COMPARISON OF CATIONIC SURFACTANTS-MODIFIED ZEOLITES AS A POTENTIAL DRUG CARRIER FOR DICLOFENAC DIETHYLAMINE

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ABSTRACT

In this paper, results of the anti-inflammatory drug - diclofenac diethylamine (DDEA) adsorption by zeolite composites with different amounts (10, 20 and 30 mmol/100g) of cationic surfactants - benzalkonium chloride (BC) and cetylpyridinium chloride (CP) were compared. It was determined that DDEA adsorption was influenced by the surfactant type and amount present at the zeolitic surface. The pharmaceutical performance of BC or CP modified zeolites-drug composites was evaluated by *in vitro* dissolution experiments. To estimate the mechanism of the drug release profile, data were fitted by mathematical models describing various kinetic. The permanent DDEA release from BC and CP composites over a period of 8 hours was achieved and release models indicated on combination of drug diffusion and ion-exchange as predominant release mechanisms in dissolution media.

Keywords: clinoptilolite, cationic surfactants, adsorption, anti-inflammatory drug, dissolution.

INTRODUCTION

In recent years, a variety of silica based morphologies, from mesoporous nanoparticles to implantable micro-carriers, have been synthesized and applied for drug delivery purposes [1]. To overcome some of disadvantages of these carriers such as a time-consuming and costly synthesis, which involves high energy consumption and use of toxic materials, the use of naturally occurring aluminosilicate is a good alternative. For example, some tectosilicates (zeolites) feature in pharmaceutical preparations as a carrier-releaser of active ingredients (drugs) [2]. The adsorption of surfactants at the solid–liquid interface may modify the properties of the solid (zeolitic) surface and favors the uptake from solution of molecules which do not adsorb onto the solid in the absence of surfactants. This phenomenon, known in the literature as 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 [3]. In our previous contribution, results on diclofenac diethylamine (DDEA) adsorption onto natural zeolite modified with different amounts of benzalkonium chloride (100, 200 and 300% of its external cation-exchange capacity -ECEC) were presented [4]. Samples were denoted as ZBC-10, ZBC-20 and ZBC-30. It was shown that modified zeolites were effective in drug adsorption and that the organic phase derived from adsorbed surfactant was the primary adsorption phase for the model drug.

In this paper adsorption of DDEA, under the same experimental conditions, onto natural zeolite previously modified with the same amounts of cetylpyridinium chloride [5] was performed. These samples were denoted as ZCP-10, ZCP-20 and ZCP-30. In order to demonstrate the feasibility of the potential use of these mineral materials for drug delivery, release behaviour of the model drug from ZBC-20 and ZPC-20 modified zeolites-drug composites was compared.

EXPERIMENTAL

Cetylpyridinium chloride (CP) (Sigma-Aldrich, St. Louis, MO, USA) was used for preparation of composites. A sample of the natural zeolitic clinoptilolite rich tuff from Zlatokop deposit, Vranje, southern Serbia (ZVB) was used as the starting material. 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 conditions for preparation of composites and their physico-chemical characterization are given elsewhere [5, 6].

Adsorption of DDEA (supplied from Galenika®, Belgrade, Serbia) on ZCP-10, ZCP-20 and ZCP-30 composites was carried out in the following way: stock solutions of the DDEA containing different initial concentrations (0.05 - 0.5 mg/ml) were prepared in a phosphate buffer at pH 7.4 (USP 30), since pKa value of the drug is 4.87 and it is sparingly soluble in water. 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 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.

The pharmaceutical performance of modified zeolites-drug composites was evaluated by *in vitro* dissolution experiments. The flat-faced punches with the diameter of 9 mm were used to compress the ZBC-20 and ZCP-20 tested drug powders in a 200 mg comprimates using an eccentric compressing machine (EKO Korsch, Berlin, Germany).

DDEA release from the comprimates was carried out in a rotating paddle apparatus (Erweka DT70, Heusenstamm, Germany) in a phosphate buffer solution pH 7.4 at 37 °C during 8 hours. All data-points were determined as the average value for 3 independent measurements. The amount of drug released was determined by HPLC analysis and expressed as a percent of the drug load in the composite-drug sample.

To evaluate drug release from the composites the release profile data were fitted by mathematical models describing various kinetic [7,8] (Table 1). The model applicability was based on the comparison of the determination coefficient (r^2).

Table 1. Applied mathematical models to the drug release data.

Model	Equation
Zero order	% diss = 100 $(1-k_0t)$
First order	% diss =100$[1-e^{k1t}]$
Higuchi	% diss = $k_ht^{0.5}$
Korsmeyer-Peppas	% diss = kt^n
Bhaskar	-log (1-% diss) = $k_bt^{0.65}$
Hixon-Crowell	% diss = 100 $[1-(1-k_ct/4.6416)^3]$

where: *% diss* is percent dissolved at time t; k_0, k_1, k_h, k, k_b, k_c are dissolution rate constants 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

Adsorption of DDEA on ZCP-10, ZCP-20 and ZCP-30 zeolite-surfactant composites followed nonlinear isotherm type as it was previously determined for adsorption on ZBC-10, ZBC-20 and ZBC-30 composites [4]. The maximum adsorption capacity (Q_m), obtained using the Langmuir model, were 175.4 mg/g for ZCP-10, 109.9 mg/g for ZCP-20 and 114.9 mg/g for ZCP-30. These values were significantly higher than DDEA adsorbed amounts by organozeolites modified with BC (24.6 mg/g for ZBC-10, 37.3 mg/g for ZBC-20 and 53.2 mg/g for ZBC-30) [4]. The obtained results indicated that the type of surfactant present at the zeolitic surface had an influence on DDEA adsorption ability. Furthermore, amphiphilic

nature of the model drug [6] could also affect overall adsorption properties of the modified zeolites.

Dissolution profiles of drug/ZBC-20 and ZCP-20 comprimates were compared and these results are shown in Figure 1. Permanent release of DDEA over a period of 8 hours in a sustained manner was observed. For both ZBC-20 [6] and ZCP-20 comprimates approximately 20% of DDEA was released. The similar DDEA release from both composites was unexpected since, adsorption of DDEA by ZCP-20 was almost three times higher than for ZBC-20 composite. Considering that DDEA is a nonsteroidal anti-inflammatory drug which has been used for dermal application, the released amounts were similar to those obtained after DDEA release from various carriers such as multiple emulsions (less than 20%) or an emulgel (26%)[10].

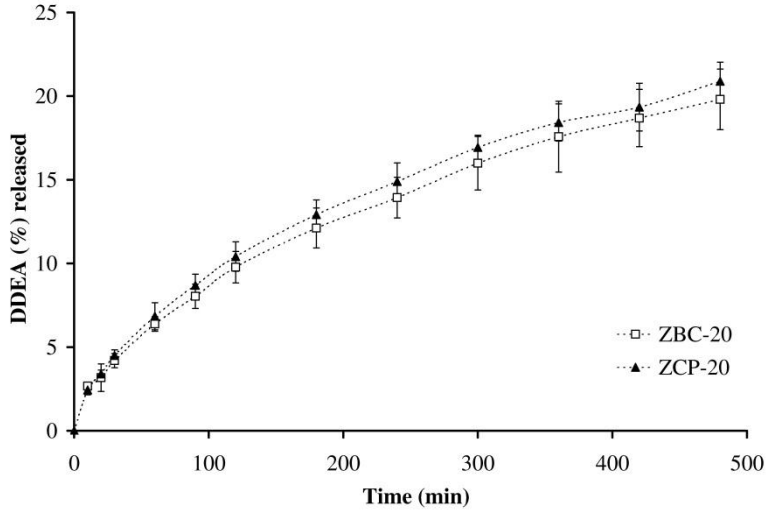

Figure 1. *In vitro* dissolution profiles of DDEA from different composites

Table 2. Values of fitted parameters by different mathematical models for DDEA release from different composites.

Model	Fitted parameters	Sample	
		ZBC-20	ZCP-20
Zero order	r^2	0.9598	0.9516
	k_0	0.0368	0.0386
First order	r^2	0.9670	0.9979
	k_1	0.0004	0.6584
Higuchi	r^2	0.9984	0.9985
	k_h	0.9560	1.0053
Korsmayer-Peppas	r^2	0.9950	0.9979
	k	0.6734	0.6584
	n	0.5518	0.5569
Bhaskar	r^2	0.9971	0.9955
	k_b	0.0017	1.0053
Hixon-Crowell	r^2	0.9661	0.9589
	k_c	0.0006	0.0007

The values of fitted parameters by different mathematical models used to describe DDEA dissolution curves are listed in Table 2. For both samples the best fitting model was Higuchi with the similiar values of dissolution rate constants (0.9560 for ZBC-20 and 1.0053 for ZCP-20). This model corresponds to a complete Fickian diffusion based transport (n=0.5) and it has been previously found for drug release from different micro- and meso- porous silica carriers [9]. However, Korsmeyer-Peppas and Bhaskar model were also in a very good agreement, indicating that the drug diffusion from the composites was not passive and that the ion-exchange between drug anions and dissolution medium was also involved.

CONCLUSION

Results reported in this paper demonstrated that DDEA-modified zeolite composites could be easily prepared by bath sorption procedure. The drug content in the obtained composites was influenced by the surfactant type and the amount present at the zeolitic surface. Significant differences observed in drug adsorption amounts could be used for preparation of drug-modified zeolite composites by selection of the most appropriate organic cation for zeolite modification. Prolonged drug release and dissolution kinetic as a combination of diffusion and ion exchange from the obtained composite offers possibility of successful application of the modified natural zeolites as carrier for drug delivery applications.

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