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Comparative study of silica nanoparticles and surface modified silica nanoparticles: Drug adsorption process and controlled release behavior

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ABSTRACT

The purpose of this study was to compare drug adsorption process and release behavior of commercial silica nanoparticles (Silica-01) and surface modified silica nanoparticles (Silica-03). Characteristics of Silica-01 and Silica-03, including specific surface area, pore size and morphology were given initially. Characteristics of diltiazem hydrochloride (DZH) loaded Silica-01 and indomethacin (IMC) loaded Silica-03 were described by differential scanning calorimeter (DSC), fourier transform infrared spectroscopy (FT-IR) and *in vitro* dissolution. It can be observed from scanning electron microscope (SEM) that Silica-03 was coated and possessed better dispersibility. Drug adsorption process revealed the competition between drug and solvent, and main influencing factors are polarity of solvent. FTIR indicated that DZH was adsorbed onto Silica-01 and IMC was adsorbed onto Silica-03 with hydrogen bond. Silica-01 and Silica-03 controlled drug release with a burst release and a sustained release, and Silica-03 could slow down burst release due to steric hinder caused by surface modification.

1. Introduction

Recently, there has been increased interest in nanosilica materials applied as drug carriers in the field of controlled drug release due to their properties and advantages, such as excellent biocompatibility, high surface area, large pore volume and the capability to be functionalized with various organic groups [1]. It is generally accepted that drugs can be entrapped into nanosilica materials by conducting *in situ* drug loading process or post-sorption process. *In situ* drug loading process is always employed to entrap drug molecules into silica xerogels [2–7] and effect of controlled drug release can be obviously obtained. Post-sorption process, containing physical sorption and chemical sorption, can be considered for usage on the basis that nanosilica materials known as adsorbents have remarkable adsorption ability. Powdered nanosilica materials, like mesoporous silica materials [8–13], load drugs using post-sorption process. Furthermore, specific methods involved in post-sorption process can be concluded into three methods, which are organic solvent immersion method, incipient wetness impregnation method and the melt method [14], respectively. Drug loading experiment conducted with powdered nano-silica materials [8–13] as drug carriers was almost accomplished by applying concentrated solvent adsorption method, which belongs to organic solvent immersion method. However, drug loading process, especially the relationship between commercial nanosilica materials, adsorbate (drug) and solvent has not been well documented.

The versatility of various surface modifications extends the application of nanosilica materials as drug carriers. In principle, surface modifications of nanosilica materials are prepared with commonly two options, co-condensation and post-grafting. Co-condensation designates simultaneous hydrolysis and condensation of silica and organic silanes in one-pot, while post-grafting refers to the grafting of functional groups on the surface after the synthesis of nanosilica materials. To the best of our knowledge, functional groups, such as amino-[15], carboxyl-[16], alkyl-[17] polyethylene glycol (PEG) [18], chitosan [19], are utilized to modify surface of nanosilica materials. With these added functional groups, drug loading capacity can be increased or drug release behavior was influenced. Since solvent can also affect drug loading process as stated in the above paragraph, it is equally meaningful to prepare nanosilica materials functionalized with modifier aiming to make them disperse well and steadily in solvent [20].

In the present work, the kind of commercial nanosilica materials used was silica nanoparticles (Silica-01) and surface modified silica nanoparicles (Silica-03). Particularly, Silica-03 was involved due to its better dispersing property in solvent. Diltiazem hydrochloride (DZH), ciprofloxacin (CIP), gatifloxacin (GAT), ibuprofen (IBU), indomethacin (IMC) were chosen as model drugs (Fig. 1) for investigation of drug adsorption process. Diltiazem hydrochloride (DZH) loaded Silica-01 and indomethacin (IMC) loaded Silica-03 were investigated with

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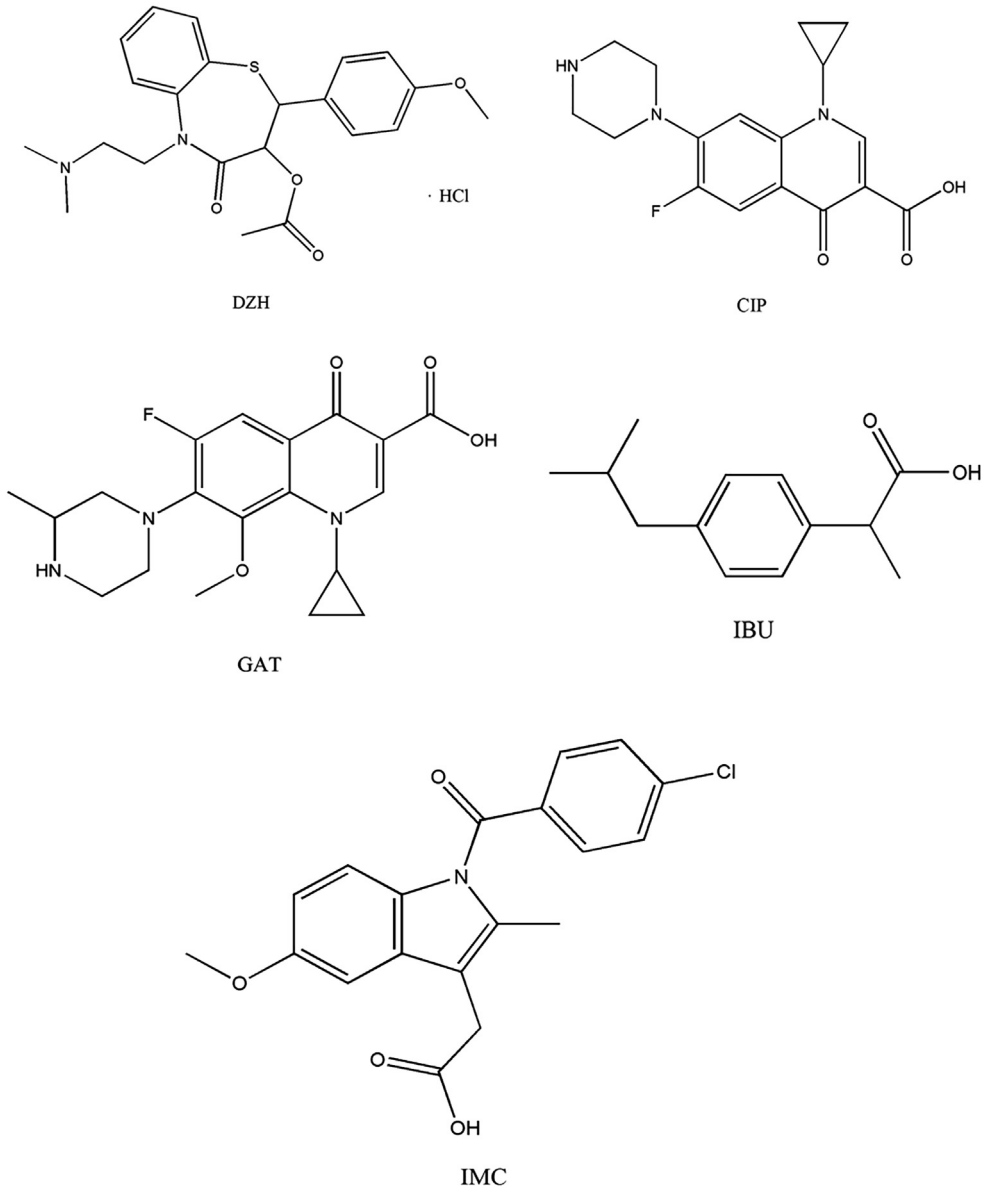


Fig. 1. Chemical structures of model drugs. DZH, diltiazem hydrochloride; CIP, ciprofloxacin; GAT, gatifloxacin; IBU, ibuprofen; IMC, indomethacin.

differential scanning calorimeter (DSC), fourier transform infrared spectroscopy (FT-IR), and *in vitro* release behavior was conducted by filling samples into capsules.

2. Materials and methods

2.1. Materials

Silica-01 and Silica-03 were kindly provided by Qinhuangdao Taiji Ring Nano-Products Co. Ltd (Hebei, China). Five model drugs, DZH, CIP, GAT, IBU, IMC, were purchased from local pharmaceutical company (China). All other chemicals were of reagent grade and were used without further purification. Deionized water was prepared by ion exchange.

2.2. Characteristics of Silica-01 and Silica-03

Results of detecting and analyzing, including appearance, particle size, specific surface area, pore size and surface treatment, were presented in Table1 according to the analysis report of Silica-01 and Silica-03.

It should be noted that Silica-03, possessing better dispersing property in solvent compared to Silica-01, was prepared with co-condensation method [20]. Briefly, a certain quantity of KH-570 (Fig. 2), the modifier, was dissolved in absolute alcohol and added dropwise into mixed solution of silica source and dilute hydrochloric acid. Then the suspension was filtered, followed by washing and drying [21]. The amount of KH-570 was quantified by thermal gravimetric analysis (TGA) with a TGA-50 instrument (Shimadzu, Japan) from 30 to 600 °C with a heating rate of 10 °C/min under purge of 40 ml/min.

Morphology of Silica-01 and Silica-03 were analyzed with SURA 35 field emission scanning electron microscope (ZEISS, Germany). The samples were gold-plated using double-sided adhesive tape prior to imaging. SEM images of Silica-01 and Silica-03 were taken after magnifying samples to the same level aiming to make comparisons.

2.3. Drug adsorption process

Concentrated solvent adsorption method was applied for loading model drugs into carriers (Silica-01 and silica-03). Three water-soluble

Table 1
Results of detecting and analyzing of Silica-01 and Silica-03.

	Appearance	Specific surface area (cm^3/g)	Surface treatment	Particle size (nm)
Silica-01	White fluffy powder	345.18	_	25.4 ± 1.46
Silica-03	White fluffy powder	324.05	KH-570	26.7 ± 1.24

$$CH_2=C(CH_3)COO(CH_2)_3Si(OMe)_3$$

Fig. 2. The molecular formula of KH-570.

drugs (DZH, CIP and GAT) and two poorly water-soluble drugs (IBU and IMC) were selected aiming to investigate the possible relationships between drug adsorption capacity (mmol/g) and drug properties. Drug adsorption process was carried out by soaking carriers into a high drug concentration acetone solution (50 mg/ml) under stirring for 24 h in order to achieve maximum drug loading, and the ratio of carrier and drug was 3:1 (w:w). Drug adsorption process was performed under ambient conditions in closed containers to prevent evaporation of acetone. Finally, the mixture was dried at 37 °C for more than a day in order to remove solvent completely. Drug adsorption capacity (mmol/g) was calculated by measuring free drug concentration with ultraviolet spectrophotometer (UV) (Shimadzu, Japan) at proper wavelength.

2.4. DSc

In order to study the physical state of Silica-01, Silica-03 and drug loaded carriers, DZH and IMC were chosen to be impregnated into Silica-01 and Silica-03, respectively. Samples were analyzed using a DSC Q1000 (TA Instrument, USA). The samples were heated from 20 to 300 °C with a heating rate of 10 °C/min under nitrogen protection. All experiments were carried out in open, crimped aluminum pans (TA Instrument, USA).

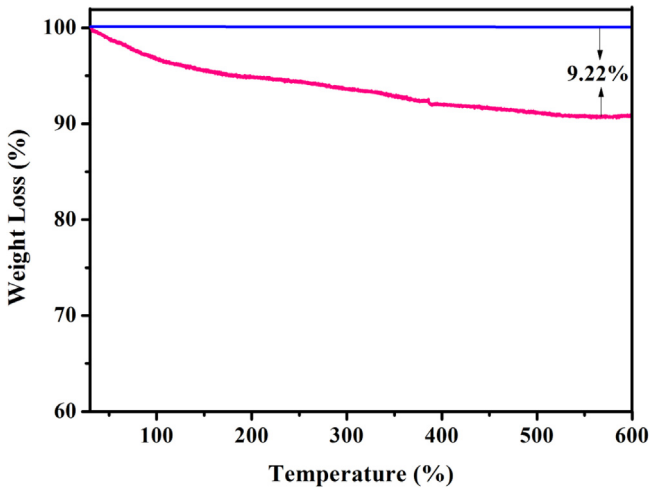


Fig. 4. TGA of Silica-03.

2.5. FTIr

FTIR spectra of Silica-01, Silica-03, DZH loaded Silica-01 and IMC loaded Silica-03 were collected on an FTIR spectrometer with significance to study molecular interaction between drug and carrier (Spectrum 1000, Perkin Elmer, USA). The IR spectra in absorbance

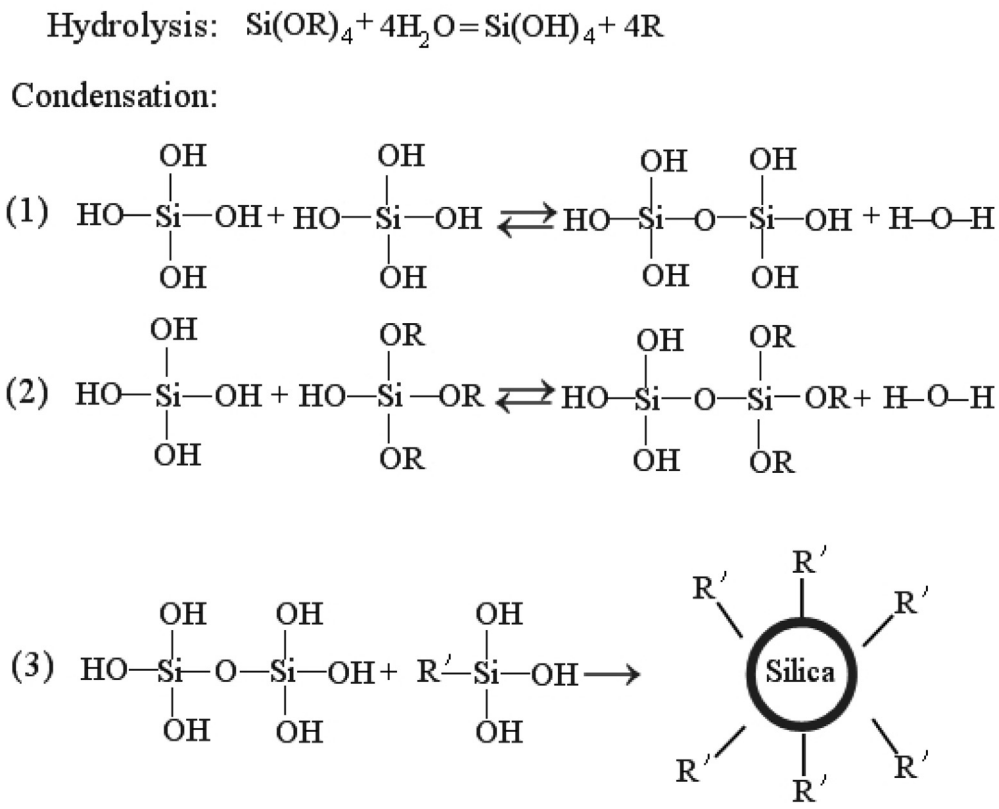
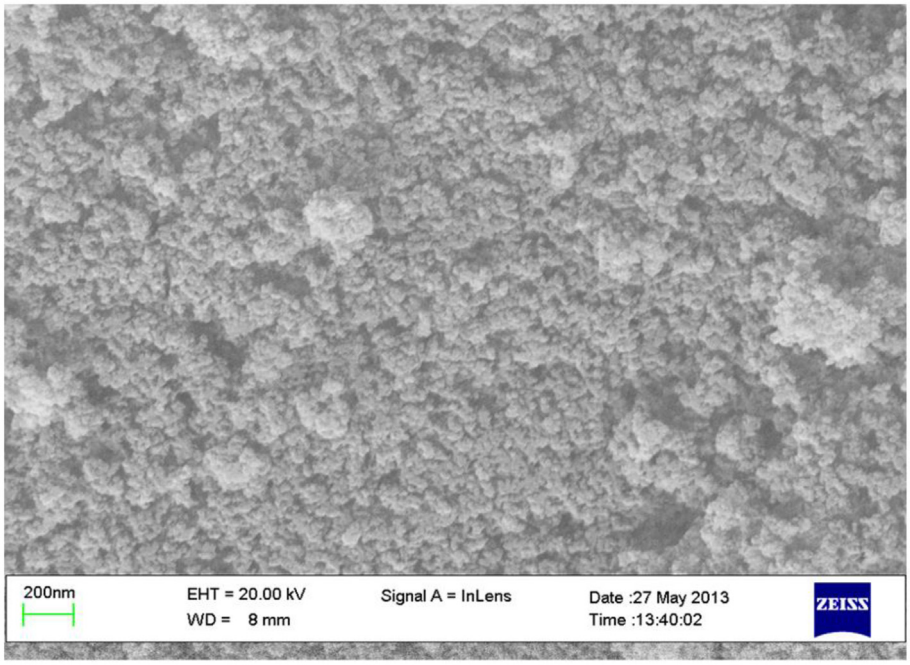
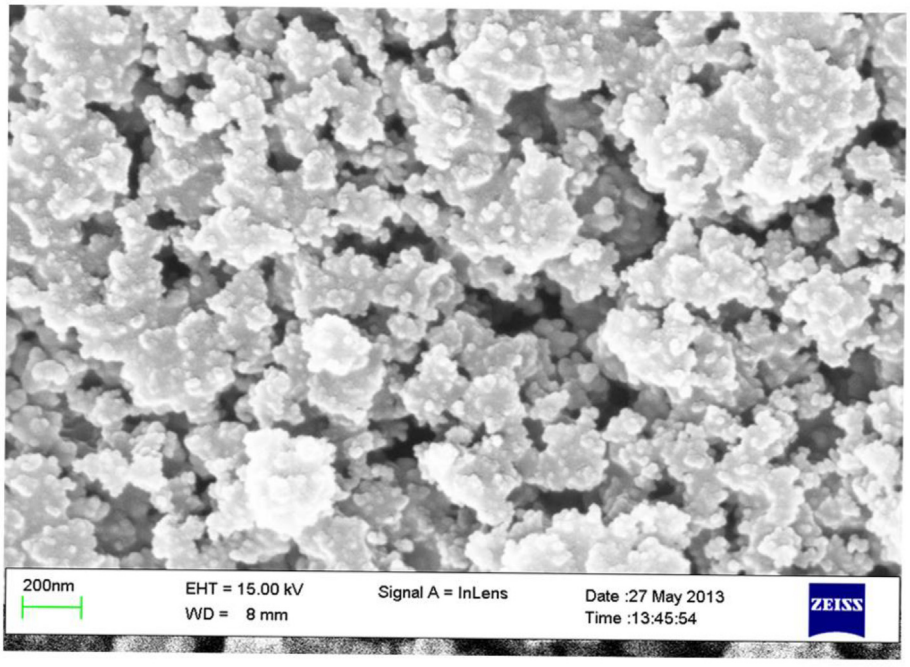


Fig. 3. Formation mechanism of A, Silica-01; B, Silica-03. R stands for $-OCH_3$ or OC_2H_5. R1 stands for the organic chain with functional groups of KH-570.



A



B

Fig. 5. SEM microphages of A, Silica-01; B, Silica-03.

mode were obtained over the spectral region 400 to 4000 cm^{-1}.

2.6. *In vitro release experiment*

To reveal drug release behavior, *in vitro* dissolution studies were conducted using a USP I basket-stirring method (100 rpm, 37 °C, 900 ml enzyme-free simulated intestinal fluid (pH6.8) prepared by dissolving potassium dihydrogen phosphate in deionized water and adjusted the pH with 1 M sodium hydroxide solution) with a ZRD6-B dissolution tester (Shanghai Huanghai Medicament Test Instrument Factory, China). In order to investigate *in vitro* release effect of drug loaded carriers, DZH loaded Silica-01 equivalent to 10 mg raw drug, 10 mg DZH, IMC loaded Silica-03 equivalent to 20 mg raw drug, and 20 mg IMC, were filled into capsules and exposed for more than 24 h to dissolution medium. Additionally, the differences between Silica-01 and Silica-03 in releasing drug were studies by testing *in vitro* release of GAT loaded Silica-01 containing 10 mg raw drug, GAT loaded Silica-03 containing 10 mg GAT. At predetermined time intervals, 5 ml samples were withdrawn from dissolution medium and then an equivalent amount of fresh medium was added to maintain a constant dissolution

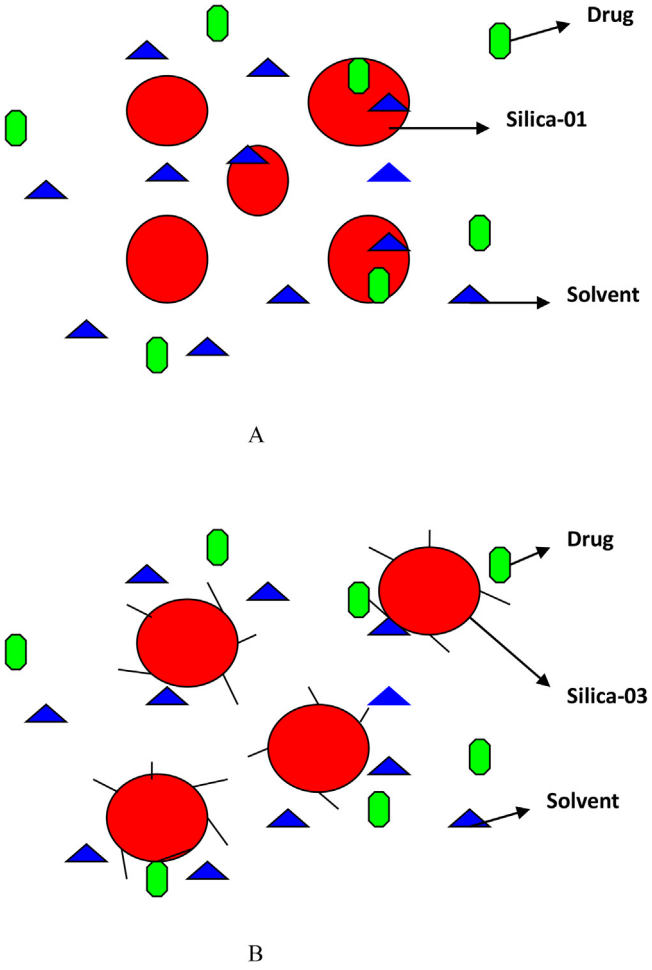


Fig. 6. Schematic illustration for drug adsorption process of A, Silica-01; B, Silica-03.

Table 2
Drug adsorption capacity (mmol/g) for five drugs in acetone with silica-01 or silica-03 as adsorbent.

Drug	Drug adsorption capacity (mmol/g) of Silica-01	Drug adsorption capacity (mmol/g) of Silica-03
DZH	0.173	0.107
CIP	0.613	0.047
GAT	0.293	0.540
IBU	0.053	0.013
IMC	0.267	0.373

volume. Samples administered through 0.45 μm microporous membrane were analyzed using UV-1750 (Shimadzu, Japan) at proper wavelength.

3. Results and discussion

3.1. Characteristics of Silica-01 and Silica-03

It can be concluded that both Silica-01 and Silica-03 had nano particle size and high specific surface area (Silica-01: 345.18 cm^3/g; Silica-03: 324.05 cm^3/g), which rendered their abilities to be drug carriers. Formation mechanism of Silica-01 and Silica-03 can be concluded as the same hydrolysis step while different condensation steps (condensation (1) and (2) for Silica-01, condensation (1), (2) and (3) for Silica-03), as shown in Fig. 3. Firstly, silica source is hydrolyzed to form silicic acid, and then condensation happens among these silicic acids to

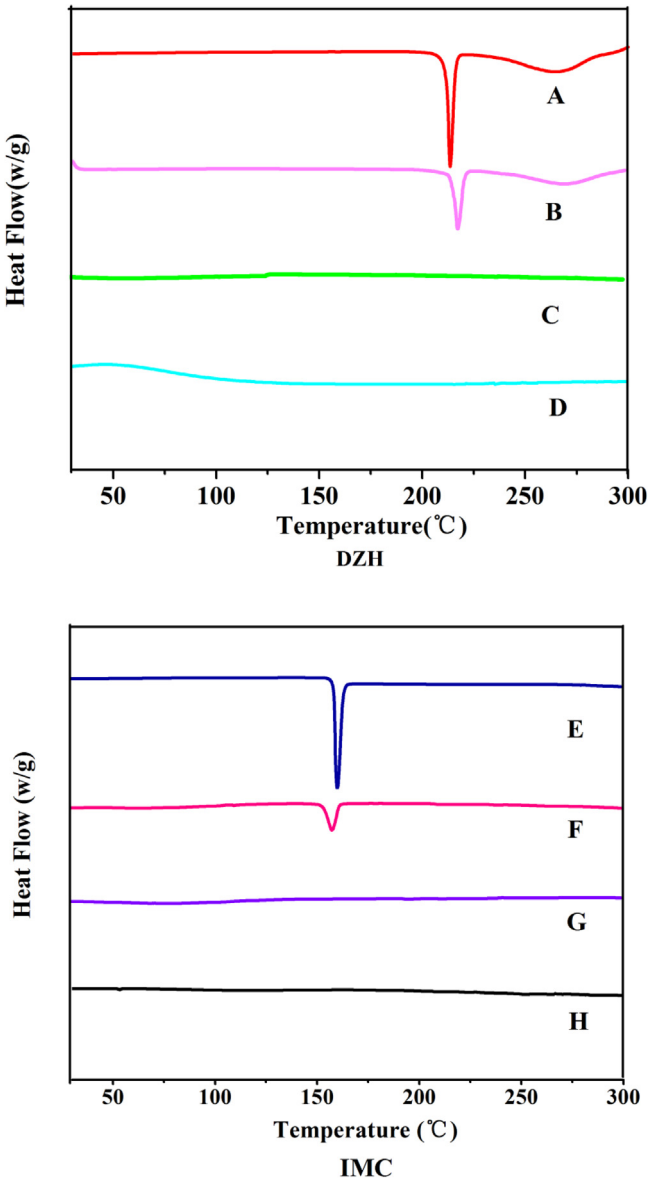


Fig. 7. DSC thermographs of two groups of samples. DZH group (A, DZH; B, physical mixture of DZH and Silica-01; C, DZH loaded Silica-01; D, Silica-01) and IMC group (E, IMC; F, physical mixture of IMC and Silica-03; G, IMC loaded Silica-03; H, Silica-03).

form silica with a large number of silanol groups or other groups on the surface. Silica-03 was synthesized with a more complex formation mechanism than Silica-01 with an extra condensation (3). Siliane coupling agent, KH-570 (CH_2 = $C(CH_3)COO(CH_2)_3Si(OCH_3)_3$), is hydrolyzed to produce —OH when silica source is hydrolyzed. As soon as this process is accomplished, the —OH or —OMe of KH-570 reacts with —OH of silica. Steric hinder caused by the organic chains of KH-570 prevents silica from growing up or agglomerating. Therefore, Silica-03 can disperse well and steadily in solvent [20], and this character has also been verified by results of drug adsorption capacity and *in vitro* release in the paper.

In the TGA measurement, the KH-570 desorbed after decomposing, which was detected as time-dependent weight reduction. The weight loss due to KH-570 was 9.22% (Fig. 4), indicating that part of silanol groups had been combined with functional groups of KH-570. SEM micrographs (see Fig. 5) showed that Silica-03 had higher degree of dispersibility because KH-570 was “capped” onto silica. In the meanwhile, particle size of Silica-03 was not much influenced with surface

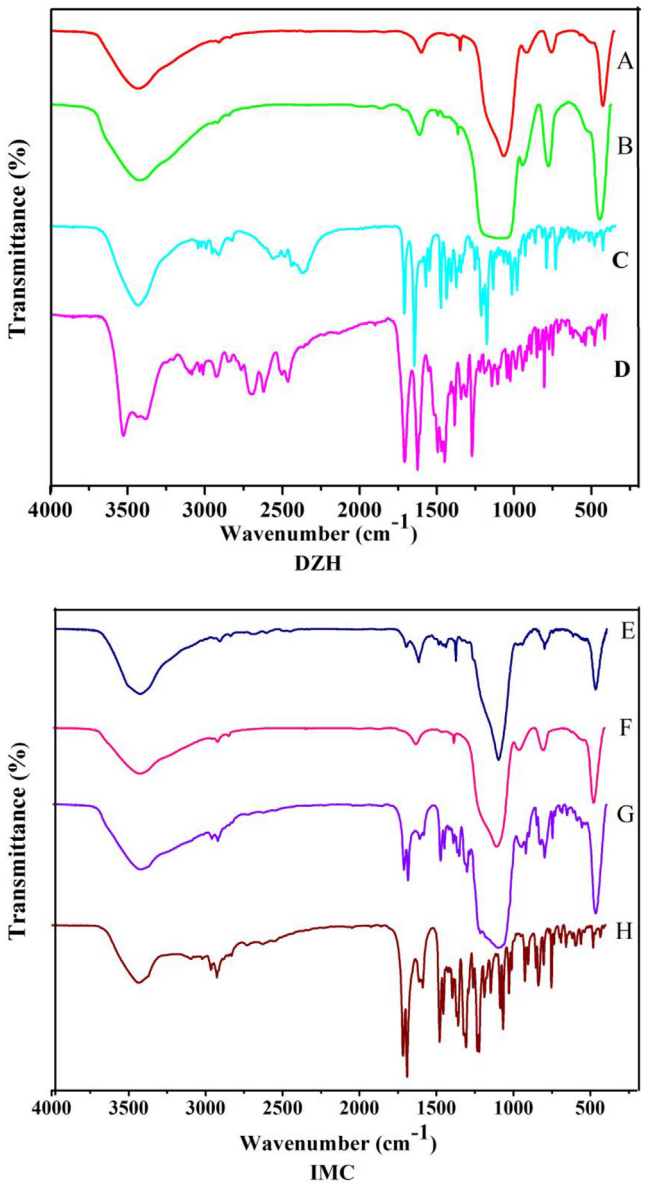


Fig. 8. FTIR spectra of two groups of samples. DZH group (A, Silica-01; B, DZH loaded Silica-01; C, physical mixture of DZH and Silica-01; D, DZH); IMC group (E, Silica-03; F, IMC loaded Silica-03; G, physical mixture of IMC and Silica-03; H, IMC).

modification evidenced by the fact that their particle size measured by dynamic light scattering had no significant difference (Silica-01 was 25.4 ± 1.46 nm and Silica-03 was 26.7 ± 1.24 nm).

3.2. Drug adsorption process studies

For most of the investigations on nanosilica materials as drug carriers, drug loading process was not always discussed in depth. In fact, there are some meaningful stories that we can tell from studying this interesting process, which may lay foundation for the manufacturing of drug loaded silica materials.

Herein, we attempt to describe drug adsorption process with visual image shown in Fig. 6 and data presented in Table 2. In drug adsorption system, there are three main roles, which are adsorbent (carriers), adsorbate (drug) and solvent. Competition between solvent and drug molecules for adsorption on to the carriers was observed. Moreover, the better dispersal ability of Silica-03 vis Silica-01 (Silica-03 with KH-570 had superior dispersion ability in organic solvent than Silica-01

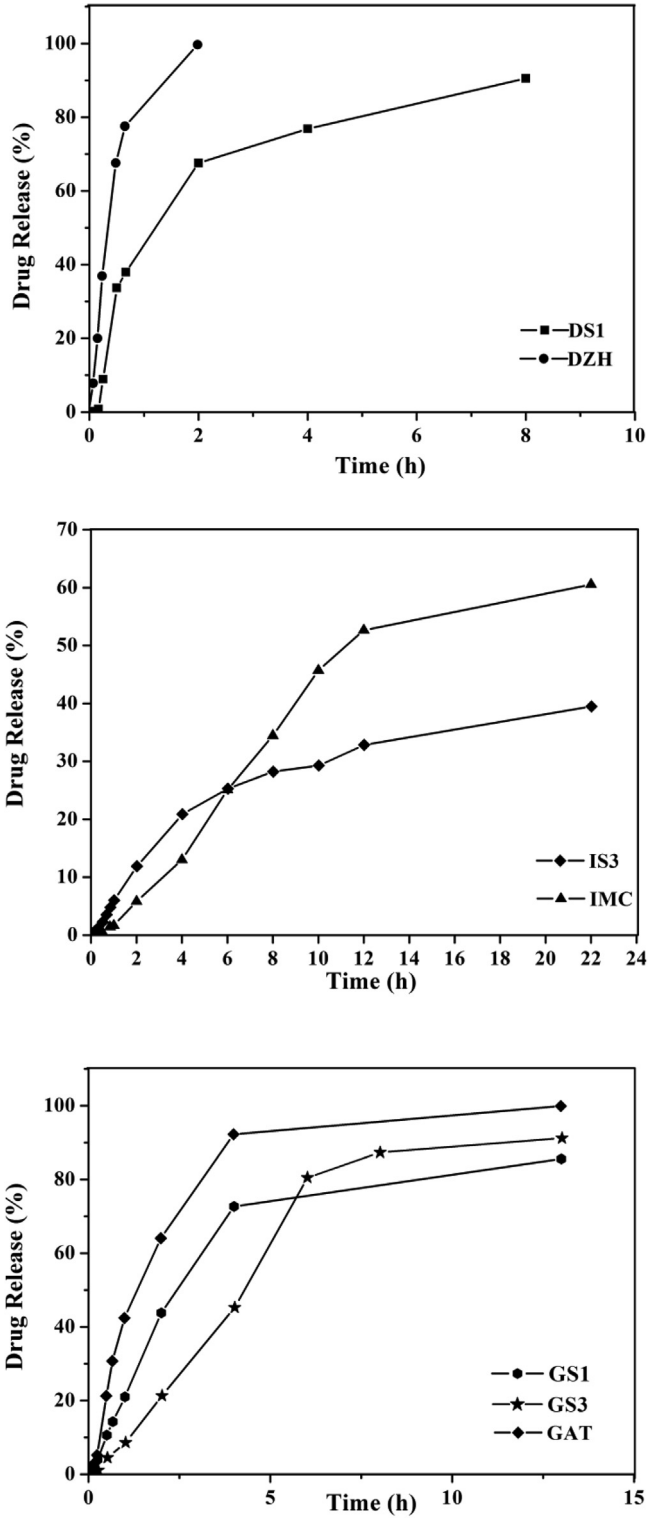


Fig. 9. *In vitro* release profiles of drug loaded carriers or raw drug in capsule. A, DZH loaded Silica-01 (DS1) and DZH; B, IMC loaded Silica-03 (IS3) and IMC; C, GAT loaded Silica-01 (GS1), GAT loaded Silica-03 (GS3) and GAT.

according to the product report of Silica-03.) also affected drug adsorption. Since drug carriers are adsorbents, and Silica-01 is a polar adsorbent while Silica-03 is a relative low-polar adsorbent due to its surface modification, the polarity of solvent largely affects adsorption process according to basic interface adsorption knowledge. As can be seen in Table 2, drug adsorption capacity for different drugs varied a lot when using the same drug carrier, indicating that drug adsorption

capacity was related with drug properties (such as drug molecular size, drug solubility in acetone, while specific relationship should be investigated further). What is more, drug carriers also influenced drug adsorption capacity significantly. As Silica-03 dispersed better in acetone, solvent could have more chances to be adsorbed onto carriers, therefore drug adsorption capacity for some drugs (DZH, CIP, IBU) were lower. However, GAT and IMC were more competitive than solvent when using Silica-03 as drug carrier, possibly demonstrating that stronger physical adsorption force can be formed between GAT, IMC and Silica-03. In conclusion, results of drug adsorption capacity were mainly related to determined factors on competitive ability of being adsorbed, including the polarity of acetone [21] and drug properties.

3.3. DSC studies

The presence or absence of crystalline drug was confirmed by DSC analysis. As shown in Fig. 7, the DSC curves of DZH and its physical mixture with Silica-01 exhibited a single endothermic peak at 214 °C, which corresponded to intrinsic melting points of DZH. However, no melting peak of DZH was identified in the DSC curves of DZH loaded Silica-01. The absence of phase transitions indicated that DZH was in a noncrystalline state after being adsorbed onto carriers. Observation of DSC curves of IMC group was in good agreement with DZH group, indicating that IMC was in a noncrystalline state after being adsorbed onto Silica-03.

3.4. FTIR studies

FTIR is known to provide surface information for identification of chemical groups. From the FTIR spectra of A and E in Fig. 8, we can observe the bending vibration peaks of Si-O-Si at 470.9 and 472.4 cm^{-1}, symmetric stretching vibration peaks of Si-O-Si at 802.6 and 804.8 cm^{-1}, antisymmetric stretching vibration peaks of Si-O-Si at 1102.9 and 1105.7 cm^{-1}, bending vibration peaks of H-O–H at 1629.9 and 1625.2 cm^{-1}, and stretching vibration peaks of Si-OH at 3441.6 and 3442.2 cm^{-1}, respectively. It should be noticed that the peak of 1720 cm^{-1} corresponded to stretching vibration of carbonyl of KH-570 was in spectrum of Silica-03, while it could not be observed in spectrum of Silica-01, indicating the successful surface modification to form Silica-03. After loading DZH into Silica-01, almost no changes can be seen, demonstrating that DZH was adsorbed onto Silica-01 mainly by hydrogen bonding. However, FTIR spectra of E and F showed that stretching vibration of carbonyl belonging to KH-570 was not detected after loading IMC, indicating that IMC was adsorbed onto Silica-03 by hydrogen bond formed with functional group of KH-570. Moreover, electrostatic or hydrophobic interactions can also attribute to physical adsorption between drug molecules and Silica-03 due to its surface modification[22].

3.5. In vitro release studies

Samples for testing were filled into the same tape of capsules to remain consistent conditions. As shown in Fig. 9 A, it was obvious that Silica-01 controlled DZH release behavior and decreased its release speed, and so are the IMC loaded Silica-03, GAT loaded Silica-01 and GAT loaded Silica-03. Release mechanism of drug loaded carriers was attributed to the ability of drug molecules to escape from carries and diffuse into release medium. Therefore, adsorption strength of drug entrapped into carriers impacted drug release behavior. In addition, it can be seen that the release profiles of DZH loaded Silica-01, IMC loaded Silica-03, GAT loaded Silica-01 and GAT loaded Silica-03 were of the same type with a high release rate at the initial stage, followed by a slow sustained release. The initial burst release may be attributed to the presence of drug molecule adsorbed on the external surface, which allowed a certain amount of drug to be released quickly into the release medium. Then the release rate slowed down due to the stronger adsorption strength of drug adsorbed into carriers. In order to compare the ability of controlling drug release when using different carriers, GAT loaded Silica-01 and GAT loaded Silica-03 were both filled into the same capsules and their release behavior were studied. It can be observed that the release profile of GAT loaded Silica-03 displayed much slower burst release but a litter faster sustained release. This result suggested that the chain terminator of Silica-03, functional groups of KH-570, delayed burst drug release significantly because this steric hinder impeded drug from escaping possibly ascribed to the interactive function between KH-570 and drug [20].

4. Conclusion

We have introduced characteristics and formation mechanisms of Silica-01 and Silica-03 (hydrolysis and condensation), and provided scanned images of their morphology. Results reflected that Silica-03 was coated and possessed better dispersibility. It was suggested that drug and solvent made competition in drug loading process, and the main influencing factors are polarity of solvent and solubility of drug in this solvent. DZH loaded Silica-01 and IMC loaded Silica-03 were in a noncrystalline state according to DSC analysis. Moreover, FTIR indicated that DZH was adsorbed onto Silica-01 and IMC was adsorbed onto Silica-03 with hydrogen bond. Finally, *in vitro* release profiles demonstrated that Silica-01 and Silica-03 controlled release behavior with a high release at initial stage, followed by a sustained release, and Silica-03 slowed down burst release due to steric hinder caused by the chain terminator of KH-570.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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