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# Inorganically modified diatomite as a potential prolonged-release drug carrier

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ABSTRACT

Inorganic modification of diatomite was performed with the precipitation product of partially neutralized aluminum sulfate solution at three different mass ratios. The starting and the modified diatomites were characterized by SEM–EDS, FTIR, thermal analysis and zeta potential measurements and evaluated for drug loading capacity in adsorption batch experiments using diclofenac sodium (DS) as a model drug. *In vitro* drug release studies were performed in phosphate buffer pH 6.8 from comprimates containing: the drug adsorbed onto the selected modified diatomite sample (DAMD), physical mixture of the drug with the selected modified diatomite sample (PMDMD) and physical mixture of the drug with the starting diatomite (PMDD). *In vivo* acute toxicity testing of the modified diatomite samples was performed on mice.

High adsorbent loading of the selected modified diatomite sample (~250 mg/g in 2 h) enabled the preparation of comprimates containing adsorbed DS in the amount near to its therapeutic dose. Drug release studies demonstrated prolonged release of DS over a period of 8 h from both DAMD comprimates (18% after 8 h) and PMDMD comprimates (45% after 8 h). The release kinetics for DAMD and PMDMD comprimates fitted well with Korsmeyer–Peppas and Bhaskar models, indicating that the release mechanism was a combination of non-Fickian diffusion and ion exchange process.



## 1. Introduction

Porous materials have been exploited for pharmaceutical purposes including development of floating drug delivery systems, sustained drug delivery systems and improvement of bioavailability of poorly water soluble drugs. Various types of pores present in these materials (open, closed, transport and blind pores) enable drug inclusion and subsequent drug release in more reproducible and predictable manner. Synthetic zeolites, silica xerogel materials, porous hydroxyapatite, porous silica–calcium phosphate composites, porous calcium carbonate microparticles and other porous materials have been used as drug carriers in sustained release formulations [1]. Another highly porous, natural and biogenic material that can be tested as an alternative to synthetic porous carriers is diatomaceous earth.

Diatomaceous earth (diatomite) is a soft, friable, very fine-grained, siliceous sedimentary rock created by the deposition of cell walls (frustules) of dead microscopic single-cell algae (diatoms) on the ocean and fresh water floors. Frustules vary in size, shape and architecture depending on the species of diatoms from which they originate, but basically they consist of two parts that fit together like two halves of Petri dish and represent a highly porous, yet rigid, amorphous silica skeletal framework.

Diatomite is industrially useful in a variety of ways because of its unique properties which include: low density, high porosity, large surface area, high absorptive capacity, low thermal conductivity and chemical inertness. The major uses of diatomite include filter aids, cement additives, fillers and absorbents [2]. There are various investigations regarding the potential use of natural or modified diatomite (chemically or thermally treated) for the removal of textile dyes [3–6], heavy metals [7–10] or organic pollutants [11–13] by adsorption process from wastewaters or polluted waters. Conversely, there are not many researches about the potential use of diatomite as a pharmaceutical excipient. Modifiable surface chemistry, biocompatibility and non-toxicity, along with the aforementioned unique physicochemical properties, impose diatomite as a promising candidate for drug delivery applications. Aw et al. [14] found that diatomite may be effective in drug delivery applications (implants and oral drug delivery systems) of poorly water soluble drugs, because for a model drug indomethacin, a non-steroidal anti-inflammatory drug (NSAID) poorly

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soluble in water, satisfying drug loading capacity (22%) and sustained drug release over two weeks was achieved. Another study [15] showed that surface modification of diatomite by covalent attachment of selected organosilanes and phosphonic acids may be an efficient method for tuning drug loading and drug release characteristics of diatomite. Again, indomethacin was used as a model drug and differences in drug loading capacities (15–24%) and release periods (6–15 days) depending on functional groups present on the surface of modified diatomite were observed. However, extremely small batches (approximately 130 mg of drug loaded diatomite/modified diatomite per batch) were produced following drug loading procedure employed in these studies [14,15]. Surface modification of diatomite in the study [15] was time-consuming and for organosilanes it involved the use of an organic solvent (toluene), which is not environmentally-friendly and may represent a health risk upon administration into human body due to solvent residue.

The aim of this study was to further investigate the potential use of diatomite as a drug carrier in prolonged-release formulations using diclofenac sodium (DS) as a model drug and adsorption as a drug loading procedure. Diclofenac sodium is another representative of NSAID which is, like indomethacin, also suitable for formulating into prolonged-release oral dosage forms, because it is completely absorbed when given orally, has a short half-life (1 to 2 h) and oral dose less than 0.5 g (75 to 150 mg daily) [16,17]. Since adsorption of DS onto natural diatomite in our preliminary experiments proved to be low, the preparation of comprimates containing the adsorbed drug in near therapeutic dose and having the acceptable size was not feasible, so the modification of diatomite was necessary. Both organic [12,15] and inorganic modifications [4,5,7,9,13] of diatomite have been investigated for various purposes so far. Zhang et al. [13] prepared diatomite coated with $Al_2O_3$ film *via* hydrolysis reaction and found it to be successful in treating wastewater containing anionic polyacrylamide. Therefore, it was assumed that the modification of diatomite with an aluminum compound *via* simple chemical reaction could improve the adsorption of diclofenac anion from water solution. Diatomite was modified with the product of forced hydrolysis of aluminum sulfate solution upon base addition by precipitation at three different mass ratios. The modification procedure was non time-consuming and environmentally-friendly since it was performed in aqueous dispersion. Also, the inorganic modification of diatomite has not been exploited in pharmaceutical purposes so far, to the best of our knowledge.

The starting and the modified diatomites were characterized by scanning electron microscopy (SEM), energy dispersive X-ray spectrometry (EDS), Fourier transform infrared spectroscopy (FTIR), thermal analysis and zeta potential measurements. The modified diatomite samples were also evaluated for drug adsorption capacity in adsorption batch experiments. *In vitro* drug release studies were performed in phosphate buffer pH 6.8 from comprimates containing: the drug adsorbed onto the selected modified diatomite sample (DAMD), physical mixture of the drug with the selected modified diatomite sample (PMDMD) and physical mixture of the drug with the starting diatomite (PMDD). Drug-release profiles for the abovementioned comprimates were fitted to various mathematical models in order to evaluate DS release mechanism and bring it in correlation with the proposed type of DS-carrier interactions. Safety issues, being important for potential pharmaceutical application of the inorganically modified diatomite, were evaluated in acute *in vivo* toxicity studies.

## 2. Experimental part

### 2.1. Materials

Peruvian food grade diatomite (DE) was purchased from Medicina Ltd., UK and used without further purification. Aluminum sulfate hexadecahydrate ($Al_2(SO_4)_3 \cdot 16H_2O$) was supplied from Centrohem d.o.o., Serbia, sodium hydroxide was purchased from Carlo Erba Reagenti, Italy, potassium phosphate monobasic from Sigma-Aldrich Chemie GmbH, Germany and absolute ethanol from Zorka-Pharma a.d., Serbia. Diclofenac sodium was supplied directly from pharmaceutical industry (Galenika a.d., Serbia). All reagents used were of analytical grade. Purified water (Ph. Eur. grade) was used through all experiments.

### 2.2. Methods

#### 2.2.1. Diatomite modification

Specified amount of diatomite was suspended in 50 ml of $Al_2(SO_4)_3$ aqueous solution (0.02 g/ml $Al_2(SO_4)_3 \cdot 16H_2O$) on a magnetic stirrer (RH basic 2, IKA®-Werke GmbH, Germany). After diatomite suspension visually became homogeneous, 60 ml of 0.1 M NaOH solution was added in a thin jet from a reservoir rotating at 60 rpm into suspension, which was at the same time still magnetically stirred. Soon after base addition, the obtained inorganically modified diatomite was separated from the medium by filtration and dried in an oven for 4 h at 60 °C. Depending on the amount of diatomite (250, 500 or 750 mg) suspended in $Al_2(SO_4)_3$ aqueous solution, the inorganically modified diatomite samples were labeled as MD250, MD500 and MD750. Before further investigations modified diatomite samples were pulverized in a mortar with a pestle.

Basic aluminum sulfate (BAS), the compound forming during modification, was precipitated alone in the absence of diatomite according to the aforementioned procedure for characterization purposes.

#### 2.2.2. SEM–EDS analysis

Scanning electron microscopy (SEM model JSM-6610LV, JEOL Ltd., Japan) in conjunction with energy dispersive X-ray spectrometry (EDS detector model X-Max Large Area Silicon Drift connected with INCA Energy 350 Microanalysis System) was applied to examine the morphology and chemical composition of the starting diatomite, modified diatomite/drug samples and basic aluminum sulfate. Samples were mounted on an aluminum carrier with double-faced adhesive carbon tape and coated with thin layer of gold before analyzing.

#### 2.2.3. FTIR analysis

The Fourier transform infrared (FTIR) spectra of the starting diatomite, basic aluminum sulfate and modified diatomite/drug samples were recorded using attenuated total reflection (ATR) technique on Nicolet 6700 FTIR spectrometer (Thermo Scientific, USA) with a diamond ATR smart accessory. Spectra over the 4000–400 $cm^{-1}$ range were obtained by the co-addition of 256 scans with the resolution of 2 $cm^{-1}$.

#### 2.2.4. Thermal analysis

Thermal analysis of the starting diatomite, basic aluminum sulfate and modified diatomite/drug samples was performed on a Netzsch STA 409 EP (Selb, Germany). Samples were heated from 20 °C to 1000 °C in an air atmosphere, at a heating rate of 10 °C $min^{-1}$.

#### 2.2.5. Zeta potential measurement

The zeta potentials of the starting and modified diatomite/drug samples were measured using a Zetasizer NanoZS90 (Malvern Instruments Ltd., UK). Aqueous suspensions (0.1 mg/ml) of the samples were dispersed using an ultrasonic bath and an average of 20 measurements was 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 manufacturer (zeta potential $-50 \pm 5$ mV).

#### 2.2.6. Adsorption batch experiments

The starting diatomite and the modified diatomite samples were accurately weighted (1.2 g) and transferred into Erlenmeyer flasks containing 80 ml of aqueous DS (4 mg/ml) solution (prepared using 10% V/V absolute ethanol as a cosolvent). The flasks were closed and shaken on a laboratory shaker (KS 260 basic, IKA®-Werke GmbH, Germany) at 200 rpm speed during 6 h. Every hour 700 μl samples of