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Release of flurbiprofen using of SBA-15 mesoporous silica: Influence of silica sources and functionalization

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ABSTRACT

In the present study, SBA-15 silica materials synthesized from different silica sources ($S15_T$ and $S15_S$) and functionalized by post-grafting method with trimethylmethoxysilane (F-$S15_T$ and F-$S15_S$) were compared as drug carriers for flurbiprofen (FBP). The physical state of the drug in the samples was characterized by differential scanning calorimetry (DSC) and X-ray diffractometry (XRD). The results showed that the FBP molecules were not arranged in a crystalline form after incorporation of FBP into the pores of the SBA-15 samples. Surface functionalization resulted in decreased surface area, pore size, and pore volume of $S15_T$ and $S15_S$, which decreased the drug-loading capacity from 27.09% to 13.59% and from 16.96% to 9.19%, respectively. The *in vitro* drug release testing demonstrated that functionalized SBA-15 samples showed slower release rates compared to the non-functionalized samples. The results indicate that F-$S15_T$ (which had the smallest pore size) showed controlled drug release profiles without burst-release while the other silica samples showed faster release profiles than F-$S15_T$, indicating that pore size and hydrophobicity influenced the rate of the drug release process. The drug release mechanism of all the samples was found to be Fickian diffusion.

1. Introduction

Over the past few decades, mesoporous silica materials have been recognized as very promising candidates for drug delivery systems due to high biocompatibility [1,2], *in vivo* biodegradability, low toxicity [3] and their capability to be functionalized with different organic groups [4]. Among them, SBA-15 has attracted considerable interest for drug delivery due to its wide pore diameter, high drug loading capacity and excellent chemical and thermal stability [5–7]. SBA-15 has larger pore size ranging from 4.6 to 30 nm [6]. SBA-15 has been used in the loading of active agents such as antibiotics [8], natural antimicrobial agents [9], anti-inflammatory drugs [10,11] antihypertensive drugs [12,13], anticancer drugs [14] and biomolecules [15,16].

Chemical nature of the surface *i.e.* drug molecule-organic group interaction/repulsion, number and location of organic groups on the surface, specific surface area, pore size and geometry, morphology of mesoporous silica particles, are considered to be critical factors affecting loading and releasing properties of the drug [17–20]. Izquierdo-Barba reported that the delivery rate of drugs decreases with the pore size of the matrix. In addition, when investigating the influence of the chemical nature of the pore surface on the delivery process, they found a noticeable decrease of the delivery rate when the surface of the matrices was modified [10]. Andersson et al. indicated that one-dimensional pore structure with cage-like pores provided high drug loading capacity and that delivery rate decreased with a decrease of the pore size [21]. It has been reported that a large pore size often results in relatively rapid drug release in these controlled release system [19]. Qu et al. studied the release of ibuprofen from several 2D hexagonal mesoporous structures. They found that ibuprofen loading amount was directly related to the BET surface area, pore geometry, and pore volume, while the release rates could be controlled by regulating the morphologies of mesoporous silica [22]. In addition, the functionalization of the pore surface of siliceous mesostructures with appropriate functional groups leads to control of the drug release from the porous matrix. Different distributions of functional groups in the mesoporous materials were obtained by two different approaches, post-grafting and one-pot (co-condensation) procedure. The post-grafting method is able to selectively functionalize the exterior or inner surface of mesostructured silica materials [23,24,25]. However, the one-pot method is able to produce homogeneously distributed organic functional groups on the pore surface. Thus, post-grafting method enables customized local surface functionalization of mesoporous materials with desirable components [26].

Despite the active research into drug delivery by means of SBA-15 mesoporous silica, there is still a lack of studies comparing the drug release capabilities of SBA-15 materials synthesized from different silica sources. This paper describes the applications of functionalized and non-functionalized SBA-15 samples synthesized from two

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different silica sources for the delivery of the non-steroidal anti-inflammatory drug FBP, which was chosen as a model drug for investigation of the influence of the structural characteristics and the organic functionalization.

2. Materials and methods

The reagents used for the synthesis and functionalization of samples were tetraethyl orthosilicate (TEOS, 99% Merck), sodium metasilicate pentahydrate (SMP, 99% Aldrich), Pluronic P123 triblock copolymer (Aldrich), hydrochloric acid (37%, Merck), trimethylmethoxysilane (TMMS, 98% Merck), toluene (˜99%, Merck), and ethanol (96%, Merck). FBP was kindly supplied from Sanovel Pharmaceuticals Inc., Turkey. All other chemicals used in HPLC analysis were higher grade.

The mesostructures of samples were determined by Philips Panalytical X'Pert-Pro diffractometer small angle X-ray diffraction (XRD) using Cu(Kα) radiation. The patterns were obtained with a step size of 0.005° between 0.6 and 3°. Wide angle XRD and differential scanning calorimeter (DSC) were utilized to examine the state of the loaded drug. DSC analysis was carried out with a Perkin Elmer Diamond DSC using a heating rate of 10 °C/min under nitrogen flow.

The BET surface areas and pore size distributions of all samples were determined by nitrogen adsorption–desorption on a Micromeritics ASAP 2020 instrument, the pore size distributions and pore volumes were calculated by the advanced Barrett–Joyner–Halenda (BJH) method using the desorption branches of the isotherms. The micropore volume was estimated from the t-plot analysis [27].

Prior to these analyses, the functionalized and drug-loaded samples were degassed at 50 °C and the non-functionalized and non-drug loaded samples were degassed at 300 °C in vacuum. The morphologies of the samples were analyzed using a scanning electron microscope (SEM) (CamScan Apollo 300).

FBP concentration in the drug loaded samples was measured by isocratic reverse phase high performance liquid chromatography (HPLC, Perkin Elmer Flexar) using a Brownlee HRes Analytical C18 column (50 × 2.1 mm, 1.9 μm). The injection volume was 5 μl, the flow rate was adjusted to 0.6 ml/min and detection was performed 254 nm. Mobile phase contained 43% of acetonitrile in an aqueous buffer solution [28]. In drug release study, the concentration of standard solution was 0.1 mg/ml FBU. In HPLC analysis, standard solution was injected six times in replicate. The %RSD value of average area of the standard solution was calculated as 0.1% (for system precision).

2.1. Synthesis and functionalization of SBA-15 samples

To determine the effect of structural characteristics on drug release rate, SBA-15 was synthesized from TEOS or SMP according to our previous study [29]. The SBA-15 samples synthesized from TEOS and SMP were denoted as $S15_T$ and $S15_S$, respectively.

To prepare functionalized SBA-15 by grafting, samples were initially dried at 80 °C for 3 h. The desired amount of dried sample was dispersed in dry toluene and TMMS was added to mixture. The obtained solution was stirred at room temperature for 24 h and then, heated under reflux for 6 h. The resulting solid was recovered by filtration, washed with dry toluene and dried at room temperature. The obtained functionalized samples prepared from TEOS and SMP were denoted as F-$S15_T$ and F-$S15_S$, respectively.

2.2. Drug loading procedures

Samples of $S15_T$, $S15_S$, F-$S15_T$, and F-$S15_S$ were loaded with FBP using a slightly modified version of the method reported by Heikkila et al. [30]. FBP was dissolved in ethanol to obtain a concentrated solution (700 mg/ml). Then, a certain amount of silica sample was soaked in this solution in a closed vial to prevent evaporation of solvent. After gentle stirring at room temperature for 24 h, FBP-loaded sample was filtered and washed with 3 ml ethanol to remove FBP adsorbed on the external surface of drug-loaded silica. The obtained silica was dried at 50 °C for 4 h to completely evaporate the solvent. The non-functionalized and functionalized drug-loaded $S15_S$ samples were named as $S15_S$/FBP and F-$S15_S$/FBP, respectively. The drug-loaded non-functionalized and functionalized $S15_T$ samples were named as $S15_T$/FBP and F-$S15_T$/FBP, respectively.

2.3. In vitro dissolution

In vitro drug release studies were performed to characterize the effects of silica source and functionalization on the release of FBP. Dissolution studies were carried out by soaking 0.024 g of drug loaded samples in 100 mL of phosphate buffer solution at pH 7.2 under 50 rpm continuous stirring at a constant temperature of 37 ± 0.5 °C. All drug-loaded samples were in the powder form. The samples were withdrawn at predetermined time intervals and FBP concentration in the release medium was estimated by HPLC analysis. In order to have a constant dissolution volume, an equal amount of fresh medium was added.

3. Results and discussion

3.1. Characterization of SBA-15 samples

The representative small angle XRD patterns of $S15_T$, $S15_S$, F-$S15_T$, and F-$S15_S$ samples are shown in Fig. 1. All samples exhibited characteristic (100), (110) and (200) peaks, which are associated with the ordered hexagonal mesoporous structure [31]. The peak intensities of F-$S15_T$ and F-$S15_S$ decreased and the positions of the peaks shifted to small angles in comparison with non-functionalized silica samples, which indicate no change of hexagonal structural arrangement during the functionalization.

Fig. 2(a) and (b) shows the SEM images of samples $S15_T$ and F-$S15_T$. It is clear that the $S15_T$ presented a wheat-like morphology with a relatively uniform size of 1 μm, which is in agreement with a previous study [32]. The wheat-like crystals were elongated when the sample was functionalized with TMMS. On the other hand, a mixed morphology comprised of dish-shaped and wheat-like crystals with relatively uniform sizes of 1 μm was observed for $S15_S$ and F-$S15_S$ (Fig. 2(c) and

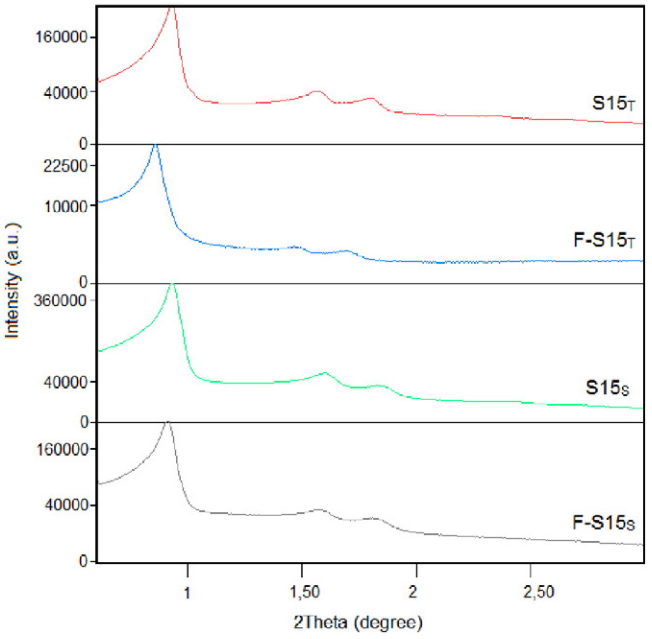

Fig. 1. Small-angle XRD patterns of non-functionalized and functionalized samples.