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Properties of diclofenac sodium sorption onto natural zeolite modified with cetylpyridinium chloride

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ABSTRACT

In this study an investigation of a model drug sorption onto cationic surfactant-modified natural zeolites as a drug formulation excipient was performed. Natural zeolite was modified with cetylpyridinium chloride in amounts equivalent to 100, 200 and 300% of its external cation-exchange capacity. The starting material and obtained organozeolites were characterized by Fourier transform infrared spectroscopy, zeta potential measurements and thermal analysis. In vitro sorption of diclofenac sodium as a model drug was studied for all surfactant/zeolite composites by means of sorption isotherm measurements in aqueous solutions (pH 7.4).

The modified zeolites with three levels of surfactant coverage within the short activation time were prepared. Zeta potential measurements and thermal analysis showed that when the surfactant loading level was equal to external cation-exchange value, almost monolayer of organic phase were present at the zeolitic surface while higher amounts of surfactant produced less extended bilayers, ordered bilayers or admicelles at the zeolitic surface. Modified zeolites, obtained in this manner, were effective in diclofenac sodium sorption and the organic phase derived from adsorbed cetylpyridinium chloride was the primary sorption phase for the model drug. The Langmuir isotherm was found to describe the equilibrium sorption data well over the entire concentration range. The separate contributions of the adsorption and partition to the total sorption of DS were analyzed mathematically. Results revealed that that adsorption and partitioning of the model drug take place simultaneously.

1. Introduction

Excipients are included in almost all therapeutic products for human and veterinary use and the total amount of excipients frequently used is greater than the amount of the active drug substance(s) in a dosage form. The properties of the final dosage form (i.e., its bioavailability and stability) are, for the most part, highly dependent on the excipients chosen, their concentration and interaction with both the active compound and each other [1,2].

A variety of minerals have been used as excipients in pharmaceutical preparations because they have certain desirable physical and physico-chemical properties, such as high adsorption capacity, specific surface area, swelling capacity and reactivity to acids. Other important properties are water solubility and dispersivity, hygroscopicity, unctuosity, thixotropy, slightly alkaline reaction (pH), plasticity, opacity and colour. Clearly such minerals must not be toxic to humans. The following minerals are commonly used as excipients in pharmaceutical preparations: oxides, carbonates, sulfates, chlorides, phosphates and phyllosilicates. More recently, some tectosilicates (zeolites) also feature in pharmaceutical preparations [3].

Zeolites are hydrated microporous tectoalumosilicates consisting of three-dimensional frameworks of SiO_4 and AlO_4 tetrahedra linked through shared oxygen atoms. The partial substitution of Si^{4+} by Al^{3+} results in an excess of negative charge which is compensated by alkali and earth alkaline cations. Zeolites are characterized by their ability (a) to lose and gain water reversibly, (b) to adsorb molecules of appropriate cross-sectional diameter and (c) to exchange their constituent inorganic cations without any major change of their structure. The heulandite group (HEU) of zeolites, including clinoptilolite ($(Na,K)_6(Al_6Si_3O)O_{72}\cdot 20H_2O$), is the most abundant zeolite in nature [4].

The use of clinoptilolite in human medicine has been demonstrated for the purpose of the external treatment of skin wounds

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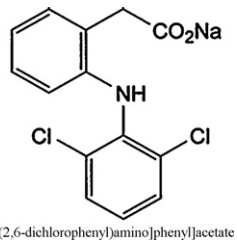

Fig. 1. Chemical structure of diclofenac sodium.

and athletes foot, in kidney dialyses for the removal of ammonia ions from body fluids, as antidiarrheal remedies, or as an active ingredient in antacid drugs [5–7], furthermore antimicrobial, antitumor and antiviral activity of clinoptilolite has also been reported [8–11].

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, smectites, kaolinite, talc, sepiolite and zeolites are well suited to acting as drug carriers and releasers [12].

Besides its common use as antimicrobial preservative in various pharmaceutical formulations, cationic surfactants have also been employed as solubilizer in drug formulations [13] and drug release testing [14], dissolution rate controlling agents [15,16] in addition to modification of micro and solid lipid nanoparticles [17,18]. Cetylpyridinium chloride is particular representative approved for use in oral dosage forms [1].

Chemical modification of zeolite with long chain organic cations results in an increased hydrophobicity of the mineral surface providing a high affinity for organic i.e., drug molecules. The enhanced coadsorption of drug molecules on solid–surfactant complexes, termed surface solubilization, adsolubilization or co-adsorption, is a surface analogue of micelle solubilization and may lead to innovative zeolite applications, such as new drug delivery systems [19–21].

In our previous study it was demonstrated that modification of zeolitic surface with cationic surfactants (benzalkonium chloride and hexadecyltrimethylammonium bromide) at different modification levels reflected on powder flow characteristics i.e., excipient functionality determined by hydrophobicity/hydrophilicity of the organozeolites [22]. In this study diclofenac sodium (see Fig. 1) is used as a model drug. The objective of the research was to investigate diclofenac sodium sorption by the natural zeolite modified with different amounts of cetylpyridinium chloride (CPC). Characterization of obtained organozeolites was performed by determination of zeta potential as well as by thermal analysis and Fourier transform infrared spectroscopy. The contribution of adsorption and partition to the overall sorption the drug molecule was described using a mathematical analogue method.

2. Experimental

A natural material used in this study for the preparation of organozeolites was the raw clinoptilolite rich zeolitic tuff from Zlatokop deposit (Vranje, southern Serbia). Based on qualitative X-ray powder diffraction analysis (XRPD), the clinoptilolite content was over 80% with trace amounts of quartz, pyrite and feldspar as accessory minerals. The raw zeolitic tuff was sieved to yield particles below 43 μm. The specific surface area of the zeolitic tuff, determined by the method of methylene blue [23], was found to be 68.6 m^2/g [24]. The complete chemical composition of the starting zeolitic tuff was as follows: 64.21% SiO_2, 11.48% Al_2O_3, 0.88% Fe_2O_3, 0.25% TiO_2, 4.55% CaO, 1.45% MgO, 1.71% Na_2O, 1.29% K_2O and 14.00% ignition loss.

The cation-exchange capacity (CEC) and external cation-exchange capacity (ECEC) of the starting zeolitic tuff, as the most important characteristics for surface modification, were also determined. Thus, the CEC of the zeolitic tuff was 146 $mmolM^+/100\,g$ [25], as measured by the ammonium chloride method [26], while its ECEC was 10 $mmolM^+/100\,g$ as determined by the method of Ming and Dixon [27]. The predominant cation associated with clinoptilolite was calcium, followed by sodium, potassium and magnesium.

Cationic surfactant cetylpyridinium chloride (CPC) (Sigma–Aldrich, St. Louis, MO, USA) was used for the preparation of organozeolites (composites). The physico-chemical and thermal properties of CPC are listed in Table 1. Potassium dihydrogen phosphate and sodium hydroxide (Lach-Ner, Brno, Czech Republic) were used for buffer preparation, while diclofenac sodium (DS) (Ph. Eur. 6 grade) was supplied directly from the pharmaceutical industry (Galenika®, Belgrade, Serbia). Double distilled water was used throughout the experiments.

The 10 wt% aqueous suspension of initial zeolitic tuff (ZVB) was treated with surfactant amounts equivalent to 100, 200 and 300% of its ECEC with the purpose of obtain composites with different surfactant loadings. 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 min. After mixing, the suspensions were filtered using ashless filter paper (MACHEREY-NAGEL 640, Düren, Germany) for achieving extremely fine precipitates. The filtrates were further centrifuged at 3000 rpm for 20 min and supernatants were used for determination of surfactant concentration. The obtained composites were washed with distilled water and dried in an oven during 2 h at 60 °C. The prepared samples are denoted as ZCPC-10, ZCPC-20 and ZCPC-30.

The zeta potentials of investigated zeolites prior and after treatment with surfactants were measured by a Zetasizer Nano ZS90 (Malvern Instruments, Malvern, UK). Aqueous suspensions (0.1 mg/ml) of testing material were dispersed using ultrasonic bath and an average of 20 measurements was taken to represent the measured potential. Prior to the measurements, the operating conditions were proved and adjusted using a calibrated latex dispersion supplied by the instrument manufacturer (zeta potential -50 ± 5 mV).

The natural zeolitic tuff and the organozeolites were also characterized by thermal analysis. Thermal analysis was performed on a Netzsch STA 409 EP (Selb, Germany). Samples were heated (20–700 °C) in an air atmosphere, at a heating rate of 10 °C min^{-1}.

Infrared spectra of the starting zeolitic tuff as well as the obtained composites were recorded in the range of 4000–400 cm^{-1} using a ThermoNicolet 6700 FTIR Spectrometer with 2 cm^{-1} resolution. The samples were dispersed in KBr and compressed into discs.

Tests determining adsorption of DS by prepared composites were carried out in batch experiments at room temperature. Stock solutions of the drug in the concentrations from 0.16 to 1.57 mmol/l in phosphate buffer at pH 7.4 (USP 30) were prepared. The batch experiments were carried out by shaking the reaction mixture containing 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 h, the samples were centrifuged 15 min at 3000 rpm. Supernatants were used for determination of the drug. The initial and final concentrations of drug were determined by HPLC analysis.

The chromatographic system Thermo Scientific Finnigan Surveyor (San Jose, CA, USA) consisted 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 Zorbax Extend