ACECLOFENAC ADSORPTION ON A NATURAL ZEOLITE MODIFIED WITH CATIONIC SURFACTANT: INDIRECT VS. DIRECT METHOD OF COMPOSITES PREPARATION

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ABSTRACT

Adsorption of aceclofenac, an anti-inflammatory drug, on a natural zeolite clinoptilolite previously modified with the cationic surfactant (hexadecyltrimethylammonium bromide) in amount equivalent to its external exchange capacity (10 mmol/100 g) was investigated. The drug adsorption was carried out in batch experiments at room temperature from the drug solutions (50 to 1000 mg/l) in phosphate buffer (pH 7.4). Aceclofenac adsorption on the natural zeolite was also investigated from drug/surfactant solutions, containing the surfactant in amount corresponding to external exchange capacity of the starting zeolite (10 mmol/100 g) and lower (4.8 mmol/100 g). Results showed that adsorption of aceclofenac was efficient in both methods of drug/modified zeolite composites preparation.

Keywords: clinoptilolite, cationic surfactant, adsorption, aceclofenac, excipient

INTRODUCTION

Inorganic materials such as oxides, carbonates, sulfates, chlorides, phosphates and phyllosilicates are commonly used as pharmaceutical excipients. Among other applications in recent years, natural zeolites have emerged as potential materials for biomedical application [1-2]. Natural zeolite clinoptilolite proved to be effective as a drug carrier mainly by means of its active external surface. In order to enhance coadsorption of organic molecules, cationic surfactants have been used to modify the surface properties of zeolites [3].

In our previous studies it was demonstrated that modification of zeolitic surface with cationic surfactant hexadecyltrimethylammonium bromide (HB) at different modification levels (10, 20 and 30 mmol/100 g) resulted in an increase of the drug (diclofenac sodium) adsorbed amounts. *In vitro* drug release investigations revealed that the prolonged drug (diclofenac sodium) release from the obtained drug-modified zeolite composites during 8 hours was achieved. In addition, the modification of the zeolitic surface also improved the excipient functionality [4].

Aceclofenac (AC), a phenylacetic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) related to diclofenac. It is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, in usual doses of 100 mg twice daily by mouth [5]. The occurrence of NSAID-related side effects and its short biological half life (approximately 4 hours) makes it a good candidate for prolonged release preparations with the aim to maintain therapeutic activity, reduce side effects and improve patience compliance. The basic physicochemical properties of AC are given in Table 1.

The aim of this study was to investigate aceclofenac adsorption by cationic surfactant modified natural zeolite clinoptilolite in batch adsorption experiments. Furthermore, to examine the possibility of more efficient method for drug/modified zeolite composite

preparation, analysis of aceclofenac adsorption from mixtures containing the drug, surfactant, cosolvent and natural zeolite was also performed.

EXPERIMENTAL

A sample of natural zeolitic (NZ) rich tuff from the Zlatokop deposit, Vranje (Serbia) was used as the starting material. The raw zeolitic tuff was sieved to yield particles below 43 μm in size. Qualitative XRPD analysis ascertained that the mineralogical composition of the NZ was primarily clinoptilolite (minimum 80 %), with trace amounts of feldspar, quartz and pyrite as accessory minerals. The cation exchange capacity (*CEC*) of the starting material was 146 mmol M^+/100g measured by the ammonium chloride method, while its external exchange capacity (*ECEC)* was 10 mmol M^+/100 g [6].

The modified zeolite (composite) was obtained by treatment of the NZ with HB in amount equivalent to 100 % its *ECEC* (10 mmol/100g) i.e. aqueous HB solution (4 mg/ml). Details of the preparation and characterization of the composite (denoted as ZHB-10) are given elsewhere [4].

The AC adsorption onto prepared composite was carried out in batch experiments at room temperature from the drug solutions (50 to 1000 mg/l) in phosphate buffer (pH 7.4) (indirect method of the composite preparation). The drug concentration in aqueous phase was determined spectrophotometrically at 274 nm and the amount of the drug uptake was calculated from the difference between the initial and final concentration in the aqueous supernatant after the equilibrium. The composite prepared from the stock solution with the highest AC concentration was dried and kept for further investigation (denoted as ZHB-10 AC/IM).

The drug/modified zeolite composites were also prepared by the adsorption onto natural zeolite clinoptilolite from: a) AC (1.4 mg/ml)/HB solution (4 mg/ml) aqueous solution and b) AC (5 mg/ml)/HB (1.92 mg/ml) solution containing of 25 % of ethanol as a cosolvent. The reaction mixtures were prepared on a high-speed disperser T25 digital Ultra-Turrax® (Staufen, Germany) at 10000 rpm for 5 min. After mixing, the suspensions were filtered and the filtrates were collected for the drug assay. The obtained drug/modified zeolites composites, prepared by direct method, were denotes as ZHB-10 AC/DM 1 and ZHB-10 AC/DM 2, respectively.

The drug concentrations in aqueous phase after the equilibrium were determined by HPLC analysis. The drug adsorption was studied by means of adsorption isotherm analysis. Photon correlation spectroscopy (PCS) was used for particle size characterization of the starting drug/surfactant mixtures using a Zetasizer NanoZS90 (Malvern Instruments, UK). The same equipment was used for zeta potential measurements of the natural and modified zeolite and the obtained drug/modified zeolite composites (by both methods of preparation).

RESULTS AND DISCUSSION

Adsorption of AC by ZHB-10 composite (modified with the cationic surfactant in amount equivalent to *ECEC* of the starting zeolite) showed a nonlinear type of isotherm (Fig. 1). The Langmuir equation was found to describe the equilibrium adsorption data well over the entire concentration range.

The maximum adsorbed amount of AC (Table 2) was higher compared to diclofenac sodium adsorbed amount (~ 24 mg/g) by ZHB-10 composite as previously described [4]. Additionally, AC adsorbed amount on the starting NZ form the drug/surfactant solution with the higher drug content (ZHB-10 AC/DM 2) was effective even at the lower surfactant concentration (corresponding to 4.8 mmol/100 g natural zeolite).

The investigated drug is hydrophobic organic substance, practically insoluble in water (Table 1), and thus it was assumed that it would interact with the hydrophobic phase created by the surfactant tail group at the zeolitic surface. In addition, its pKa value indicates that at pH 7.4 it exists in anionic form. However, slightly higher adsorbed amount obtained for AC that for diclofenac sodium [4], despite their similar chemical structure (Table 1), could be explained by the overall hydrophobic-hydrophilic interactions of the drug molecules and the surfactant deposits on the clinoptilolite surface.

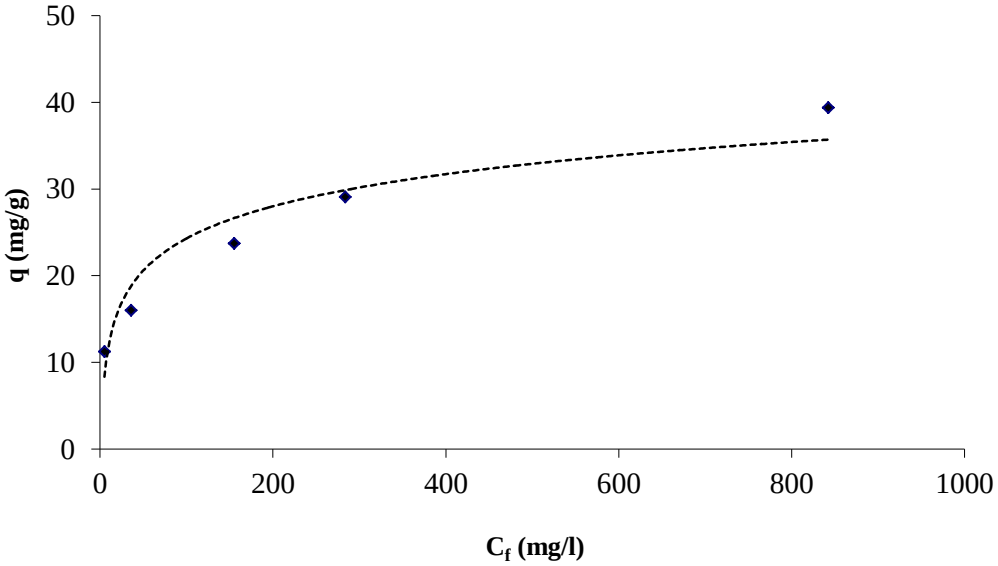


Figure 1. Adsorption of AC by ZHB-10 composite

Table 1. Overview of the basic physicochemical properties of aceclofenac

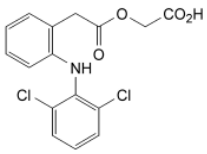
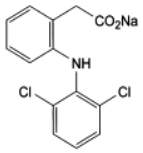
Compound	Structural formula	MWt	pKa	Solubility
Aceclofenac		354.2	4.7	Practically insoluble in water, freely soluble in acetone, soluble in ethanol (96 per cent).
Diclofenac sodium		318.1	4.0	Sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), slightly soluble in acetone.

Table 2. Adsorbed AC amounts by different drug/modified zeolite composites

Sample	ZHB-10 AC/IM	ZHB-10 AC/DM 1	ZHB-10 AC/DM 2
Adsorbed amount (mg/g)	39.4	12.2	32.4

Zeta potential measurement showed that the initial zeta potential of NZ (–27.4 mV) [7] after AC adsorption changed to –19.7 mV for ZHB-10 AC/IM, –10.6 mV for ZHB-10 AC/DM 1 and –13.3 mV for ZHB-10 AC/DM 2. From these results it is obvious that adsorption of AC induced changes in the surface charge since the zeta potential of ZHB-10 was ~ 1 mV.

The PCS analysis of the AC (1.4 mg/ml)/HB (4 mg/ml) solution revealed a bimodal distribution with the mean particles size of ~15 nm and ~200 nm. The smaller particle population was related with the HB micelles formation (as the surfactant concentration was higher than its critical micelle concentration), while the larger particle population were ascribed to AC-loaded-HB co-aggregates. Furthermore, as concentration of the drug was increased up to (5 mg/ml) and the cosolvent ethanol was introduced into HB solution, the monodispersed particles with mean size ~600 nm was recorded, likely indicating formation of complex supramolecular co-aggregates comprising the drug, the surfactant and the co-surfactant. These assumptions were consistent with the observations reported by Hosseinzadeh and Gheshlagi [8] on the concentration-dependent formation of supramolecular aggregates in aqueous solution of diclofenac sodium and HB.

CONCLUSION

Drug (aceclofenac)/cationic surfactant (hexadecyltrimethylammonium bromide) modified zeolite composites were prepared by both batch method and adsorption from drug/cationic surfactant aqueous and aqueous-ethanolic solution on a natural zeolite clinoptilolite. Adsorption was successful even when the cationic surfactant amount was lower than ECEC value of the starting zeolite and it was influenced by overall hydrophobic-hydrophilic interactions of the drug molecules and the surfactant deposits on the clinoptilolite surface. Presented result confirmed that surface adsolubilization could have a great attractiveness in the development of prospective pharmaceutical excipient. Further investigations of pharmaceutical technical characteristics and drug release from the obtained composites would reveal their possible use in various pharmaceutical applications.

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