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An investigation of diclofenac sodium release from cetylpyridinium chloride-modified natural zeolite as a pharmaceutical excipient

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Dedicated to Prof. Carmine Colella on the occasion of his 70th birthday.

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ABSTRACT

In this paper, investigations of zeolite – cationic surfactant – drug composites as drug carriers were performed. For that purpose, after adsorption of the model drug – diclofenac sodium (DS) onto composites obtained by the modification of natural zeolite (NZ) with cetylpyridinium chloride (CPC) at the three different levels, i.e., 10, 20 and 30 mmol/100 g (ZCPC-10, ZCPC-20 and ZCPC-30, respectively), the release of the drug, at pH 6.8, was studied. The results of DS release from ZCPC-10 composite (DS/ZCPC-10) were compared with the DS release from corresponding physical mixture, as well as from physical mixture of NZ and DS. Characterization of the composites after adsorption of DS and the physical mixtures was realized by zeta potential measurements and by thermal analysis.

Results showed that the prolonged release of DS from all the three composites, as well as from physical mixture containing ZCPC-10 and DS was achieved over a period of 8 h. The drug release from both DS/ZCPC-10 (max 55%) and corresponding physical mixture (max 38%) was remarkably lower than that from the physical mixture of NZ and DS (max 85%). The kinetic analysis for all the three composites, as well as for the physical mixture of ZCPC-10 and DS, showed that drug release profiles were best fitted with the Korsmeyer-Peppas and Bhaskar release models, indicating a combination of drug diffusion and ion exchange as the predominant release mechanisms in the dissolution medium.

1. Introduction

Pharmaceutical dosage forms contain both pharmacologically active compounds and excipients added to aid the formulation and the manufacture of the subsequent dosage form for administration to patients [1]. According to Ph. Eur. 7.0, an *excipient* (auxiliary substance) is any constituent of a medical product that is not an active substance. For example, adjuvants, stabilizers, antimicrobial preservatives, diluents and antioxidants are excipients [2]. In earlier days, excipients were considered inactive ingredients. Over time, pharmaceutical scientists learned that excipients are not inactive and frequently have substantial impact on the manufacture and quality, safety, and efficacy of the drug substance(s) in a dosage form [3]. A key facet of some excipients is that whilst they have no therapeutic value *per se*, they can have a dictating role on how the active pharmaceutical ingredient is presented to the body and the resultant therapeutic effect. The types of excipients that can, for example, delay or extend the release of a drug substance are very important to achieving the desired bioavailability of the active ingredient (without consideration of its solubility) at the required location in the body [4].

Oxides, carbonates, sulfates, chlorides, phosphates and phyllosilicates are minerals commonly used as pharmaceutical excipients [5]. More recently, some tectosilicates (zeolites) also feature in pharmaceutical preparations due to their adsorptive and ion exchange properties [6–8]. The mineral–organic interaction can be used to control the release of drugs, thereby improving their therapeutic properties. Zeolites are well-suited to act as drug carriers and releasers due to their large specific surface area and high adsorption capacity [9]. In order to enhance the adsorption of drug molecules, cationic surfactants have been used to modify the surface properties of zeolites. Surfactants can replace only the native inorganic cations at the external surface of the zeolite (external cation exchange capacity of zeolite – *ECEC*), while bilayers are form with sufficient amounts of surfactants. Thus, adsorption of cationic surfactants onto zeolitic surface usually includes ion exchange (when amount of surfactant is below the *ECEC* of the zeolite) and, in addition to ion exchange, hydrophobic interactions (when the amount of surfactant is above the *ECEC* of the zeolite). In this

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way, the adsorption of surfactants at the solid–liquid interface may modify the properties of the solid surface and favor the uptake of molecules from solution that do not adsorb onto the solid in the absence of surfactants. This phenomenon, termed surface solubilization, adsolubilization or co-adsorption [10], is the surface analog of micelle solubilization and has been studied in the context of solid surfaces modified by surfactant used for drug delivery [11–13].

The long term and biological stability of zeolites modified with hexadecyltrimethylammonium (HDTMA) chloride over a wide range of pH values was demonstrated [14], with minimum surfactant desorption and a lack of microbiological toxicity, making them potential candidates as drug formulation excipients. Adsolubilization of drugs by zeolite–surfactant complexes may lead to prospective zeolite application, e.g., as new drug delivery systems [15–17].

In a previous study, the adsorption of diclofenac sodium (DS) by composites obtained by modification of natural zeolite (NZ) with cetylpyridinium chloride (CPC) in amounts equivalent to 100%, 200% and 300% of its *ECEC* (ZCPC-10, ZCPC-20 and ZCPC-30) was investigated at pH 7.4 [18]. It was determined that the presence of CPC at the zeolite surface significantly increased DS adsorption and the amount of drug adsorbed increased with increasing initial concentration of DS in solution. In addition, it was observed that the amount of DS adsorbed increased with increasing amount of CPC at the surface of the composites, suggesting that the organic cations were the relevant sites responsible for DS adsorption. Cetylpyridinium chloride modified zeolites (ZCPCs) were characterized by zeta potential measurements, thermal analysis and Fourier transform infrared spectroscopy.

In the present study, experiments of DS release from the three cetylpyridinium chloride-modified zeolites (ZCPC-10, ZCPC-20 and ZCPC-30)/drug composites (DS/ZCPCs) were performed with the aim of determining the feasibility of the application of these mineral materials as prospective carriers for anti-inflammatory drugs. The release of the drug from a physical mixture of ZCPC-10 and DS was also investigated, in order to determine whether a prolonged release of the drug could also be achieved. The obtained results were compared with the DS release from its physical mixture with NZ. For an explanation of DS release from the composites, the obtained results are discussed together with the results of the adsorption of DS by the same composites [18]. The composites after DS adsorption (DS/ZCPCs), as well as the physical mixture of ZCPC-10 and DS, were characterized by determination of the zeta potential and by thermal analysis. The obtained results are compared with the corresponding results obtained previously for the ZCPCs [18].

2. Experimental

2.1. Zeolite modification and drug adsorption

A sample of natural zeolitic (NZ) rich tuff from the Zlatokop deposit, Vranje, southern 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^+/100 g measured by the ammonium chloride method, while its *ECEC* was 10 mmol M^+/100 g [19]. The composites ZCPC-10, ZCPC-20 and ZCPC-30 were obtained by treatment of the NZ with the three different levels of cetylpyridinium chloride. The adsorption of DS by these composites was followed in a buffer solution at pH 7.4. Details of the preparation and characterization of the composites, and the adsorption and determination of the drug are given elsewhere [18]. The structure and the physicochemical and thermal properties of DS are presented in Table 1.

After adsorption experiments, obtained DS/ZCPC composites (denoted as DS/ZCPC-10, DS/ZCPC-20 and DS/ZCPC-30) were filtered using ashless filter paper (Macherey-Nagel 640, Düren, Germany), whereby extremely fine precipitates were obtained. The composites were dried at 60 °C and kept for further characterization and drug release experiments.

2.2. Characterization

The zeta potentials of the investigated composites after drug adsorption (DS/ZCPCs) were measured using a Zetasizer Nano ZS90 (Malvern Instruments, Malvern, UK). Aqueous suspensions (0.1 mg/ml) of the test material were dispersed using an ultrasonic bath and an average of 20 measurements were taken to represent the measured potential. Prior to the measurements, the operating conditions were confirmed and adjusted using a calibrated latex dispersion supplied by the instrument manufacturer (zeta potential −50 ± 5 mV).

Diclofenac sodium, the DS/ZCPCs composites, as well as physical mixtures of both ZCPC-10 and NZ with DS were characterized by thermal analysis. Thermal analysis (DTA/DTG) was performed on a Netzsch STA 409 EP (Selb, Germany). Samples were heated (20–800 °C) in an air atmosphere, at a heating rate of 10 °C min^{-1}.

2.3. Drug release determination

The release of the drug from DS/ZCPCs composites was determined from the composites that were collected at the end of the DS adsorption experiments from the stock solutions with the highest initial drug concentration. Testing was also performed for physical mixtures containing DS and either ZCPC-10 or NZ. The physical mixtures containing DS were prepared by geometric dilution using a pestle and mortar. The mixtures were ground for 15 min to assure adequate homogenization.

The flat-faced punches with a diameter of 9 mm were used to compress the DS/ZCPCs or physical mixtures into 200 mg comprimates using an eccentric compression machine (EKO Korsch, Berlin, Germany). The comprimates were made with a compression pressure sufficient to achieve resistance to crushing of around 30 N, with no signs of capping. In this way, the same conditions during release studies for all the samples were attained and the comprimates were placed in the dissolution medium in the same manner. All the comprimates disintegrated during first 5 min of testing.

The release of diclofenac sodium from the comprimates was performed in a rotating paddle apparatus (Erweka DT70, Heusenstamm, Germany) in 600 ml of phosphate buffer solution pH 6.8 (USP 30). The rotating paddle rate was 50 rpm and the temperature was maintained at 37 ± 0.5 °C. At fixed time intervals, 2 ml samples were withdrawn, filtered through a 0.45 μm MF-Millipore® membrane filter (Millipore Corporation, Bedford, USA) and assayed for DS. Sink conditions were maintained at all times. All data points were determined as the average value for three independent measurements. The amount of drug released was determined by HPLC analysis and expressed as the percentage of the drug content.

The HPLC analysis was performed on a HP1100 Hewlett-Packard (Beaverton, OR) system equipped with a binary pump, a Rheodyne injector (sample loop 20 μl) and a 1100 UV detector; the system was controlled by an IBM PC Pentium Vectra XA computer. The chosen column was a Phenomenex® C18 (125 × 4 mm, 3 μm particle size). The mobile phase consisted of methanol and water (80:20, v/v) and the pH of the mobile phase was adjusted to 2.5 with ortho-phosphoric acid. The column temperature was 30 °C and the flow rate was 0.75 ml/min. The UV detection was realized at 254 nm.