CATIONIC SURFACTANTS-MODIFIED NATURAL ZEOLITES: POTENTIAL EXCIPIENTS FOR ANTI-INFLAMMATORY DRUGS

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ABSTRACT

The aim of this study was to prepare and characterize a potential drug support system based on surfactant/zeolite composites for anti-inflammatory drugs. In order to increase the adsorbing capacity the external surface of the natural zeolite clinoptilolite was modified with benzalkonium chloride in the treatments raging from 100% to 300% of the zeolite external cation exchange capacity. Adsorption of diclofenac diethylamine and ibuprofen on the prepared organozeolites from drug solutions (0.05 - 0.5 mg/ml) in phosphate buffers pH 7.4 was investigated. Drug adsorption on organozeolites showed a nonlinear type of isotherm and maximum adsorption capacities were 53.19 mg/g for diclofenac diethylamine and 20.04 mg/g for ibuprofen. It was shown that the presence of benzalkonium chloride at the zeolite surface improved adsorption of the model drugs.

Keywords: clinoptilolite, cationic surfactant, adsorption, excipient, anti-inflammatory drug

INTRODUCTION

Almost all therapeutic products, including therapeutic products for human and veterinary use, include excipients. The total amount of excipients frequently used is greater than the amount of the active drug substance(s) in a dosage form. Excipients may be added to improve the compressibility of the active drug, stabilize the drug from degradation, decrease gastric irritation and control the rate of drug absorption from the absorption site. Furthermore, they may increase drug bioavailability in addition to affect the drug dissolution rate by altering the medium in which the drug is dissolving or by reacting with the drug itself. As with drug substances, excipients are derived from natural sources or are synthesized either chemically or by other means. They range from simple, usually highly characterized, organic, or inorganic molecules to highly complex materials that are difficult to fully characterize [1, 2].

The commonly used minerals as excipients in pharmaceutical preparations are: oxides, carbonates, sulfates, chlorides, phosphates and phyllosilicates. More recently, some tectosilicates (zeolites) also feature in pharmaceutical preparations [3]. The mineral–organic interaction can be used to control the release of active ingredients (drugs) with improved therapeutic properties. Here the minerals first serve as a carrier, and then as a releaser of the active ingredient. Because of their large specific surface area and high adsorption capacity, zeolites are well suited to acting as drug carriers and releasers [4].

In this paper the natural zeolitic tuff with high content of clinoptilolite was modified with different amounts of cationic surfactant benzalkonium chloride. Investigation of diclofenac diethylamine and ibuprofen adsorption by obtained composites was performed with a view to a potential use of these materials as prospective carriers for anti-inflammatory drugs.

EXPERIMENTAL

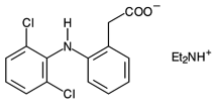
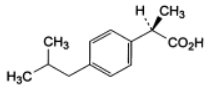
A sample of the natural zeolitic rich tuff from Zlatokop deposit, Vranje, southern Serbia (ZVB) was used as the starting material in this study. Raw zeolitic tuff was sieved to yield particles below 43 μm. Qualitative X-ray powder diffraction (XRPD) analysis ascertained that the mineralogical composition of ZVB was primarily clinoptilolite (minimum 80%), with trace amounts of feldspar, quartz and pyrite. The cation exchange capacity (CEC) of the starting material was 146 $mmolM^+/100g$ measured by 1M NH_4Cl method, while its ECEC was 10 $mmolM^+/100$ g [5].

Cationic surfactant benzalkonium chloride (BC) (Fluka, Buchs, Switzerland) was used for the preparation of modified zeolites (composites). To obtain composites with different loadings, the 10 wt% aqueous suspension of the initial zeolitic tuff was treated with surfactant amounts equivalent to 100%, 200% and 300% of its ECEC. The suspensions were stirred at 5000 rpm using laboratory mixer at 50 ºC for 15 min. After the reaction time, the suspensions were filtered and the 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. Obtained composites were washed with distilled water and dried in an oven for 2 hours at 60 °C. The prepared samples were denoted as ZBC-10, ZBC-20 and ZBC-30.

The starting zeolitic tuff and modified zeolites were characterized by FTIR spectroscopy 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 prepared by processing compressed KBr disks.

Adsorption of anti-inflammatory drugs, diclofenac diethylamine (DDEA) and ibuprofen (IB) (both of pharmacopoeial quality) (Table 1) on prepared composites were carried out in batch experiments at room temperature. Stock solutions of the testing drugs containing different initial concentrations of each drug (50 to 500 mg/l) were prepared in phosphate buffer at pH 7.4 (USP 30). 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 at 250 rpm at room temperature during 1 hour and then filtered. Supernatants were used for HPLC determination of the drug concentration. The amounts of the drug sorbed were calculated from the difference between the initial and final concentrations in the supernatants after equilibrium.

Table 1. Structural formulas and physicochemical properties of the model drugs.

Compound	Structural formula	MWt	pKa
Diclofenac diethylamine *Diethylammonium 2-[(2,6-dichloroanilino) phenyl]acetate*		369.3	4.87
Ibuprofen *(2RS)-2-[4-(2-methylpropyl)phenyl]propanoic acid*		206.3	4.55

RESULTS AND DISCUSSION

The amounts of sorbed BC after modification procedure obtained by HPLC analysis were found to be 9.24, 17.25 and 28.02 mmol/100g for ZBC-10, ZBC-20 and ZBC-30, respectively. These results were in agreement with the initial surfactants levels confirming the efficient modification procedure.

The IR spectra for the natural zeolitic tuff (ZVB) and ZBC composites are shown in Figure 1. 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 [6]. 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 amounts of the adsorbed BC. No relevant variations in the frequency of the bands assigned to the clinoptilolite after the treatment with the BC were observed, which indicates that the zeolite structure remains unaltered after the modification, and that surfactant is present only at the zeolite surface.

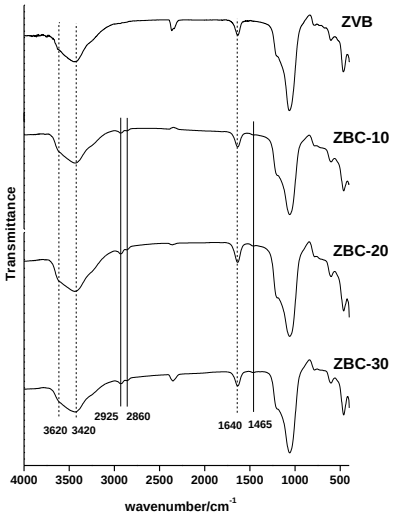


Figure 1. IR transmittance spectra for ZVB and ZBC composites.

Adsorption of DDEA and IB by ZBC composites was studied through the determination of the adsorption isotherms. The isotherms obtained by plotting the amounts of the drug adsorbed per weight unit of each adsorbent (mg/g) against the equilibrium concentrations of the each drug in the solution (mg/l) are presented at Figure 2a-b

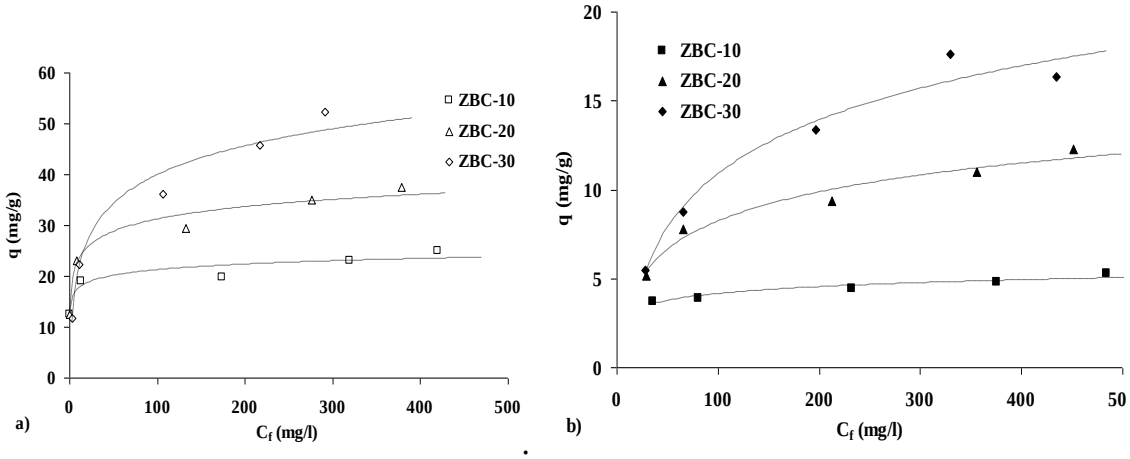


Figure 2. Adsorption of a) DDEA and b) IB by composites ZBC-10, ZBC-20 and ZBC-30.

As seen from the Figure 2a-b, DDEA and IB adsorption by composites followed nonlinear isotherms. It is observed that adsorbed amounts of both drugs increased with the initial concentrations of the each drug in solution and that the adsorbed amounts of the DDEA and IB increased with increasing the amount of surfactant at the surface of ZBC. 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 Parameters of the Langmuir isotherm are presented in Table 2.

From the maximum adsorption capacity (Q_m) presented in Table 2, it can be seen that compared to DDEA, IB showed the lowest adsorption by all ZBC composites. Both of investigated drugs are weak acids (Table 1) and thus at pH 7.4, they all exist in anionic form. Possible explanation for at least twice higher Q_m for DDEA then for IB at each surfactant level could be its amphiphilic nature, as it was previously shown with diclofenac sodium adsorption on modified zeolites [7].

Table 2. Parameters of Langmuir isotherm for drugs adsorption by different composites.

Sample	DDEA			IB		
	Q_m (mg/g)	K (l/mg)	R^2	Q_m (mg/g)	K (l/mg)	R^2
ZBC-10	24.57	0.084	0.989	5.40	0.032	0.990
ZBC-20	37.31	0.087	0.992	13.14	0.018	0.996
ZBC-30	53.19	0.043	0.978	20.04	0.012	0.985

CONCLUSION

Results reported in this paper demonstrate that natural zeolite clinoptilolite modified with different levels of benzalkonium chloride is prepared without altering the starting zeolite structure. It was shown that DDEA and IB adsorption by composites increased with increasing the amount of BC at the zeolitic surface. From maximum adsorption capacities it is evident that all three composites were much more effective in adsorbing DDEA than IB from aqueous solutions. The presented results alongside with the verified non-toxic nature of these materials make them a promising candidate for further research exploring the potential use of these low cost and abundant materials as excipients for advanced drug carrier system.

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