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Original Research Paper

Tailoring morphological and interfacial properties of diatom silica microparticles for drug delivery applications

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ABSTRACT

Diatomaceous earth (DE), naturally available silica, originated from fossilized diatoms has been explored for use in drug delivery applications as a potential substitute for synthetic silica materials. The aim of this study is to explore the influence of particle size, morphology and surface modifications of diatom silica microparticles on their drug release properties. Raw DE materials was purified and prepared to obtain high purity DE silica porous particles with different size and morphologies. Comparative scanning electron microscope and particle characterization confirmed their particle size including irregularly shaped silica particles (size 0.1–1 μm, classified as "fine"), mixed fractions (size 1–10 μm, classified as "mixture") and pure, unbroken DE structures (size 10–15 μm, classified as "entire"). Surface modification of DE with silanes and phosphonic acids was performed using standard silanization and phosphonation process to obtain surface with hydrophilic and hydrophobic properties. Water insoluble (indomethacin) and water soluble (gentamicin) drugs were loaded in DE particles to study their drug release performances. *In vitro* drug release studies were performed over 1–4 weeks, to examine the impact of the particle size and hydrophilic/hydrophobic functional groups. The release studies showed a biphasic pattern, comprising an initial burst release for 6 h, followed by near-zero order sustained release. This study demonstrates the potential of silica DE particles as a natural carrier for water soluble and insoluble drugs with release controlled by their morphological and interfacial properties.

1. Introduction

In recent years, various mesoporous silica particles have been synthesized and applied for drug delivery purposes with the aim to address common therapeutic problems such as limited drug solubility, leading to poor bioavailability and undesirable pharmacokinetics in drug release over several weeks required for therapeutic implants. However, their synthesis is often time-consuming, expensive and complicated, involving toxic materials. Nature, on other hand, has developed elegant biologically based self-assembly synthetic routes to produce biosilica with complex 3-dimensional (3-d) porous structures [1]. The most outstanding example is diatoms, single cell photosynthetic algae, with distinct silica cell walls called frustules, consisting of highly ordered pore structures, species characteristic patterns and hierarchical pore organisation with unique mechanical, molecular transport, optical and photonic properties [2,3]. We recently recognized the potential of diatom biosilica and showed for the first time their capability for drug delivery applications [4,5]. The pill-box structures of diatom frustules with hollow and large inner space, nanoscale pores, high surface area, excellent biocompatibility, high permeability, low density, non-toxicity and low cost render diatom silica a promising biomaterial for local drug delivery. Diatom silica can be easily functionalized, protected and designed for controlled drug release through their micro- and nanoporous surfaces offering distinct advantages over existing synthetic microparticle drug delivery systems.

Texture [6] and surface functionalization [7] of porous drug carriers is known to be important factors controlling diffusion and, hence, drug delivery rate. However, interestingly, factors such as particle size and shape (morphology) of drug carriers were not well explored. Morphology governs the extension of the interface between the drug-carrier and simulation fluid (phosphate buffer saline, PBS, pH = 7.4) and hence impacts the release phenomenon of drug molecules [8]. It was observed that the effect of the different diffusion pathways with varied microparticle radius/size is also hypothesized to potentially alter the release rate.

In this work, a combined impact of morphology and surface functionalization of diatom particles as a natural drug carrier on their drug release performance was explored. The DE particles in the form of entire diatom capsules (10 μm), their nano/micro fractures, and mixture (entire plus fractures) were prepared and used.

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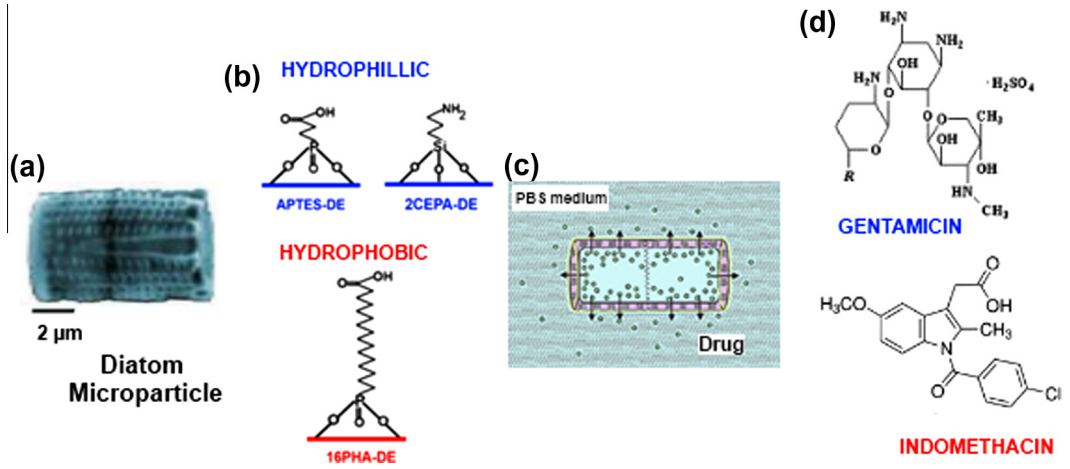

Fig. 1. SEM image of single diatom structure and proposed surface functionalization of diatom silica using organosilane and two phosphonic acids to render the surface either hydrophilic or hydrophobic. The scheme of *in vitro* drug release from diatom into the phosphate buffer using two model drugs (indomethacin and gentamicin) with hydrophobic and hydrophilic properties.

The schematic model of the surface modification of prepared DE particles using silanes and phosphonic acid with hydrophilic and hydrophobic properties, together with the scheme of diatom structure loaded with drug showing drug release process is presented in Fig. 1. To explore the impact of surface properties on drug loading and release performance of DE particles, two model drugs with different hydrophobic (indomethacin) and hydrophilic (gentamicin sulphate) nature were employed.

2. Experimental

2.1. Materials and methods

White sedimentary rocks of diatomaceous earth (DE) minerals from fossilized freshwater diatoms were obtained from Mount Sylvia Pty. Ltd. (Queensland, Australia). Powders of indomethacin (IND) and gentamicin sulphate (GEN) drug supplied by Sigma–Aldrich, Australia were used as model hydrophobic (saturation solubility of 6 mg/ml in ethanol) and hydrophilic (saturation solubility of 50 mg/ml in water) drugs respectively. Chemical modifiers i.e. 2-carboxyethyl-phosphonic acid (2-CEPA), 16-phoshono-hexadecanoic acid (16-PHA), 3-aminopropyltrieth-oxy silane (APTES) and all other reagents of analytical grade were also obtained from Sigma–Aldrich. High purity Milli-Q water (18.2 MΩ) was used throughout the study.

2.2. Processing of natural diatomite (DE) material

DE rocks were initially crushed using a standard Jaw Crusher (Rocklabs) to produce small fragments of DE. Crushed DE was then pulverized using a benchtop ring mill for specific time periods, i.e. 5 s, 15 s and 120 s to obtain DE particles of three different sizes, following the mentioned classification. The pulverized sample were collected and purified to remove any non-siliceous impurities and larger aggregates using previously described procedures, which involved sonicating and washing with water 4–5 times, followed by particle size separation by filtration and sedimentation to obtain different proportions of DE silica as drug carriers [9]. The washed sample were refluxed in 30% H_2O_2 (50 v/v%) at 90 °C for up to 4 h and dried up, in order to increase available hydroxyl groups for modification process.

2.3. Surface functionalization of DE microparticles

To tailor the interfacial properties of DE particles with different sizes, selected organic modifications were performed by a standard silanization/phosphonation process using refluxing process as described in our previous work [10]. Amine-functionalised samples were prepared by treating them with 3-aminopropyltriethoxysilane as follows: 1.0 g of DE sample was suspended in 30 ml of toluene and maintained under a static dry nitrogen atmosphere. 0.32 ml of water was added to this mixture, which was then stirred for 1–2 h at ambient temperature to allow the water to disperse throughout the matrix. At this point, 1.7 ml of APTES was added and the mixture taken to reflux for 6 h. The modified DE particles were collected by filtration after repeated rinsing with isopropanol before being dried in a vacuum desiccator at ambient conditions [11].

For surface treatment with 2-carboxyethyl-phosphonic and 16-phosphono-hexadecanoic acid, 1 mM ethanolic solution of each phosphonic acid was added to the DE microparticles, followed by sonication to remove possible multilayer formation of

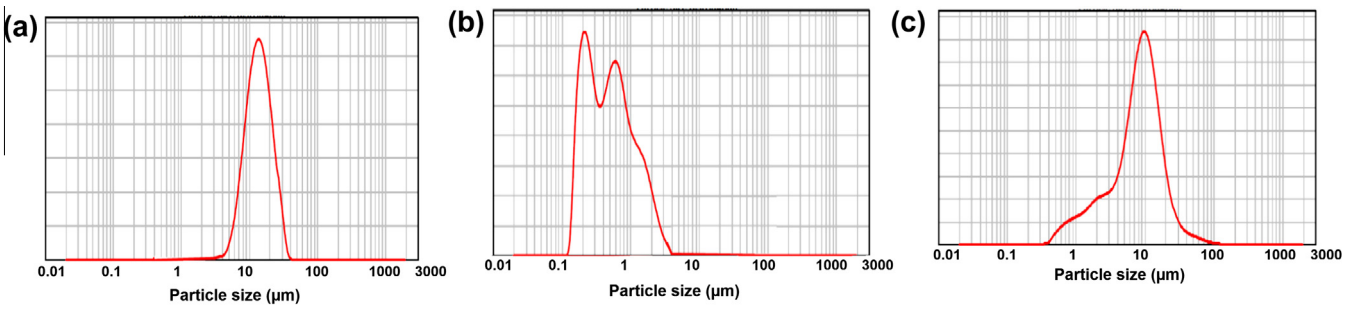

Fig. 2. Particle size distribution curve for (a) entire DE frustules (b) fine DE particles and (c) a mixture of DE proportions (entire and fractured).