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Surface functionalization of SBA-15 particles for ibuprofen delivery

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Abstract−We have synthesized SBA-15 particles and functionalized their surface with different functional groups (amine, diamine, and sulfonic acid groups) to use them as carrier materials in drug delivery. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), nitrogen sorption, and zeta potential measurements were used to characterize the synthesized particles. After surface functionalization, the surface of the sulfonic acid-functionalized particles was more acidic than that of the other particles. Using ibuprofen as a model drug, we found that the release rate increased at higher pH. Furthermore, the particles with the sulfonic acid groups exhibited higher release rate than those with the amine and diamine groups. We explained the difference in the release rate using different electrostatic interaction between drug and particle surface that was caused by the surface functionalization. These results should enable design of drug carrier materials based on the SBA-15 particles with the desired release rate.

Key words: SBA-15 Particles, Mesoporous, Surface Functionalization, Ibuprofen, Release

INTRODUCTION

Mesoporous materials, which are the materials containing pores with diameters between 2 and 50 nm, find many applications in areas such as ion exchange, adsorption, catalysis, etc. [1-4]. One of their potential applications is as a carrier material in drug delivery. The goal of such carrier materials is to control the dosage and duration of the drug effect without harming the patients. Therefore, materials used as drug carriers are required to have biocompatibility, high drug-loading capacity, and tissue specificity [5]. They should also be designed to prevent premature release and to release drug at a proper rate, i.e., controlled release [5]. For instance, it is desirable to have a burst of release when a high dose is required for acute infections or inflammations, but the release rate often needs to be reduced to prevent premature release. Recently, a stimulus-responsive system in which release is controlled by the external conditions (pH, temperature, etc.) is also being investigated [6].

Most drug delivery systems currently use polymer materials as drug carriers. However, they have limitations such as premature degradation of the active agent, non-uniform distribution of drug in matrix, poor thermal and chemical stability, and rapid elimination by the immune system [7].

Mesoporous silica particles are a good candidate for drug delivery because of their biocompatibility, uniform structure, tunable pore size with narrow distribution, large pore volume and surface area, and ease of surface functionalization [7,8]. Mesoporous silica particles such as MCM-41 and SBA-15 have been extensively studied for both drug and gene delivery because they have ordered structure that contains unidimensional mesopores with a uniform size ranging from about 2 to 8 nm [9-13].

Pore size, pore volume, surface area, particle morphology, and surface properties of mesoporous silica materials play important role in drug loading and release. The size of drug molecules during loading is generally determined by the pore size, and the surface area and drug-surface affinity can also affect the drug loading capacity [7]. Controlling the drug-surface affinity by surface functionalization also affects the drug release rate. To prevent premature release, surface functionalization of MCM-41 and SBA-15 particles with amine groups has been successfully applied to reduce the release rate of ibuprofen [11-13]. Increasing the surface hydrophobicity of carrier materials was also shown to reduce the drug release rate by preventing water from entering pores [7].

In this study, we performed surface functionalization of SBA-15 particles with three different functional groups: amine, diamine, and sulfonic acid groups. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), nitrogen sorption, and zeta potential measurements were used to characterize the functionalized particles. We used these particles as drug carrier for oral administration and compared their drug loading and release characteristics. Ibuprofen was chosen as a model drug because of its molecular size (1.0×0.6 nm^2) [14], pharmacological activity, and short biological half-life (2 h) [15]. Ibuprofen is one of the most frequently studied drugs in the drug delivery system and is generally used to reduce fever and treat pain or inflammation caused by many conditions such as headache, toothache, back pain, or minor injury.

This work is expected to give insight on the effect of parameters (pore size and volume, surface area, and surface properties) on drug delivery, and hence to help the design of carrier materials with the desired physicochemical properties.

MATERIALS AND METHODS

1. Materials

Tetraethoxysilane (TEOS), Pluronic 123 triblock copolymer [poly (ethylene glycol)$_{20}$-poly(propylene glycol)$_{70}$-poly(ethylene glycol)$_{20}$]

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(MW: ~5800), 3-aminopropyl triethoxysilane (APTES), N-[3-(trimethoxysilyl)propyl]-ethylenediamine, 2-(4-chlorosulfonylphenyl)-ethyltrimethoxysilane, and formic acid were purchased from Aldrich. Ibuprofen (minimum 98% GC) was purchased from Sigma. Hydrochloric acid, sodium hydroxide, methyl alcohol, ethyl alcohol, and ammonium hydroxide were purchased from Duksan Co. Hexane and PBS (phosphate buffered saline) buffer were purchased from Showa Co. and Invitrogen Co., respectively. All chemicals were used without further purification.

2. Synthesis of the Functionalized SBA-15 Particles

2-1. Synthesis of Unmodified SBA-15 Particles

SBA-15 particles were prepared using the previously reported procedure [4,16]. We dissolved 1.4 g of Pluronic 123 triblock copolymer in a solution that contained 50 mL of water and 5.52 mL of HCl (38 wt%). After stirring for 3 h at room temperature, 3.44 g of TEOS was added to the solution. The solution was then vigorously stirred for 10 min and reacted at 40 °C for 24 h under static condition, followed by aging at 100 °C for 24 h. To remove the copolymers, we added 1.5 g of particles to a mixture of 9 mL of HCl (38 wt%) and 160 mL of methanol and refluxed for 24 h. Final particles were then separated by centrifugation, washed with distilled water, and dried at 70 °C for 12 h.

2-2. Amine-functionalized SBA-15 Particles

To functionalize the SBA-15 particle surface with the amine groups, we added 1 g of particles to the solution that contained 1 mL of APTES and 50 mL of ethanol, and reacted at ~80 °C for 12 h under reflux. After the reaction, the particles were separated by centrifugation, washed with a large amount of water, and dried at 70 °C for 12 h.

2-3. Diamine-functionalized SBA-15 Particles

The surface of the SBA-15 particles was modified with diamine groups based on the recipe by Sun et al. [17]. 10 g of SBA-15 particles was stirred with 5 mL of distilled water and 95 mL of ethanol for 30 min. Then, we added 1 mL of N-[3-(trimethoxysilyl)propyl]-ethylenediamine to the mixture, and adjusted pH to ~4 by adding formic acid. The mixture was refluxed at 90 °C for 12 h. After cooling, the suspension was centrifuged, washed several times using ethanol, and dried at 70 °C for 12 h.

2-4. Sulfonic Acid-functionalized SBA-15 Particles

Sulfonic acid-functionalized SBA-15 particles were prepared according to the recipe by Barbé et al. [18]. 3.6 g of 2-(4-chlorosulfonylphenyl)-ethyltrimethoxysilane was added to suspension that contained 1 g of SBA-15 particles in 50 mL of toluene. The mixture was refluxed at 110 °C for 12 h. The resulting white solid particles were centrifuged and washed with toluene, followed by methanol, and distilled water. We dispersed the suspension in excess 0.1 M H_2SO_4 solution and stirred it overnight. Final particles were centrifuged, washed with distilled water, and dried at 70 °C for 12 h.

3. Drug Loading and Release

To load ibuprofen on the SBA-15 particles, 0.17 g of dried particles was added to 10 mL of hexane-ibuprofen solution (0.025 g/mL) and soaked for 3 days under stirring. The ibuprofen concentration in solution was measured with a Shimadzu UV-1650 spectrophotometer at a wavelength of 272 nm. We estimated the amount of drug loaded onto sample from the change in the UV intensity before and after loading. After loading, the particles were separated by centrifugation and dried at 100 °C in the oven.

For release experiments, we added 0.017 g of ibuprofen-loaded particles to 10 mL of phosphate buffer solution at pH 7.4 (0.155 M NaCl) under minimum stirring, and adjusted the solution pH to 2 or 5 using HCl or NaOH if needed. The temperature during release experiments was kept at 37 °C to simulate the human body temperature. The amount of released ibuprofen was estimated by using a UV spectrophotometer at a wavelength of 273 nm.

4. Characterization

Scanning electron microscopy (SEM, JEOL JSM6500-Fmicroscope) and transmission electron microscopy (TEM, JEOL JEM-2100) were used to observe the morphology of particles. To determine the isoelectric point of the synthesized particles, suspensions at different pH values were prepared by adding HCl or NaOH. In all suspensions, we kept NaCl concentration at 0.15 M. Zeta potential of the particles at different pH values was measured with a Malvern Zetasizer Nano-ZS instrument.

Textural properties of the mesoporous silica were estimated using the nitrogen sorption method. The adsorption/desorption isotherms of nitrogen at 77 K were measured with a Micromeritics ASAP 2020 analyzer. Prior to the measurements, the mesoporous silica particles

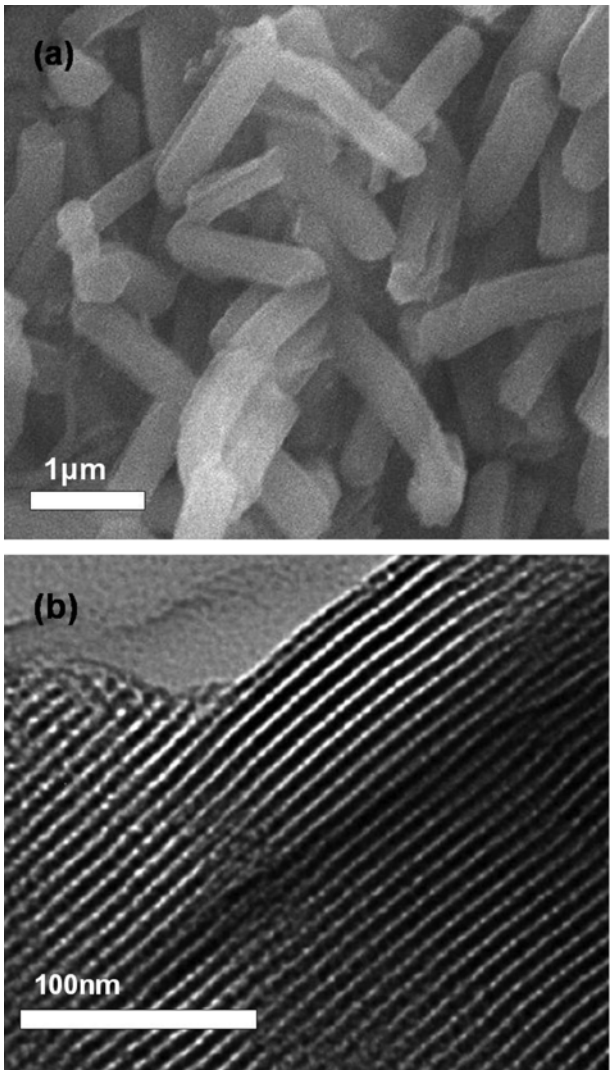

Fig. 1. (a) SEM and (b) TEM micrographs of the unfunctionalized SBA-15 particles.

were degassed at 120 °C for 6 h. Brunauer-Emmett-Teller (BET) method was used to calculate the specific surface area and the Barrett-Joyner-Halenda (BJH) method based on the desorption branch of the isotherm was used to estimate the pore size and pore volume.

RESULTS AND DISCUSSION

SEM image of the unmodified SBA-15 particles in Fig. 1(a) shows that unmodified SBA-15 particles exhibit typical a rod-like structure whose length is ~2 μm. We also used TEM to observe the microstructure of the synthesized SBA-15 particles. Fig. 1(b) shows the TEM image of the unmodified SBA-15 particles, which clearly shows the presence of cylindrical mesopores inside the SBA-15 particles.

We then functionalized the surface of the unmodified SBA-15 particles with three different types of functional groups: amine, diamine, and sulfonic acid groups. These functional groups on the particle surface are expected to exhibit different interaction with drug molecules in drug delivery. To understand the effect of different functional groups on the particle surface, we measured the zeta potential of particles as a function of pH as shown in Fig. 2. As expected, the zeta potential decreased with pH for all particles. The isoelectric point (IEP) at which the zeta potential is zero can be used to estimate the surface acidity of the particles. Fig. 3 shows that the isoelectric point was different for different functional groups, which confirms a successful functionalization. Furthermore, IEP increased in the order of sulfonic acid<amine<diamine-functionalized particles, which corresponds to the order of decreasing acidity. Thus, surface functionalization of SBA-15 particles resulted in particles with different surface acidity.

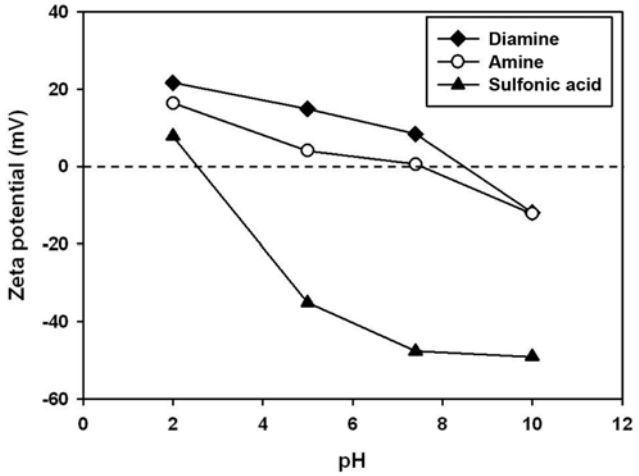

Fig. 2. Zeta potential of the functionalized SBA-15 particles as a function of pH.

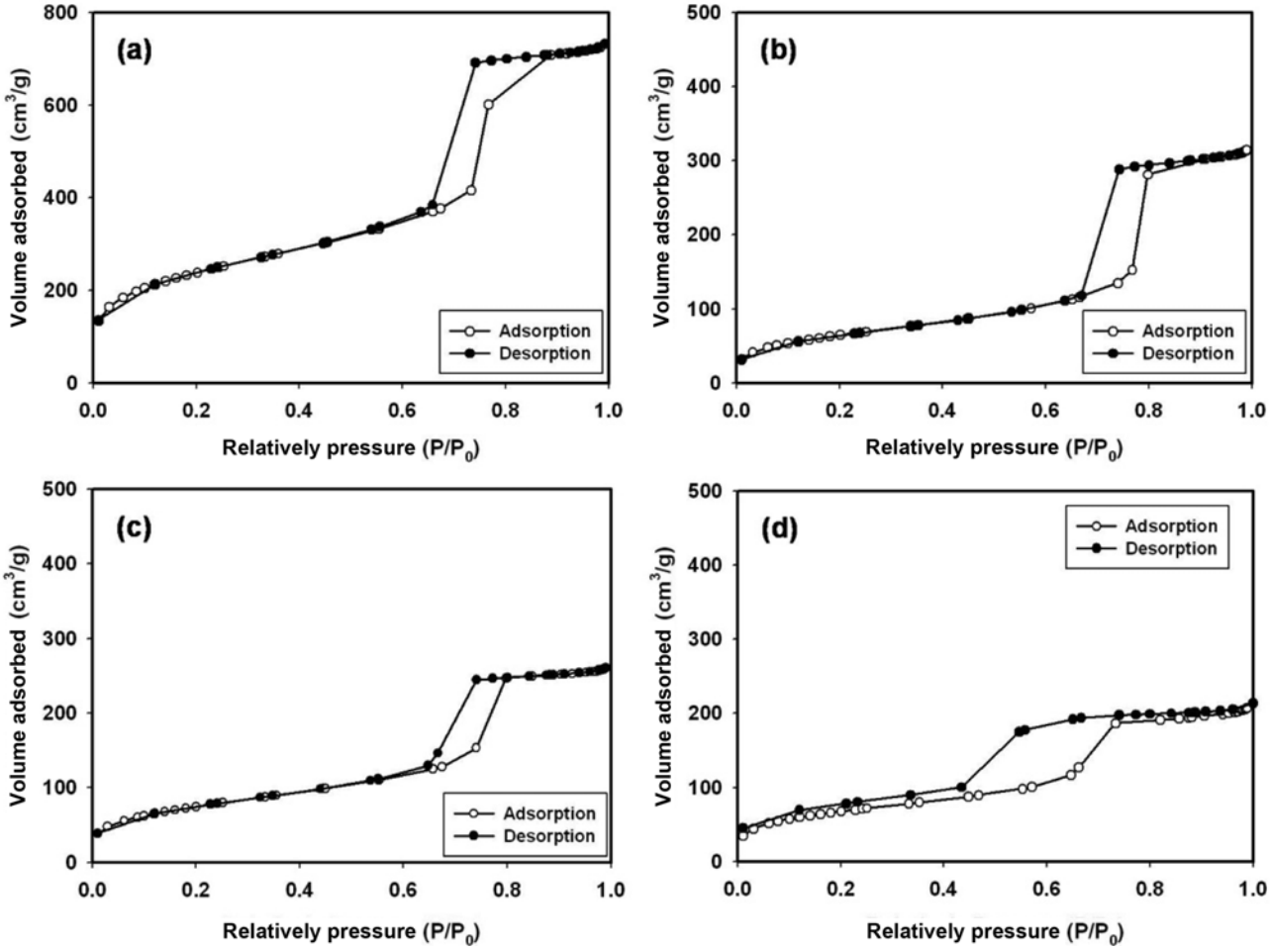

Fig. 3. Adsorption/desorption isotherms of the SBA-15 particles: (a) unmodified; (b) amine; (c) diamine; (d) sulfonic acid.

Table 1. Textural properties and ibuprofen loading capacity of the SBA-15 particles with different surface groups

Surface group	BET surface area (m^2/g)	BJH pore size (nm)	Pore volume (cm^3)	Loading (%)
None	857.6	6.1	1.08	
Amine	238.2	6.5	0.488	57.8
Diamine	273.5	6.2	0.415	53.3
Sulfonic acid	246.3	4.2	0.339	35.0

Fig. 3 shows the nitrogen adsorption/desorption isotherms of the synthesized particles before and after surface functionalization. It is clear that the amount of nitrogen adsorbed decreased after surface functionalization for all particles. Table 1 summarizes the textural properties of mesoporous SBA-15 particles, which shows that the surface area and pore volume significantly decreased after surface functionalization, while the change in pore size was negligible in most cases.

Functionalized SBA-15 particles were then used as carrier materials in drug delivery. First, we loaded ibuprofen, which is a model drug, onto the SBA-15 particles. After loading, we measured the loading capacity, which is defined as the amount of the loaded ibuprofen with respect to the total amount of ibuprofen used in the loading experiment. Table 1 shows that the particles with amine and diamine groups on the surface exhibited higher loading capacity than those with sulfonic acid groups. Drug loading capacity is usually related to the pore size, surface area, pore volume, and surface properties of the carrier materials. Because pores of all particles are similar in size and also large enough for the entrapment of ibuprofen, as shown in Table 1, we suspect that acid-base interaction between the carboxylic acid group of ibuprofen and amine groups on the amine and diamine-functionalized SBA-15 particles enhanced the loading of ibuprofen.

It is well known that ibuprofen is mainly absorbed in the stomach and proximal intestine during oral administration [19]. Since the pH in the human body changes from 1-2 in the stomach body to 5-7 in the antrum, and 7-8 in the proximal intestine [20,21], we performed the ibuprofen release experiments at pH 2, 5, and 7.4.

Fig. 4 shows the ibuprofen release profiles of the functionalized SBA-15 particles as the pH is varied. Here we defined the released amount as the wt. % of the released ibuprofen from the initially loaded amount. Ibuprofen release rate increased as the pH was increased for all particles. For instance, ibuprofen release was slowest at pH 2, which is close to the pH of stomach body, while it was fastest at pH 7.4, which is close to the pH of proximal intestine. Since the pKa value of ibuprofen is ~4.4, ibuprofen exists mostly in unionized form at pH 2, but as an anion at pH 7.4. Thus, an increase in pH should also increase the solubility of ibuprofen. We suspect that increased solubility at higher pH resulted in faster release. In addition, the surface of SBA-15 particles becomes more negatively charged (i.e., sulfonic acid), or less positively charged (i.e., amine and diamine) at higher pH as shown in Fig. 2. Since the carboxylic acid group of ibuprofen molecules also becomes more ionized (negatively charged) at higher pH, there should exist a stronger electrostatic repulsion (sulfonic acid), or weaker (amine and diamine) electrostatic attraction between drug and particle, which should increase the release rate at higher pH.

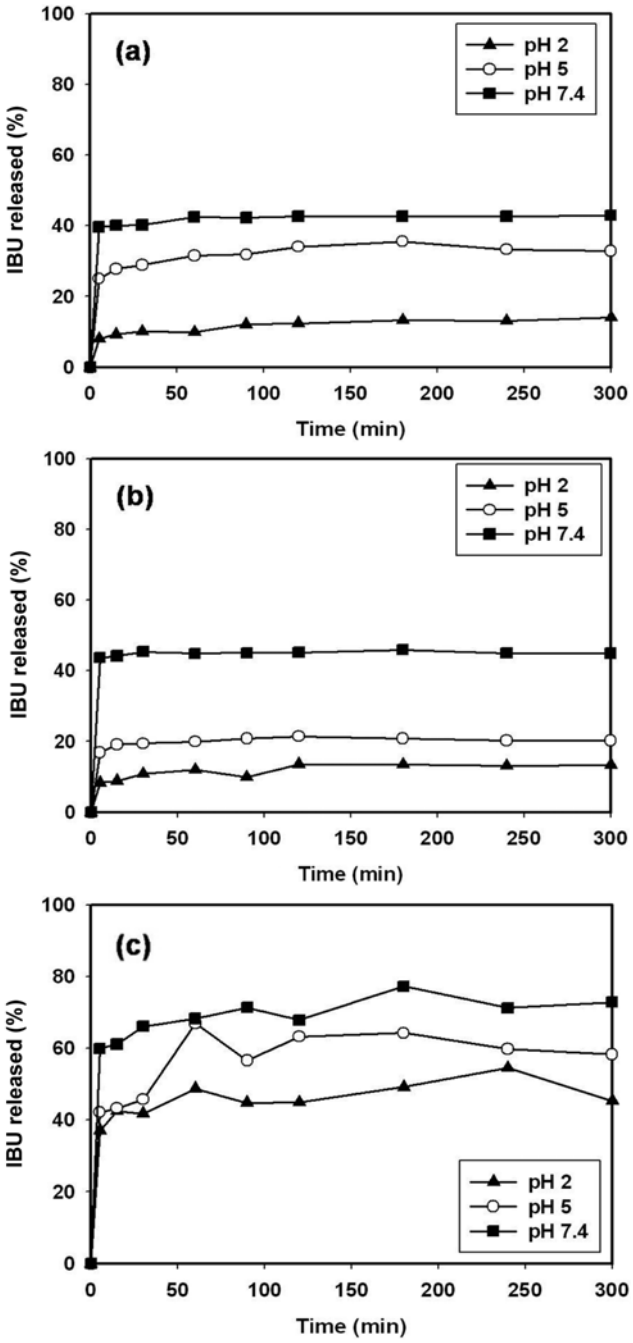

Fig. 4. Effect of pH on the ibuprofen release profiles of the functionalized SBA-15 particles: (a) amine; (b) diamine; (c) sulfonic acid.

Fig. 5 compares the effect of surface functional groups on the ibuprofen release profiles. Clearly, release is faster for sulfonic acid-functionalized particles than the other particles. Fig. 2 shows that the surface of the sulfonic acid-functionalized SBA-15 particles is more acidic than the amine or diamine-functionalized particles, suggesting that the surface of sulfonic acid-functionalized particles is more negatively charged, or less positively charged than the other particles at all pH values. Thus, there should be a stronger electrostatic repulsion, or weaker electrostatic attraction between the surface of sulfonic acid-functionalized particles and ibuprofen, which

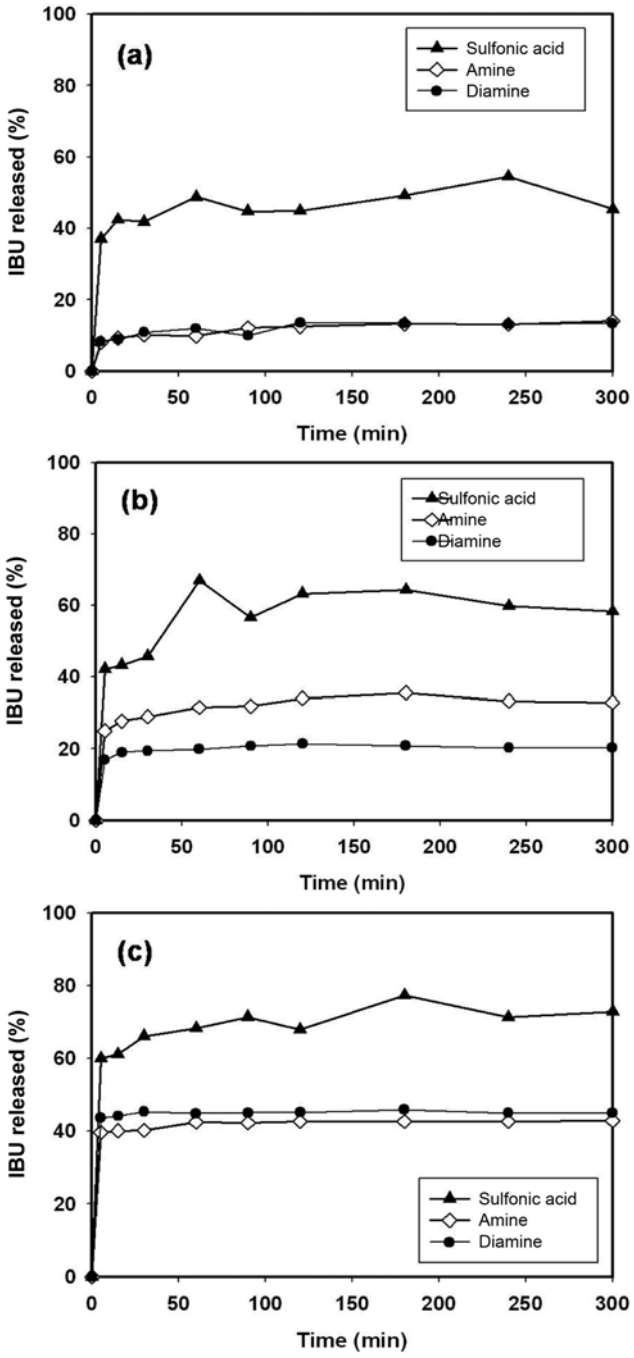

Fig. 5. Effect of surface functional groups on the ibuprofen release profiles of the functionalized SBA-15 particles: (a) pH=2; (b) pH=5; (c) pH=7.4.

should enhance the release rate.

As shown in Table 1, the textural properties (BET surface area and pore size and volume) of all particles are similar. Thus, we can conclude that the electrostatic interaction between the SBA-15 particle surface and drug plays a dominant role on the ibuprofen release rate.

CONCLUSIONS

We have functionalized the surface of the mesoporous SBA-15 particles with different functional groups (amine, diamine, and sulfonic acid groups) and used them as carrier materials for ibuprofen delivery. We confirmed the successful functionalization by the zeta potential measurements, and found that the surface of the sulfonic acid-functionalized particles was more acidic than the particles functionalized with amine and diamine groups. Drug loading capacity was found to be lower for the sulfonic acid-functionalized particles than the other particles. For all particles, ibuprofen release rate was higher as the pH was increased. We also found that ibuprofen release from the sulfonic acid-functionalized particles was faster than the other particles. We rationalized the difference in release rate with the change in the electrostatic interaction between drug and particle surface that was caused by the surface functionalization. By controlling the surface properties of SBA-15 particles, therefore, it should be possible to prepare novel drug carriers with the desired release rate.

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