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Functionalized mesoporous materials for adsorption and release of different drug molecules: A comparative study

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ABSTRACT

The adsorption capacity and release properties of mesoporous materials for drug molecules can be improved by functionalizing their surfaces with judiciously chosen organic groups. Functionalized ordered mesoporous materials containing various types of organic groups via a co-condensation synthetic method from 15% organosilane and by post-grafting organosilanes onto a pre-made mesoporous silica were synthesized. Comparative studies of their adsorption and release properties for various model drug molecules were then conducted. Functional groups including 3-aminopropyl, 3-mercaptopropyl, vinyl, and secondary amine groups were used to functionalize the mesoporous materials while rhodamine 6G and ibuprofen were utilized to investigate the materials' relative adsorption and release properties. The self-assembly of the mesoporous materials was carried out in the presence of cetyltrimethylammonium bromide (CTAB) surfactant, which produced MCM-41 type materials with pore diameters of ~2.7–3.3 nm and moderate to high surface areas up to ~1000 m^2/g. The different functional groups introduced into the materials dictated their adsorption capacity and release properties. While mercaptopropyl and vinyl functionalized samples showed high adsorption capacity for rhodamine 6G, amine functionalized samples exhibited higher adsorption capacity for ibuprofen. While the diffusional release of ibuprofen was fitted on the Fickian diffusion model, the release of rhodamine 6G followed Super Case-II transport model.

1. Introduction

At present, the most common ways of delivering drugs to humans are oral administration and injection. However, these methods have lower efficiency for some therapies. Some therapeutic agents are unstable or poorly soluble drugs; therefore, new delivery systems are currently required. Functionalized nanostructured materials are increasingly considered as great candidates to make drug delivery vehicles and controlled drug release systems. This is because they have suitable platforms that can help minimize adverse reactions and unwanted side effects, that many conventional drugs used today often pose [1]. With some drug administration methods, the drugs have to often pass through various physiological obstacles before they reach their desired target, thus decreasing the amount of drug that gets to the targeted site. The inability to deliver controlled therapeutic concentration of drugs to the desired location can result in a decrease in the efficacy of the drug [1]. Increasing the concentrations of drugs to be delivered by using nanomaterial based drug delivery vehicles with improved adsorption capacity and controlled drug release properties can enhance the efficacy of the drugs.

Since their discovery in the early 1990s [2,3], a class of nanostructured materials called mesoporous silicates such as MCM-41 have attracted the attention of many scientists as drug delivery vehicles [4] because of their outstanding features such as high surface area (typically 1000 m^2/g), high porosity (typical pore volumes of 0.5–1.5 cm^3/g), well-ordered, tunable nanometer pores (typically 2–15 nm pore diameter) [5–7] and "non-cytotoxic" properties [8,9]. In fact, different types of mesoporous silica nanomaterials were already proved to be capable of carrying high dosages of a variety of drugs in their mesopores [4,10–12]. Additional benefits of mesoporous silica materials for drug delivery include the simplicity of tuning their pore sizes by changing their templates in order to better accommodate drug molecules of different sizes as demonstrated by extensive works by Vallet-Regí and co-workers [13] as well as other researchers [13,14]. While smaller drug molecules and biomolecules can be accommodated in mesoporous materials with smaller as well as bigger pore sizes, larger drug molecules require materials with bigger pore diameters [15]. Furthermore, mesoporous silica materials contain residual silanol groups, that can further be functionalized by different organic groups in order to modify their surface properties [16,17]. This creates favorable surface–drug interactions, which in turn result in improved adsorption capacity

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of the materials for drug molecules. Lin and co-workers have shown that the organic functionalization of mesoporous materials can also influence their biocompatibility [18]. In addition to surface functional groups, the morphology and size of the mesoporous materials also have an important influence on drug release characteristics [19].

Generally, surface functionalization of mesoporous silica materials via covalent bonding of organic groups can be achieved by two methods: i.e., post-grafting synthesis [20] and co-condensation [20]. Although the post-grafting method results in well-ordered functionalized mesostructured materials, it often produces non-uniformly distributed organic groups because the organic moieties can congregate more on the channel pore mouth and on the exterior surfaces [21]. The Co-condensation synthetic method of mesoporous materials involves a one-step procedure and allows better control of the loading and distribution of the organic groups [22] although it often produces materials with less ordered mesoporous structures. In particular, low degree of structural integrity and long-range periodicity as well as lower surface area would be produced when the organosilane concentration in the synthesis exceeds ~25% [22].

Herein comparative investigations of the adsorption capacity and drug release properties of mesoporous materials whose surfaces are functionalized with judiciously chosen organic groups via post-grafting or co-condensation of various organosilanes were conducted. Furthermore, two different hydrophobic and hydrophilic molecules were used as model drugs in the study. The approach of organic functionalization of mesoporous materials for drug delivery has been considered previously [23–25]. The most studied system is ibuprofen adsorption on organic-functionalized matrices. When the MCM-41 or SBA-15 surface is functionalized with amino groups [23c,d], there is an ionic interaction between the carboxylate groups of ibuprofen and the ammonium groups on the matrix surface. The hydrophobicity of an ordered mesoporous silica can also be altered by modification of the surface with alkyl chains [23e]. As a result, the hydrophobic interaction with hydrophobic drugs can be improved. For instance, erythromycin release from functionalized matrices was much slower compared to unmodified material [23g]. Here a comparative study between grafting and co-condensation as well as the use of different functional groups and two different (model) drug molecules have been performed. Functional groups including 3-aminopropyl, 3-mercaptopropyl, vinyl, and secondary amine groups were used to functionalize the mesoporous materials while rhodamine 6G (R6G) and ibuprofen were used as probe molecules to investigate the materials' adsorption and release properties. The objectives of our study is to obtain the relative effect of functional groups as well as type of synthetic method to the functionalized materials on the adsorption and release properties of the materials for different molecules. The self-assembly of the mesoporous materials was carried out with cetyltrimethylammonium bromide (CTAB) surfactant producing MCM-41 type materials with pore diameters of ~2.7–3.3 nm and moderate to high surface areas up to ~1000 m^2/g. By changing the organic groups, the properties of the mesoporous materials were tuned from hydrophobic to hydrophilic and their adsorption and release properties for different (model) drug molecules such as rhodamine 6G and ibuprofen varied.

Rhodamine 6G and ibuprofen were chosen as probe molecules in our study because of their differences in hydrophilicity (or hydrophobicity), which allows the investigation of interaction of different molecules with functionalized mesoporous materials [24]. Furthermore, they are easy to probe by UV–Vis absorption spectroscopy. The solubility of rhodamine 6G and ibuprofen is dependent on solvent and pH of solution. For instance, the solubility of rhodamine 6G is 20 g/L in water; 40 g/L in butanol, 80 g/L in ethanol, 15 g/L in propanol and 100 g/L in diethylene glycol. Rhodamine 6G has increased solubility at higher pH [26]. Ibuprofen, which is a relatively weak acid with pka value of 4.4, has low solubility in water or at acidic pH. Ibuprofen has an intrinsic solubility of ~0.06 mg/mL in water. Ibuprofen is sparingly soluble in hexane and freely soluble in ethanol, octanol and dimethyl sulfoxide and chloroform with values of >10 g/L in acetone, >10 g/L in ethanol, 33 g/L in octanol, and 3.3 g/L in hexane. The solubility of ibuprofen increases sharply with pH, i.e. the drug is largely insoluble at low pH, but is readily soluble at alkaline pH. For example in water, its solubility is $\sim 0.5 \times 10^{-1}$ g/L at pH < 2.00 but $\sim 1 \times 10^{2}$ g/L at pH = 7.5 [27]. Based on these properties or because rhodamine 6G is quite soluble in water while ibuprofen is rather soluble in solvents such as hexane and ethanol, we have considered rhodamine 6G to be a hydrophilic probe molecule while ibuprofen is considered hydrophobic in this study. Therefore, they are expected to show different adsorption and release properties in organic functionalized mesoporous materials.

Our studies indicated that while the samples functionalized with mercaptopropyl and vinyl groups resulted in high adsorption capacity for rhodamine 6G, those functionalized with amine groups showed higher adsorption capacity for ibuprofen. Similarly, the drug release properties also varied from sample to sample, depending on the type of functional groups they contained. Furthermore, differences in adsorption capacity and drug release properties between the materials synthesized via co-condensation and those synthesized via post-grafting were also observed. The results of our study may give further insights into rational synthetic approaches to functionalized mesoporous materials with improved adsorption capacity and release properties for a variety of hydrophobic and hydrophilic drugs.

2. Experimental section

2.1. Materials and reagents

Tetraethoxysilane (TEOS), 3-aminopropyltriethoxysilane (APTS), rhodamine 6G, cetyltrimethyammonium bromide (CTAB), ibuprofen sodium salt, 3-mercaptopropyltrimethoxysilane (MPTS), vinyltrimethoxysilane (VTS), NaCl, $NaHCO_3$, KCl, $K_2HPO_4 \cdot 3H_2O$, $MgCl_2 \cdot 6H_2O$, $CaCl_2$, Na_2SO_4, $NH_2C(CH_2OH)_3$, and bis(triethoxysilylpropyl)amine (BTSPA) were obtained from Sigma-Aldrich. Hydrochloric acid (36.5%) and anhydrous toluene were purchased from Fisher Scientific.

2.2. Synthesis of functionalized mesoporous materials via co-condensation

A solution of 33.4 mL distilled water and 15 mL ammonium hydroxide was prepared and 2.30 mmol CTAB was dissolved in it by stirring. Then, a mixture of 17 mmol TEOS and 3.0 mmol of one of the organosilanes (MPTS, VTS, APTS, or BTSPA) was added. The solution was stirred at room temperature for 2 h and then stored in oven at 80 °C for two days. The sample was cooled down and filtered over Whatman-1 filter paper. The solid was washed thoroughly with large amount of distilled water and dried under ambient condition resulting in organic-functionalized mesostructured materials containing 3-mercaptopropyl, vinyl, 3-aminopropyl, or N,N-diproplyamine groups, respectively. The surfactant template was extracted by stirring 2 g of the functionalized mesostructured material with a solution of 50 mL methanol and 10 mL HCl for 5 h at 50 °C. The solution was filtered over a Whatman filter paper. The solid was washed three times with