijašević[4], Aleksandra Radulović[5], Rolf Daniels[6] and Jela Milić[1]

[1]Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia, [2]Faculty of Physical Chemistry, University of Belgrade, Belgrade, Serbia, [3]Department of Drug Analysis, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia, [4]Institute for Technology of Nuclear and Other Mineral Raw Materials, Belgrade, Serbia, [5]Institute of General and Physical Chemistry, Belgrade, Serbia and [6]Institute of Pharmaceutical Technology, Faculty for Chemistry and Pharmacy, University of Tübingen, Tübingen, Germany

Abstract

Context: In this study an investigation of cationic surfactants-modified natural zeolites as drug formulation excipient was performed. *Objective*: The aim of this work was to carry out a study of the purified natural zeolitic tuff with high amount of clinoptilolite as a potential carrier for molecules of pharmaceutical interest. *Materials and methods*: Two cationic surfactants (benzalkonium chloride and hexadecyltrimethylammonium bromide) were used for modification of the zeolitic surface in two levels (equal to and twice as external cation-exchange capacity of the zeolitic tuff). Prepared samples were characterized by Fourier transform infrared spectroscopy, thermogravimetric, high-performance liquid chromatography analysis, and powder flow determination. Different surfactant/zeolite composites were used for additional investigation of three model drugs: diclofenac diethylamine, diclofenac sodium, and ibuprofen by means of adsorption isotherm measurements in aqueous solutions. *Results*: The modified zeolites with two levels of surfactant coverage within the short activation time were prepared. Determination of flow properties showed that modification of zeolitic surface reflected on powder flow characteristics. Investigation of the model drugs adsorption on the obtained composites revealed that a variation between adsorption levels was influenced by the surfactant type and the amount present at the surface of the composites. *Discussion and conclusion*: In vitro release profiles of the drugs from the zeolite-surfactant-drug composites revealed that sustained drug release could be attained over a period of 8 hours. The presented results for drug uptake by surfactant-zeolite composites and the afterward drug release demonstrated the potential use of investigated modified natural zeolite as excipients for advanced excipients in drug formulations.

Key words: *Adsorption; cationic surfactants; clinoptilolite; dissolution; drug carrier; excipients; mathematical model; physicochemical properties; zeolitic tuff*

Introduction

With extremely few exceptions, drug products are combined with substances that serve a variety of functions in the formulation. Excipients can be defined according to their functional roles as solubility or bioavailability modifiers, stability enhancers, crystal-form stabilizers, buffers and pH-adjusting agents, propellants, tablet binders, dispersing agents, and the like[1]. Many studies have been focused on providing information about this rapidly evolving area, for which regulatory guidance is only developing.

Colloidal anhydrous silica and various aluminosilicates are used as excipients in pharmaceuticals, cosmetics, and food products because of their adsorbent, anticaking, bulking, binding, stabilizing, and other similar properties[2]. Zeolites are naturally occurring or synthesized silicate and aluminosilicate crystalline materials with a regular and microporous structure

Address for correspondence: Danina Krajišnik, Department of Pharmaceutical Technology and Cosmetology, Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia. Tel: +381 113951360, Fax: +381 11 3972840. E-mail: danina@pharmacy.bg.ac.rs

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(pore size from 0.3 to 1 nm). They are based on a three-dimensional framework of SiO_4 and AlO_4 tetrahedra that result in an extended uniform network of channels and pores. Owing to the presence of AlO_4 tetrahedra, the framework is negatively charged. These negative charges are balanced by the extra-framework ions that keep the overall structure neutral. Water molecules are loosely bound and can be easily removed upon heating, resulting in a high surface area and an accessible pore volume[3]. Their nanosized pores and the possibility of different chemical compositions (Si/Al ratio, charge balancing cations) in their framework give rise to very selective interactions with adsorbed molecules, depending on their size, shape, heat of adsorption, and chemical characteristics[4]. Zeolites have therefore become a challenging subject in various areas of chemical research and are now widely used in industrial, agricultural, environmental, and biological technology[5].

Among other applications in recent years, natural zeolites have emerged as potential materials for medical application[6]. In human medicine, zeolites have been used for the purpose of external treatment of skin wounds and athletes' foot, in kidney dialyses for the removal of ammonia ions from body fluids[5], as antidiarrheal remedies[7], or as an active ingredient in antacid drugs[8]. Taking into account that in vivo and in vitro toxicity studies showed the biologically inert behavior of the natural zeolite clinoptilolite[7,9], zeolites appear as potential candidates for controlled release of drugs, since the presence of well-defined porosity would afford more homogeneous matrix-drug complexes and hence a better control of the releasing rate[10]. For example, pharmaceutical zeolite-based compositions containing zinc and erythromycin have been used in the treatment of acne[11]; Zeolite Y acts as a slow release agent for a number of antihelmintic drugs[12]; a CuX zeolite type has been used as a support for cyclophosphamide in an antitumoral therapy[13].

In order to enhance sorption of drug molecules, cationic surfactants have been used to modify the surface properties of zeolites. The enhanced coadsorption of organic molecules on solid–surfactant complexes is ascribed to the partition of organic solutes between the aqueous bulk phase and admicelles on the solid surface. This has been termed surface solubilization or adsolubilization[14]. Adsolubilization of drugs by zeolite–surfactant complexes may lead to new uses, such as new drug delivery systems. Zeolite–surfactant complexes are capable of incorporating hydrophobic compounds or to solubilize water-insoluble compounds in the hydrophobic core. The adsolubilization of the drug chloroquine (in amount of 0.15 μmol/g) on small pore synthetic zeolite–surfactant complexes was described[15]. Clinoptilolite–surfactant composites as drug support systems for sulfamethoxazole and metronidazole were also evaluated[16]. Nowadays it is also important to investigate adsorption from aqueous solutions as useful and safe alternative to already reported organic media such as *n*-hexane, dimethyl sulfoxide, dimethylformamide, and diethylether, employed for drugs adsorption on zeolites[10,17,18].

The aim of this work was to carry out a study of the purified natural zeolitic tuff with high amount of clinoptilolite as a potential carrier for molecules of pharmaceutical interest. For this purpose, modification of the zeolite surface, according to external cation exchange capacity of the zeolitic tuff within a short activation time was performed using two cationic surfactants: benzalkonium chloride and hexadecyltrimethylammonium bromide. Different surfactant/zeolite composites were used for additional investigation of three model drugs: diclofenac diethylamine, diclofenac sodium, and ibuprofen by means of adsorption isotherm measurements in aqueous solutions. Characterization of zeolite/surfactant and zeolite/surfactant/drug composites was performed by Fourier transform infrared (FTIR) spectroscopy, thermogravimetric (TG) analysis and high performance liquid chromatography (HPLC). Additionally, the drug-release studies from zeolite/surfactant/drug complexes were carried out to evaluate drug-release profiles and to bring them in correlation with the structure of zeolite/surfactant composites, taking into account potential drug–composite interactions. The drug-release profiles were analyzed using a set of generally recommended mathematical models.

Materials and methods

Materials

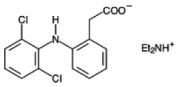
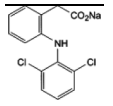
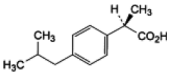
A sample of natural zeolitic rich tuff from Zlatokop deposit (Vranje, Southern Serbia), denoted as ZVB, was used as the starting material in this study. Raw zeolitic tuff was sieved to yield particles below 43 μm. Qualitative X-ray powder diffraction (XRPD) analysis ascertained that the mineralogical composition of ZVB was primarily clinoptilolite/heulandite (minimum 85%), with feldspar and quartz as accessory minerals. Daković et al.[19] published results of scanning electron microscopy (SEM) of the starting zeolitic tuff and reported that the natural zeolitic mineral occurs predominantly as well-formed fine-sized crystals. Many well-defined plates display tabular morphology characteristic for a monoclinic crystal system of clinoptilolite. The specific surface area of the zeolitic tuff, determined by the method of methylene blue[20], was found to be 68.6 m^2/g [21]. The basic physicochemical characteristics of the zeolitic tuff are given elsewhere[22,23]. Clinoptilolite has already been investigated and found not to be toxic and thus can be used in human as well as in veterinary medicine[6]. The zeolitic tuff was used without any

Table 1. Chemical composition of the mineral adsorbent.

Component	SiO_2	Al_2O_3	Fe_2O_3	TiO_2	CaO	MgO	Na_2O	K_2O	I.L.[a]
Content (%)	62.41	11.48	0.88	0.25	4.55	1.45	1.71	1.29	14.00

[a]Ignition loss.

Table 2. Overview of the structural formulas and physicochemical properties of the model drugs.

Compound	Structural formula[a]	MWt	p*K*a	Solubility in water[b]
Diclofenac diethylamine *Diethylammonium* 2-[(2,6-*dichloroanilino*) *phenyl*]*acetate*		369.3	4.87	Sparingly soluble
Diclofenac sodium {2-[(2,6-*dichlorophenyl*)*amino*] *phenyl*}*acetate*		318.1	4.0	Sparingly soluble
Ibuprofen (2*RS*)-2-[4-(2- *methylpropyl*)*phenyl*] *propanoic acid*		206.3	4.55	Practically insoluble

[a]Structural formulas from British Pharmacopoeia 2007. [b]Approximate volume of solvent in millilitres per gram of solute (Ph. Eur. 6): sparingly soluble: from 30 to 100; practically insoluble: more than 10,000.

further purification in the modification process with cationic surfactants and for subsequent drug-adsorption studies. Chemical composition of the starting zeolitic tuff, determined by atomic absorption spectrophotometry, is given in Table 1.

Among the others, the most important characteristics of the zeolitic tuff for surface modification are total cation-exchange capacity (CEC) and external cation-exchange capacity (ECEC). Thus, the CEC of the zeolitic tuff was 146 mmolM^+/100 g[23], as measured by the ammonium chloride method[24], while its ECEC was 10 mmolM^+/100 g as determined by the method of Ming and Dixon[25]. The predominant cation associated with clinoptilolite was calcium, followed by sodium, potassium, and magnesium.

All the reagents used were of analytical grade. Potassium dihydrogen phosphate and sodium hydroxide (Lach-Ner, Brno, Czech Republic) were used for buffer preparation, while diclofenac diethylamine, diclofenac sodium, and ibuprofen (all of pharmacopoeial quality) (see Table 2) were supplied directly from the pharmaceutical industry (Galenika®, Serbia) and used without further purification. Double-distilled water was used throughout the experiments.

Methods

Zeolite modification

Two cationic surfactants, benzalkonium chloride (BC) (Fluka, Buchs, Switzerland) and hexadecyltrimethylammonium bromide (HB) (Sigma-Aldrich, St.Louis, MO, USA), were used for the preparation of modified zeolites (composites). To obtain composites with different loadings, the 10 wt% aqueous suspension of initial zeolitic tuff was treated with surfactant amounts equivalent to 100% and 200% of its ECEC. The adsorption reactions were carried out using a mixer (Janke & Kunkel, IKA-WERK, RE 166, Staufen, Germany) at 5000 rpm and 50°C with an activation time of 15 minutes. After mixing, the suspensions were filtered using ashless filter paper (MACHEREY-NAGEL 640, Düren, Germany) for obtaining extremely fine precipitates. The liquids were further centrifuged at 1500 × *g* in course of 20 minutes and supernatants were used for HPLC determination. The sorbed surfactant amounts were calculated as the difference between initial concentrations and surfactant concentrations in the supernatant after the modification process.

Composites were washed with distilled water and dried in an oven for 2 hours at 60°C. The prepared samples are denoted as ZBC-1, ZBC-2 (modified with BC), and ZHB-1, ZHB-2 (modified with HB).

Characterization by Fourier transform infrared spectroscopy

FTIR spectra of the starting zeolitic tuff as well as those of the obtained composites ZBC-1, ZBC-2, ZHB-1, and ZHB-2 were recorded in the range of 400–4000 cm^{-1} using a MIDAC M 2000 Series Research Laboratory FTIR Spectrometer at 4 cm^{-1} resolution. The samples were dispersed in KBr and compressed into disks.

Thermogravimetric analysis

TG analysis of the starting zeolitic tuff and cationic surfactant/zeolite composites was performed on a Netzsch STA 409 PC/PG thermoanalytical device (NETZSCH-Gerätebau GmbH, Selb, Germany). The samples were heated from 20°C to 598°C in a He flow (100 mL/min), with a heating rate of 10°C/min. Baseline measurements were made using Al_2O_3.

Drug adsorption and isotherm study

Tests determining the liquid phase adsorption of investigated drugs, diclofenac diethylamine (DDEA), diclofenac sodium (DS), and ibuprofen (IB), on prepared composites were carried out in batch experiments at room temperature. Stock solutions of the testing drugs in the concentrations ranging from 50 to 500 mg/L in phosphate buffer at pH 7.4 (USP 30) were prepared. The batch experiments were carried out by shaking the reaction mixture comprising 200 mg of each composite and 50 mL of drug solutions on a laboratory shaker (Heidolph Unimax 1010 DT, Schwabach, Germany) at 250 rpm at room temperature. After 1 hour, the samples were centrifuged for 15 minutes at 1500 × *g*. Supernatants were used for HPLC determination of the drug concentration.

The drug uptake, q (mg/g), was calculated using the following equations:

$$q = \frac{(C_i - C_f) \cdot V}{m} \tag{1}$$

and

$$\% \text{ adsorption} = \frac{(C_i - C_f) \cdot 100}{C_i}, \tag{2}$$

where C_i and C_f are the concentrations (mg/L) of the drugs in initial and final solutions, respectively, V is the volume of the reacting solutions (l), and m is the weight (g) of the adsorbents. All the experiments were done in duplicate.

The drugs adsorption by ZHB and ZBC composites was studied through the evaluation of the adsorption isotherms. An adsorption isotherm is a mathematical expression that relates the concentration of adsorbate at the interface to its equilibrium concentration in the liquid phase.

The adsorption isotherms of the model drugs DDEA, DS, and IB on investigated composites ZBC-1, ZBC-2, ZHB-1, and ZHB-2 were recorded. These isotherms were obtained by plotting the amount of drugs adsorbed per weight unit of each adsorbent (mg/g) against the equilibrium concentration of the drugs in the solution (mg/L). The Langmuir and the Freundlich isotherm models were used to fit the equilibrium sorption data. The applicability of both isotherm equations was compared based on the correlation coefficients (R^2). The Langmuir model[26]:

$$Q_e = \frac{Q_m K C_e}{1 + K C_e}, \tag{3}$$

assumes monolayer coverage of adsorbate over a homogenous adsorbent surface, and at equilibrium a saturation point is reached when no further adsorption can occur.

The Langmuir linearized isotherm is given by the following equation:

$$\frac{C_e}{Q_e} = \frac{1}{Q_m K} + \frac{1}{Q_m} C_e, \tag{4}$$

where C_e is the equilibrium concentration (mg/L), Q_e is the amount of solute adsorbed by the solid (mg/g), Q_m is the maximum amount of solute that can be adsorbed by solid (mg/g) and is equal to the Q_e for a complete monolayer, and K (L/mg) is a constant related to the binding energy. When adsorption follows the Langmuir equation, a plot of C_e/Q_e versus C_e should be a straight line and K and Q_m can be estimated by linear regression.

High performance liquid chromatography assay

Determination of surfactants. The chromatographic system Thermo Scientific Finnigan Surveyor (Thermo Fisher Scientific, San Jose, CA, USA) consists of a LC Pump Plus, an Autosampler Plus, and a UV–Vis Plus Detector. The data were collected and analyzed with the ChromQuest™ 4.2. chromatography data system. Separations were performed using a Supelcosil™ LC-8 4.6 mm × 25 cm, 5 µm particle column. The sample volume of 5 µL was introduced through a partial loop, while the flow rate of the mobile phase was 2 mL/min and the column temperature was set at 30°C. The UV detection was performed at 210 nm. A mixture of acetonitrile-5 mM sodium heptan sulfonate with 0.1% (v/v) of TEA (70:30, v/v) was used as the mobile phase. pH of the mobile phase was adjusted to 3.5 with *ortho*-phosphoric acid.

Determination of drugs. A similar chromatographic system as the one described above was utilized, and the data were once again collected with the ChromQuest™ 4.2. chromatography data system. Separations were in this case performed using a Zorbax Extend C_{18} 4.6 mm × 15 cm, 5 µm particle column instead. The sample volume of 5 µL was introduced through a partial loop. Flow rate of the mobile phase was 1 mL/min and the column temperature was set to 30°C. UV detection was performed either at 254 nm (for DS and DDEA), or at 264 nm (for IB). A mixture of methanol–water (80:20, v/v) was used as the mobile phase. pH of the mobile phase was adjusted to 2.5 with *ortho*-phosphoric acid.

Powder flow determination

Flow properties of the initial and modified zeolite powders were characterized using flowmeter (Erweka flow meter type; GDT, Heusenstamm, Germany) in agreement with Eur.Ph.6 procedure and flowability, Hausner ratio (HR), and Carr's index (CI) were determined.

Comprimate preparation

The flat-faced punches with the diameter of 9 mm were used to compress the ZHB-20- and ZBC-20-tested drug powders in a 200 mg comprimates using an eccentric compressing machine (EKO Korsch, Berlin, Germany). The comprimates were made with the compression pressure sufficient for achieving resistance to crushing around 30 N, with no signs of capping. By doing so, the same conditions during release studies for all the samples were attained and placing the comprimates in the dissolution media was done in the same manner.

In vitro drug release studies

Drug release from the comprimates consisting of modified zeolite–drug composites was performed in a rotating paddle apparatus (Erweka DT70, Heusenstamm, Germany) in 300 mL of phosphate buffer solutions: pH 6.8 for DS; pH 7.2 for IB, and pH 7.4 for DDEA (USP 30) at 37°C. The rotating paddle speed was 50 rpm. At predetermined times, 2 mL samples were withdrawn, filtered, and assayed. All data-points were determined as the average value for three independent measurements. The amount of drug released was expressed as a percent of the drug load in composite–drug sample.

Mathematical modeling of release profiles

Individual dissolution data were fitted to various mathematical models with the nonlinear regression module of Statistica 5.0 for Windows (Statsoft, Tulsa, OK, USA). In nonlinear regression analysis, the Quasi-Newton and Simplex methods minimized the least square error. The model parameters with their standard errors and descriptive statistics of regression for each model were estimated by the nonlinear regression module of Statistica. Depending on these estimations, suitable mathematical models to describe the dissolution profiles were determined.

To evaluate the kinetics of sustained release, mathematical models[27] have been used for the parametric representation of dissolution data (Table 3). After fitting the individual unit dissolution data to these models, the selection was based on the comparison of the following criteria: (i) higher determination coefficient (r^2), (ii) smaller absolute difference between each fitted and actual percent dissolved (R_{max}), and (iii) smaller residual mean square root (*RMS*).

Table 3. Applied mathematical models to the drug release data.

Zero-order	% diss = 100 (1-kt)
First-order	% diss =100[1-e^{kt}]
Hixson-Crowell	% diss = 100 [1-(1-kt/4.6416)^3]
Higuchi	% diss = $kt^{0.5}$
Korsmeyer-Peppas	% diss = kt^n

Where % diss is percent dissolved at time t, k is the dissolution rate constant and n is exponent dependent on shape and mechanism ($n \leq 0.5$ (diffusion controlled release), $n > 1$ (erosion controlled release), $0.5 < n < 1$ (mixed mechanism)).

Results and discussion

The starting zeolitic tuff (ZVB) and modified zeolites with BC and HB were characterized by FTIR spectroscopy, and their IR spectra are shown in Figure 1. The IR spectra for ZVB and ZBC composites are shown in Figure 1a. The features positioned at 3620, 3420, and 1640 cm^{-1} (dashed line) are characteristic bands of the clinoptilolite connected to acidic hydroxyls Si–O(H)–Al, hydrogen-bonding hydroxyl groups, and bending vibration of absorbed water, respectively[28]. However, three new bands appear (solid line), implying the presence of BC on the composite, two bands assigned to the C–H stretching vibrations of the hydrocarbon chain, 2925 and 2860 cm^{-1}, and a third one band corresponding to the C–H bending of the methyl and methylene groups at 1465 cm^{-1}. The relative intensity of these bands increased with increasing amount of the adsorbed BC.

The IR spectra of ZVB and ZHB composites are shown in Figure 1b. Besides the characteristic bands of the clinoptilolite (dashed line), both composites showed two bands around 2920 and 2855 cm^{-1} (solid line), which were attributed to asymmetric and symmetric stretching CH_2 vibration of the HB, respectively[29]. Similar to BC composites, the relative intensity of these bands increased with the adsorbed amount of the HB. The vibrational bands for composites are a characteristic of organic compounds at the zeolite surface. No relevant variations in the frequency of the bands assigned to the clinoptilolite after the treatment with the BC or HB were observed, indicating unaltered zeolite structure after the modification, and the presence of surfactants only at the zeolite surface. Average diameters of surfactants used in this study are approximately 1.2 (BC) and 1.5 nm (HB), therefore they are larger than the dimensions of the largest zeolitic channel—0.75 × 0.31 nm[30]. This indicates the adsorption of surfactants at the external surface of the clinoptilolite, as previously reported[31–33].

TG curves of the starting zeolite and ZBC and ZHB composites together with the TG curves of BC and HB are presented in Figure 2. Temperature ranges for mass loss were 190–295°C for HB, along with 125–212°C and

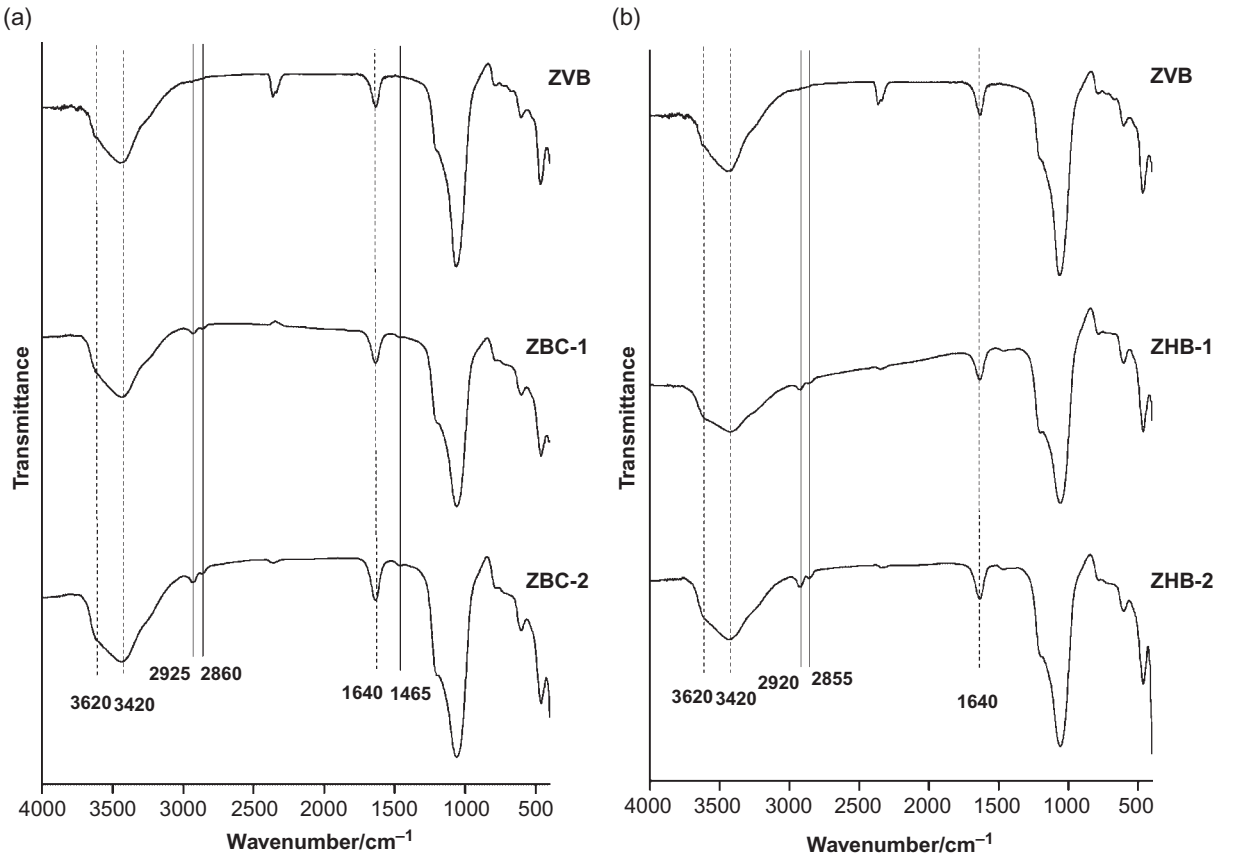


Figure 1. IR transmittance spectra for ZVB and (a) ZBC and (b) ZHB composites.

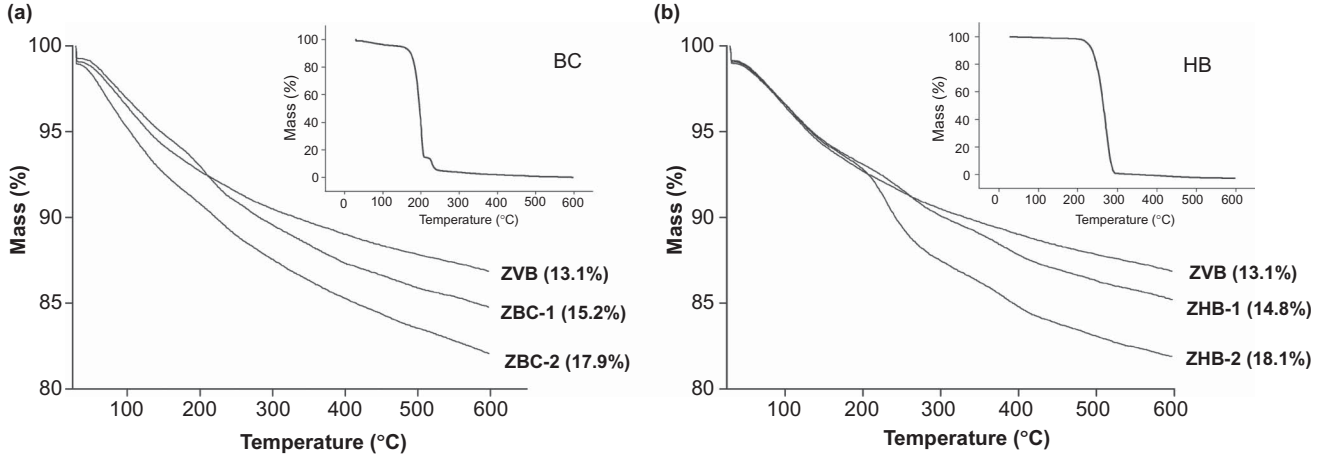


Figure 2. TG curves of ZVB and (a) ZBC and (b) ZHB composites. The insets show the TG curves of BC and HB alone.

212–246°C for BC. The starting zeolitic tuff, as was reported before[23], continuously loses water (13.1% for ZVB) and therefore makes quantitative determination of mass loss due to surfactant presence at the surface of investigated composites not clearly visible. However, this analysis showed higher mass loss due to the presence of both surfactants and water in composite samples, and the mass loss increased with the initial surfactant loadings (15.2% and 17.9% for ZBC-1 and ZBC-2; 14.8% and 18.1% for ZHB-1 and ZHB-2, respectively). This indicates that more surfactant is loaded, in accordance with initial experimental setup for first and second surfactant adsorption level. In line with the TG findings, the amount of surfactant obtained by HPLC is found to be 9.0 and 18.9 mmol/g for ZHB-1 and ZHB-2 in addition to 9.2 and 17.2 mmol/g for ZBC-1 and ZBC-2,

respectively, in accordance with BC adsorption level, which was equal to and twice as ECEC of zeolitic tuff.

Determination of flow properties showed that modification of zeolitic surface reflected on powder flow characteristics. For ZVB, values of 1.22 for Hausner ratio (HR) and 17.86 for Carr's index (CI) were obtained, which corresponded to fair flow character (Ph. Eur. 6). The fair flow character for composites ZBC-1 and ZHB-1 was also determined, since values of observed parameters were 1.22 (HR) and 18.42 (CI) for sample ZBC-1, that is, 1.26 (HR) and 20.59 (CI) for sample ZHB-1. Changes of flow characteristics for samples modified with higher surfactant content were discovered. For sample ZBC-2 values of 1.13 (HR) and 11.76 (CI) were found, which corresponded to good flow character. This flow type for sample ZHB-2 (1.16 for HR and 13.91 for CI) was also detected. Improvement of powder flow properties could be explained by changes of zeolitic surface after modification procedure. It was previously reported[34] that zeolitic surface becomes completely hydrophobic when surfactant amount during modification process was equal to 100% of ECEC of zeolitic tuff, that is, hydrophilic when it was 200% of its ECEC. Furthermore, it was demonstrated that particular pharmaceutical technical characteristics of a solid dosage form were affected by hydrophobicity/hydrophilicity of pharmaceutical excipients[35].

The adsorption isotherms of the model drugs DDEA, DS, and IB on investigated composites ZBC-1, ZBC-2, ZHB-1, and ZHB-2 are presented in Figure 3a–c. Since the adsorption of DDEA, DS, and IB by ZHB and ZBC composites followed nonlinear isotherms, the Langmuir and the Freundlich isotherm models were used to fit the equilibrium sorption data. The better fits of the experimental data were obtained using the Langmuir model. As it was previously reported, this model is suitable for isotherm evaluation in a system comprising inorganic or functionalized sorbents[36, 37].

All three investigated drugs (Table 2) are hydrophobic organic molecules, slightly to poorly soluble in water, and thus it was assumed that all of them may appear in the hydrophobic phase created by surfactant tail groups at the zeolitic surface. In addition, we investigated the interaction of all drugs of interest with initial clinoptilolite, and no adsorption was detected. As seen from Figure 3a–c, the adsorbed amounts of all three drugs increased with the initial concentration of each drug in solution. It is also observed that the adsorbed amount of all three drugs increases with increasing amount of surfactant at the surface of the ZHB and ZBC composites. The results indicate that organic cations at the zeolitic surface are responsible for drugs adsorption by the ZHB and ZBC composites. Similar adsorption of drugs by cationic surfactants at the zeolite surface was reported by Rivera and Farías[16]. Namely, they investigated adsorption of sulfamethoxazole and metronidazole by zeolite

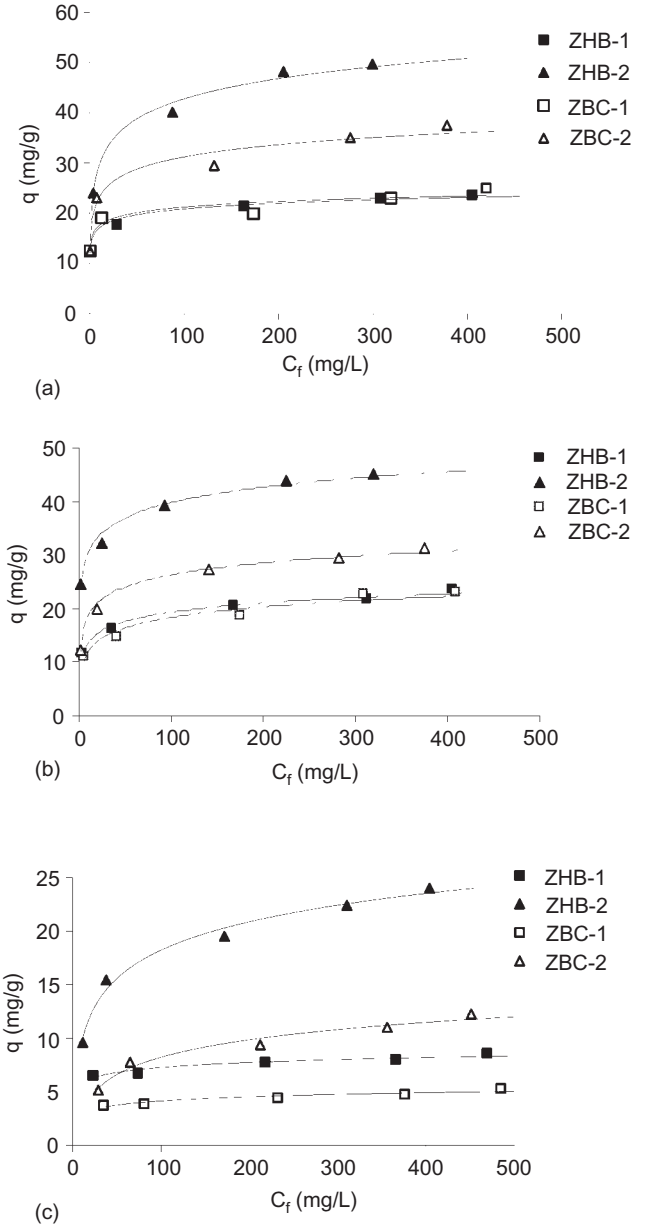


Figure 3. Adsorption of (a) DDEA, (b) DS, and (c) IB by various composites.

modified with cationic (BC), anionic (sodium laurylsulfate), and nonionic (Tween 80) surfactants and found that only composites prepared with BC showed a direct relationship between the amount of adsorbed drug and the amount of surfactant per gram of zeolite.

The calculated maximum (Q_m) of the ZHB composites adsorption capacities for DDEA are 23.81 and 50.25 mg/g for ZHB-1 and ZHB-2, respectively (Table 4). For DDEA adsorption by ZBC composites, the values obtained for Q_m are 24.57 mg/g for ZBC-1 and 37.31 mg/g for ZBC-2. For DS adsorption by ZHB and ZBC composites, the following values of Q_m are obtained: 23.58 mg/g for ZHB-1, 45.87 mg/g for ZHB-2, 23.81 mg/g for ZBC-1 and 31.35

Table 4. Parameters of Langmuir isotherm for drugs adsorption by different composites.

	Diclofenac diethylamine			Diclofenac sodium			Ibuprofen		
Sample	Q_m (mg/g)	K (L/mg)	R^2	Q_m (mg/g)	K (L/mg)	R^2	Q_m (mg/g)	K (L/mg)	R^2
ZBC-1	24.57	0.084	0.989	23.81	0.045	0.992	5.40	0.032	0.990
ZBC-2	37.31	0.087	0.992	31.35	0.094	0.997	13.14	0.018	0.996
ZHB-1	23.81	0.122	0.998	23.58	0.070	0.996	8.68	0.055	0.996
ZHB-2	50.25	0.124	0.996	45.87	0.114	0.998	24.88	0.036	0.994

mg/g for ZBC-2. It is noted that the adsorption of both diclofenac salts by ZHB-1 and ZBC-1 was very similar, while much higher adsorption of DDEA and DS was achieved by ZHB-2 than by ZBC-2. Compared to diclofenac salts, IB showed the lowest adsorption by ZHB and ZBC composites. However, higher values for maximum adsorption capacity were obtained for IB adsorption by ZHB composites than for ZBC composites.

It was already reported that sorption of nonionic organic compounds by smectite minerals modified with HB is due to essentially linear solute partitioning into the hydrophobic phase formed by the large alkyl chains of the HB ions and is presented with the linear adsorption isotherms[38]. Shen[39] studied adsorption of relatively polar phenol on HB- and benzyltrimethyl ammonium (BTMA)-smectites at pH 7. He reported a linear isotherm for adsorption of phenol on HB-smectites, and a nonlinear Langmuir isotherm for phenol adsorption on BTMA-smectite. Since HB and BC are long chain organic cations, the nonlinear adsorption isotherms obtained for adsorption of DDEA, DS, and IB to the ZHB and ZBC composites observed in this study, may be an indication that the partitioning is not the only mechanism responsible for adsorption of these drugs by the surfactants modified zeolitic tuff. The obtained results indicate that the type of surfactant present at the zeolitic surface also has an influence on the adsorptions of DDEA, DS, and IB. Furthermore, it is well known that the sorption properties of organic compounds from water to clays or zeolites modified with surfactants are closely related to solute properties such as water solubility and polarity[35]. In our adsorption study the phosphate buffer was used for the limited solubility of the investigated drugs in water. The dissociation constants (pK_a) of DDEA, DS, and IB (Table 2) showed that the investigated drugs are weak acids, and thus at pH 7.4, they all exist in anionic form. Experimental results showed that adsorption of both diclofenac salts was much higher and occurred in a very similar manner. Possible explanation for this phenomenon is that DDEA and DS exhibit surface activity due to their amphiphilic nature[40,41]. Although the drug adsorption took place below their CMCs (8 mM for DS and 20 mM for DDEA at 20°C)[40], it is possible that the interactions between drug molecules and surfactants deposits on the clinoptilolite surface induced favorable drug uptake.

In a preliminary study, model drug desorption from the composites during a 6-hour period was detected[42]. For this reason, an in vitro drug release study was performed according to general USP 30 instructions for *Extended release dosage forms* using the modified zeolite–drug comprimates in order to predict the behavior of drug-modified zeolite composites in vivo. It was of interest to obtain the information on general drug-release profiles, as well as on the prospective difference between the profiles of two composites regarding the used surfactant. Furthermore, the obtained release profiles were analyzed employing appropriate mathematical models.

Dissolution profiles of the tested drugs from ZBC-2 and ZHB-2 comprimates are shown in Figure 4a–c. The study showed permanent releasing of the drugs for both comprimates over a period of 8 hours in a sustained manner. DDEA comprimates released approximately 20% of the drug for both ZBC-2 and ZHB-2 composites. For composites containing DS and IB the percentage of the drugs released was almost twice higher: 43% for ZBC-2 and 30% for ZHB-2, that is, 45% for ZBC-2 and 44% for ZHB-2. Drug-release studies were also performed from the noncompressed composites and no significant difference in the amounts of drugs released were observed. Furthermore, the comprimates disintegrated during the first hour of the experiment.

The release profiles of DS from both ZBC-2 and ZHB-2 comprimates were in good agreement ($r^2 > 0.98$) with the Korsmeyer–Peppas model. The values of release exponent n were 0.32 and 0.37 for ZBC-2 and ZHB-2, respectively indicating that diffusion of drug is the predominant release mechanism. The release exponent $n = 0.5$ (Higuchi model), which corresponds to a completely Fickian diffusion-based transport of drug to the dissolution medium was the best fitting model for the DDEA and IB composites, as it has been previously found for drug release from different micro- and mesoporous silica carriers[43,44]. It can be seen that DS release is faster from ZBC-2 ($k = 6.05$) than from ZHB-2 ($k = 3.13$) and it could be attributed to different drug-surfactant interactions (hydrophobic and partially electrostatic), which are dependent on the surfactant type. On the other hand, this difference was less pronounced for IB ($k = 2.20$ for ZBC-2 and 2.21 for ZHB-2) and for DDEA ($k = 1.05$ for ZBC-2 and 0.95 for ZHB-2). Furthermore,

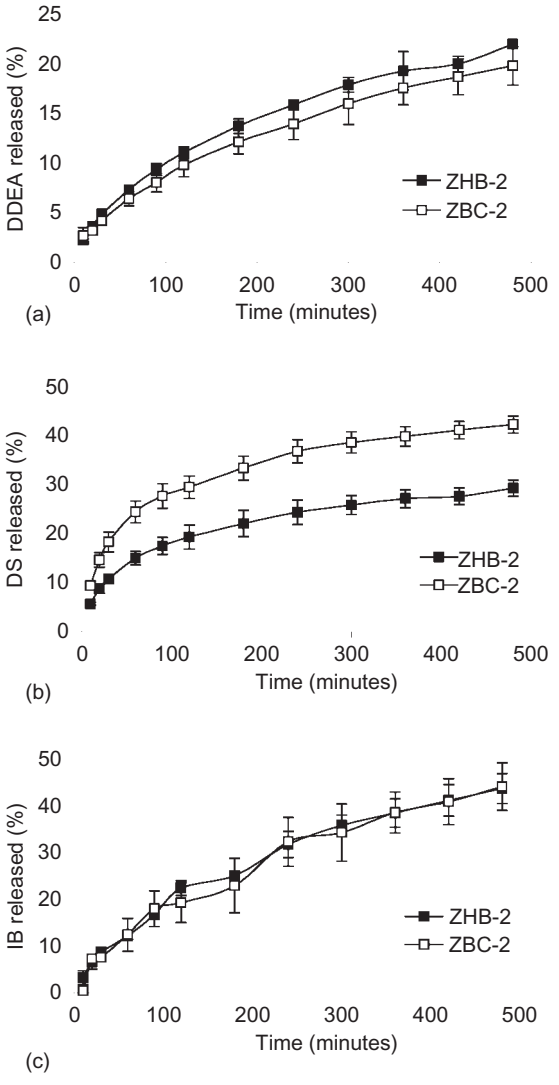


Figure 4. Release profiles of (a) DDEA, (b) DS, and (c) IB from modified zeolite-drug composites.

this slow and sustained release process may also be interpreted as an ion-exchange process between the loaded drugs and the metal ions of the buffer medium, as previously reported[45].

Thus, the achieved sustained release of tested anti-inflammatory drugs during 8 hours could be a promising pathway for drugs with a short half-life and/or adverse effects caused by administration of conventional pharmaceutical dosage form.

Conclusion

In this study cationic surfactant/zeolite composites are prepared by modification of natural zeolitic tuff of high clinoptilolite content with benzalkonium chloride and hexadecyltrimethylammonium bromide. Further investigation of model drugs (diclofenac diethylamine, diclofenac sodium, and ibuprofen) adsorption from aqueous solutions on the obtained composites reveals that variations between adsorption levels is influenced by the surfactant type and the amount present at the surface of the composites. In vitro drug release study performed in order to predict the behavior of the model drugs-modified zeolite composites in biological fluids shows the achievement of the drug release in a sustained manner during 8 hours. The drug release profiles are in good agreement with the Korsmeyer–Peppas and Higuchi model, indicating that diffusion of the drug is predominant release mechanism with a difference in dissolution rate for different zeolite/surfactant composites. Distinction in dissolution rates is in agreement with drug adsorption findings and could be explained by combination of hydrophobic and partially electrostatic interactions in drug/zeolite/surfactant samples. The presented results for drug uptake by surfactant/zeolite composites and afterward drug release may encourage further research exploring the potential use of investigated modified natural zeolite as excipients for advanced drug carrier systems.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Crowley PJ, Martini LG. (2007). Excipients for pharmaceutical dosage forms. In: Swarbrick J, ed. Encyclopedia of pharmaceutical technology. 3rd ed. New York: Informa Healthcare USA, Inc., 1609–21.
2. Rowe RC, Sheskey PJ, Owen SC, eds. (2006). Handbook of pharmaceutical excipients. 5th ed. London & Washington, DC: Pharmaceutical Press and American Pharmacists Association, 58, 182, 378, 418, 428, 434, 767.
3. Ming DW, Mumpton FA. (1989). Zeolites in soil. In: Dixon JB, Weed SB, eds. Minerals in soil environments. 2nd ed. Madison, WI: Soil Science Society of America, 873–911.
4. Arruebo M, Fernández-Pacheso R, Irusta S, Arbiol J, Ibarra MR, Santamaria J. (2006). Sustained release of doxorubicin from

zeolite–magnetite nanocomposites prepared by mechanical activation. Nanotechnology, 17:4057–64.
5. Mumpton FA. (1999). La roca magica: Uses of natural zeolites in agriculture and industry. Proc Natl Acad Sci USA, 96:3463–71.
6. Pavelic K, Hadzija M. (2003). Medical applications of zeolites. In: Auerbach SM, Carrado KA, Dutta PK, eds. Handbook of zeolite science and technology. New York: Marcel Dekker, 1143–74.
7. Rodríguez-Fuentes G, Barrios MA, Iraizoz A, Perdomo I, Cedré B. (1997). Enterex: Anti-diarrheic drug based on purified natural clinoptilolite. Zeolite, 19:441–8.
8. Rodríguez-Fuentes G, Denis AR, Barrios Álvarez MA, Iraizoiz AC. (2006). Antacid drug based on purified natural clinoptilolite. Microp Mesop Mater, 94:200–7.
9. Adamis Z, Tátrai E, Honma K, Six E, Ungváry G. (2000). In vitro and in vivo tests for determination of the pathogenicity of quartz, diatomaceous earth, mordenite and clinoptilolite. Ann Occup Hyg, 44:67–74.
10. Horcajada P, Márquez-Alvarez C, Rámila A, Pérez-Pariente J, Vallet-Regí M. (2006). Controlled release of ibuprofen from dealuminated faujasites. Solid State Sci, 8:1459–65.
11. Cerri G, De Gennaro M, Bonferoni MC, Caramella C. (2004). Zeolites in biomedical application: Zn-exchanged clinoptilolite-rich rock as active carrier for antibiotics in anti-acne topical therapy. Appl Clay Sci, 27:141–50.
12. Dyer A, Morgan S, Welles P, Williams C. (2000). The use of zeolites as slow release anthelmintic carriers. J Helminthol, 74:137–41.
13. Uglea CV, Albu J, Vătăjanu A, Croitoru M, Antoniu S, Panaitescu L, et al. (1994). Drug delivery systems based on inorganic materials. I. Synthesis and characterisation of a zeolitecyclophosphamide system. J Biomater Sci Polym Ed, 6:633–7.
14. Sharma R, ed. (1999). Surfactant adsorption and surface solubilization. Washington, DC: American Chemical Society.
15. Hayakawa K, Mouri Y, Maeda T, Satake I, Sato M. (2000). Surfactant-modified zeolites as a drug carrier and the release of chloroquin. Colloid Polym Sci, 278:553–8.
16. Rivera A, Farías T. (2005). Clinoptilolite–surfactant composites as drug support: A new potential application. Microp Mesop Mater, 80:337–46.
17. Charnay C, Bégu S, Tourné-Péteilh C, Nicole L, Lerner DA, Devoisselle JM. (2004). Inclusion of ibuprofen in mesoporous templated silica: Drug loading and release property. Eur J Pharm Biopharm, 57:533–40.
18. Rimoli MG, Rabaioli MR, Melisi D, Curcio A, Mondello S, Mirabelli R, Abignente E. (2008). Synthetic zeolites as a new tool for drug delivery. J Biomed Mater Res A, 87:156–64.
19. Daković A, Kragović M, Rottinghaus GE, Sekulić Ž, Milićević S, Milonjić SK, et al. (2010). Influence of natural zeolitic tuff and organozeolites surface charge on sorption of inozable fumonisin B1. Colloid Surf B, 76:276–8.
20. Yousef RI, El-Eswed B. (2009). The effect of pH on the adsorption of phenol and chlorophenols onto natural zeolite. Colloid Surf A, 334:92–9.
21. Kragović MM, Daković AS, Milićević SZ, Sekulić ŽT, Milonjić SK. (2009). Influence of organic cations sorption on the point of zero charge of natural zeolite. Hem Ind (in Serbian), 63:325–30.
22. Daković A, Matijašević S, Rottinghaus GE, Dondur V, Pietrass T, Clewett FM. (2007). Adsorption of zearalenone by organomodified natural zeolitic tuff. J Colloid Interface Sci, 311:8–13.
23. Gvozdić D, Stojić V, Šamanc H, Fratrić N, Daković A. (2008). Apparent efficiency of immunoglobulin absorption in newborn calves orally treated with zeolite. Acta Vet (Beogr), 58(4):345–55.
24. Daković A, Tomašević-Čanović M, Dondur V, Stojšić D, Rottinghaus GE. (2001). In vitro adsorption of zearalenone by octadecyldimethylbenzyl ammonium-exchanged clinoptilolite-heulandite tuff and bentonite. In: Galarneau A, Di Renzo F, Fajula F, Vedrina J, eds. Zeolites and mesoporous materials at the dawn of the 21st century, studies in surface science and catalysis, vol. 135. Proceedings of 13th international zeolite conference. Montpellier: Elsevier, 5276–83.
25. Ming DW, Dixon JB. (1987). Quantitative determination of clinoptilolite in soils by a cation-exchange capacity method. Clays Clay Miner, 35:463–8.
26. Adamson AW, Gast PA. (1997). Physical chemistry of surfaces. 6th ed. New York: Wiley, 391–4.
27. Costa P, Sousa Lobo JM. (2001). Modeling and comparison of dissolution profiles. Eur J Pharm Sci, 13:123–33.
28. Korkuna O, Leboda R, Skubiszewska ZJ, Vrublevska T, Gunko VM, Ryczkowski J. (2006). Structural and physicochemical properties of natural zeolites: Clinoptilolite and mordenite. Microp Mesop Mater, 87:243–54.
29. Guangming C, Suhuai L, Shijuan C, Zongneng Q. (2001). FTIR spectra, thermal properties, and dispersibility of a polystyrene/montmorillonite nanocomposite. Macromol Chem Phys, 202:1189–93.
30. Baerlocher CH, Meier WM, Olson DH, eds. (2001). Atlas of zeolite framework types. 5th ed. New York: Elsevier Science.
31. Haggerty GM, Bowman RS. (1994). Sorption of chromate and other inorganic anions by organo-zeolite. Environ Sci Technol, 28:452–8.
32. Pérez Cordoves AI, Granda Valdés M, Torres Fernández JC, Pina Luis G, García-Calzón JA, Díaz García ME. (2008). Characterization of the binding site affinity distribution of a surfactant-modified clinoptilolite. Microp Mesop Mater, 109:38–48.
33. Rožić M, Ivanec Šipušić D, Sekovanić L, Miljanić S, Čurković L, Hrenović J. (2009). Sorption phenomena of modification of clinoptilolite tuffs by surfactant cations. J Colloid Interface Sci, 331:295–301.
34. Li Z, Bowman R. (1998). Sorption of perchloroethylene by surfactant-modified zeolite as controlled by surfactant loading. Environ Sci Technol, 32:2278–82.
35. Zhu L, Ren X, Yu S. (1998). Use of cetyltrimethylammonium bromide-bentonite to remove organic contaminants of varying polar character from water. Environ Sci Technol, 32(21): 3374–8.
36. Jonat S, Hasenzahl S, Gray A, Schmidt PC. (2005). Influence of compacted hydrophobic and hydrophilic colloidal silicon dioxide on tableting properties of pharmaceutical excipients. Drug Dev Ind Pharm, 31:687–96.
37. Mallick S, Pattnaik S, Swain K, De PK, Mondal A, Ghoshal G, et al. (2007). Interaction characteristics and thermodynamic behaviour of gatifloxacin by aluminium hydroxide. Drug Dev Ind Pharm, 33:535–41.
38. Song DI, Shin WS. (2005). Three-parameter empirical isotherm model: Its application to sorption onto organoclays. Environ Sci Technol, 39(4):1138–43.
39. Shen YH. (2004). Phenol sorption by organoclays having different charge characteristics. Colloid Surface A, 232:143–9.
40. Kriwet K, Müeller-Goymann CC. (1993). Binary diclofenac diethylamine–water systems: Micelles, vesicles and lyotropic liquid crystals. Eur J Pharm Biopharm, 39:234–8.
41. Fini A, Fazio G, Feroci G. (1995). Solubility and solubilization properties of non-steroidal anti-inglammatory drugs. Int J Pharm, 126:95–102.
42. Krajisnik D, Dondur V, Milojevic M, Milic J. (2008). Mesoporous and functionalized materials in drug supports and delivery systems. 10th annual conference of the Materials Research Society of Serbia, Herceg Novi, Montenegro, book of abstracts p. 98.
43. Andersson J, Rosenholm J, Areva S, Lindén M. (2004). Influences of material characteristics on ibuprofen drug loading and release profiles from ordered micro- and mesoporous silica matrices. Chem Mater, 16:4160–7.
44. Heikkilä T, Salonen J, Tuura J, Hamdy MS, Mul G, Kumar N, et al. (2007). Mesoporous silica material TUD-1 as a drug delivery system. Int J Pharm, 331:133–8.
45. Joshi GV, Kevadiya BD, Patel HA, Bajaj HC, Jasra RV. (2009). Montmorillonite as a drug delivery system: Intercalation and in vitro release of timolol maleate. Int J Pharm, 374(1–2):53–7.