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ORIGINAL RESEARCH

Increasing the oral bioavailability of poorly water-soluble carbamazepine using immediate-release pellets supported on SBA-15 mesoporous silica

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Background and methods: The aim of this study was to develop an immediate-release pellet formulation with improved drug dissolution and adsorption. Carbamazepine, a poorly water-soluble drug, was adsorbed into mesoporous silica (SBA-15-CBZ) via a wetness impregnation method and then processed by extrusion/spheronization into pellets. Physicochemical characterization of the preparation was carried out by scanning electron microscopy, transmission electron microscopy, nitrogen adsorption, small-angle and wide-angle x-ray diffraction, and differential scanning calorimetry. Flowability and wettability of the drug-loaded silica powder were evaluated by bulk and tapped density and by the angle of repose and contact angle, respectively. The drug-loaded silica powder was formulated into pellets to improve flowability.

Results: With maximum drug loading in SBA-15 matrices determined to be 20% wt, in vitro release studies demonstrated that the carbamazepine dissolution rate was notably improved from both the SBA-15 powder and the corresponding pellets as compared with the bulk drug. Correspondingly, the oral bioavailability of SBA-15-CBZ pellets was increased considerably by 1.57-fold in dogs ($P < 0.05$) compared with fast-release commercial carbamazepine tablets.

Conclusion: Immediate-release carbamazepine pellets prepared from drug-loaded silica provide a feasible approach for development of a rapidly acting oral formulation for this poorly water-soluble drug and with better absorption.

Keywords: ordered mesoporous silica, poorly water-soluble drug, carbamazepine, extrusion, spheronization, pellets, bioavailability

Introduction

Nowadays, the greatest challenge for oral drug delivery systems is to improve the bioavailability of poorly water-soluble drugs. Although several formulation strategies, including solid dispersions,[1] emulsion-based systems,[2] nanosizing,[3] and cyclodextrin inclusion complexes,[4] have had promising results, use of these technologies in the marketplace has been very limited to date. Together with the growing number of poorly soluble compounds, this underscores the need to explore new formulation approaches.

Because in vitro dissolution is directly correlated with bioavailability in pharmaceutical research, an emerging approach to enhance dissolution is encapsulation of hydrophobic amorphous drugs in ordered mesoporous silica materials. Using the International Union of Pure and Applied Chemistry definition, the term "mesoporous" refers to porous materials that have pores between 2 nm and 50 nm in diameter. The outstanding features of ordered mesoporous silica materials, including their highly regular mesoporous structure, high surface area, large pore volume, tunable pore

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size, good biocompatibility, and thermal stability, have led to these materials becoming important drug carriers.[5] Mobil Composition of Matter-41 (MCM-41)[6] and Santa Barbara Amorphous-15 (SBA-15)[7] are the most common mesoporous silica materials that have been investigated as drug carriers. Since the first report by Vallet-Regi et al in 2001 using MCM-41 as a new drug delivery system,[8] investigations using this product have indicated that mesoporous silica holds great promise in enhancement of dissolution for poorly soluble drugs.[9–12]

However, in most of the previous studies, dissolution was evaluated directly in drug-loaded powdery mesoporous materials rather than preparing specific dosage forms.[13,14] That is because the angle of repose of drug-loaded silica powder is often more than 40 degrees, indicating poor flowability and leading to difficulty in packing the powder into capsules. Some researchers have put drug-loaded silica directly into capsules regardless of its poor flowability,[15] although Mellaerts et al[16] mixed drug-loaded silica with excipients to improve the flowability for capsule packing. Drug-loaded silica can be pressed into tablets without any pharmaceutical excipients by direct compression,[17–19] but the quality of the tablets is not ensured due to the poor compressibility. Finally, Limnelle et al[20], Vialpando et al,[21] and Kiekens et al[22] have reported being able to compress drug-loaded silica with suitable excipients into tablets with acceptable quality.

Surprisingly, to the best of our knowledge, there have been no reports to date regarding a pharmaceutical formulation based on preparing ordered mesoporous silica as pellets. In fact, pellets are frequently used as a multiparticulate solid dosage form in controlled-release delivery systems and offer several advantages over conventional single-unit solid dosage forms. The physiological advantages of pellets, including reduced gastric irritation, an extended gastrointestinal transit time, and a minimal gastric emptying effect, are attributed to more even distribution of the pellets in the gastrointestinal tract. The pellets also have technological advantages, including good sphericity, a smooth and large surface, narrow size distribution, and low friability, which ensure uniformity of drug content and successful coating, with a minimized risk of dose "dumping". Further, pellets can offer considerable flexibility in dosing and adjustment of drug release by coating or unit combination.[23] Immediate-release pellets based on mesoporous silica could enhance the oral bioavailability of poorly water-soluble drugs by markedly increasing the dissolution rate. Also, drug-release behavior can be modulated by polymeric coating of the pellets to obtain adequate and rapid drug dissolution for immediate action, followed by gradual and continuous drug release to maintain the plasma drug concentration over an extended period of time. This controlled-release system is expected to improve the dissolution and bioavailability of poorly water-soluble drugs, as well as improve the safety and efficacy of drug delivery.

In this study, SBA-15 mesoporous silica was synthesized and combined with excipients to create immediate-release pellets as a drug carrier using the method of extrusion/spheronization. Of the silica-based ordered mesoporous materials available, SBA-15 was chosen because it has mesochannels with by far the largest pore size and thick walls, an adjustable pore size in the range of 3–30 nm,[7] and a high drug-loading capacity.[13]

Extrusion/spheronization is a well established technique for production of pellets. Up until now, microcrystalline cellulose has been the most widely used excipient for preparing pellets via extrusion/spheronization because it has good binding properties and can provide the necessary plasticity to the wet mass, which ensures both successful extrusion/spheronization.[24] Nevertheless, the reluctance of microcrystalline cellulose pellets to disintegrate in aqueous media may result in slow drug release, especially in the case of poorly water-soluble drugs.[25] Because drug-loaded mesoporous silica itself has the ability to dissolve rapidly, it is necessary for the pellets to disintegrate quickly. Therefore, easily dissolving sugars and sugar alcohols might be good candidates as diluents, and disintegrants could also be added to accelerate disintegration of the pellets.

Carbamazepine, an effective antiepileptic agent with low solubility (113 μg/mL, 25°C)[26] and high permeability, is designated as a class II agent according to the Biopharmaceutic Classification System.[27] Given that dissolution of poorly water-soluble drugs like carbamazepine is the rate-limiting step for absorption, it is important to improve the dissolution rate and thus enhance drug absorption and bioavailability. The main objective of the present work was to develop a carbamazepine pellet formulation with improved drug dissolution and adsorption based on incorporation of the drug into SBA-15 mesoporous silica (SBA-15-CBZ). This work is also expected to expand the use of silica-based ordered mesoporous materials as drug delivery systems.

Materials and methods

Materials

Carbamazepine was purchased from Jiangshu Suzhou Hengyi Pharmaceuticals Co, Ltd (Jiangsu, China). Commercial fast-release carbamazepine 100 mg tablets were purchased from Guangdong Huanan Pharmacy Ltd (Guangdong, China).

Triblock copolymer Pluronic® P123 (poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), PEO_{20}-PPO_{70}-PEO_{20}, average molecular weight 5750) and tetraethyl orthosilicate were obtained from Sigma-Aldrich (St Louis, MO). Hydrochloric acid (HCl) and anhydrous ethanol were purchased from Fuchen Chemicals Reagent Factory (Tianjin, China). Silicified microcrystalline cellulose (Prosolv® 90) was sourced from JRS Pharma (Rosenberg, Germany). Sorbitol crystals (Neosorb® P60 W, Roquette Pharma, Lestrem, France) and sodium carboxymethyl starch (Shandong Liaocheng Anxin Pharmaceutical Excipients Co, Ltd, Shandong, China) were also used. Deionized water was obtained from an Ultra Bio Mk2 ultrapure system (Elga, Marlow, UK). All other products and solvents were of chemical grade and used without further purification.

Synthesis of SBA-15 mesoporous silica

SBA-15 mesoporous silica was synthesized according to the procedure reported by Zhao et al,[7] with some modifications under our laboratory conditions. The triblock copolymer, Pluronic P123, was used as a template in acidic conditions and tetraethyl orthosilicate was used as the silicon source. Briefly, 4.0 g of the template was dissolved in a mixture of 30 mL water and 120 mL of HCl solution (2 M) in a three-necked flask, and the resulting mixture was stirred continuously at 38°C until all the P123 was dissolved. Subsequently, 9.2 mL of tetraethyl orthosilicate was added dropwise to this solution, followed by stirring for 24 hours at 38°C, and then allowed to crystallize at 100°C for another 48 hours in a round-bottomed flask. The solid product was filtered and washed with ethanol, and dried at room temperature. Finally, the silica powder collected was calcined at 550°C for 8 hours to eliminate the template completely.

Loading carbamazepine into SBA-15

A wetness impregnation method was used to load carbamazepine into the SBA-15 mesoporous silica. Briefly, SBA-15 was added to an ethanol solution containing carbamazepine (25 mg/mL) at drug to carrier ratios of 1:9, 1:4, and 1:2.3 (w/w). Ethanol was used as the loading solvent because it is safe, nontoxic, and can dissolve large amounts of carbamazepine. Afterwards, the mixture was ultrasonicated in a closed vial for 10 minutes and brought to adsorption equilibrium under magnetic stirring at room temperature for 24 hours in order to achieve maximum drug loading in the SBA-15 pore channels. Finally, the mixture was evaporated at 60°C on a rotary evaporator (Eyela N-1001, Tokyo, Japan) until dry in order to remove the ethanol completely.

The carbamazepine content in the matrix was determined by suspending 30 mg of the loaded samples in 10 mL of ethanol solution. The suspensions were sonicated for 4 hours and subsequently centrifuged at 5000 rpm for 10 minutes. The supernatant was collected and assayed by ultraviolet spectrophotometry (TU-1901, Beijing Purkinje General Instrument Co, Ltd, Beijing, China) at λ 284 nm.

Preparation of SBA-15-CBZ pellets

Pellets were prepared using the extrusion/spheronization method. A 50 g combination containing carbamazepine-loaded SBA-15 mesoporous silica (25%, w/w), microcrystalline cellulose (20%, w/w), sorbitol (50%, w/w), and sodium carboxymethyl starch (5%, w/w) was thoroughly premixed in a mixer with multidirection movement (Wenzhou Pharmaceutical Machine Factory, Wenzhou, China) for 15 minutes. Next, 21 g of deionized water was added slowly to the powder mixture, with blending continuing for another 10 minutes. The resulting wet mass was extruded at a speed of 40 rpm using a single screw extruder (Chongqing Eagle Pharmaceutical Machinery Co, Ltd, Chongqing, China) equipped with a dome-shaped extrusion screen (1.2 mm in thickness, 1 mm in perforation diameter). The extrudates were spheronized for 3 minutes at 800 rpm in a spheronizer (Chongqing Eagle Pharmaceutical Machinery Co, Ltd) with a rotating plate of regular crosshatch geometry. Finally, the pellets were collected and dried in a hot air oven (DHG-9240 A, Keelrein Instrument Co, Ltd, Shanghai, China) at 40°C for 12 hours to reach a constant weight.

SEM and TEM characterization

The morphology of the silica materials and pellets was characterized by scanning electron microscopy (SEM, JSM-6330F, JEOL, Tokyo, Japan), with the samples being gold-plated prior to imaging. The porous structure of the samples was analyzed by transmission electron microscopy (TEM, JEM-1400, JEOL), and their pore size was measured by analySIS version 5.0 software (Olympus, Tokyo, Japan). Before examination, the silica materials were dispersed in absolute ethyl alcohol and ultrasonicated for 10 minutes.

Small-angle and wide-angle x-ray diffraction

Small-angle and wide-angle x-ray diffraction patterns for the samples were collected using an x-ray diffractometer (D-MAX 2200 VPC, Rigaku, Japan) with a CuKα radiation (λ 0.154 nm) beam operating at 40 kV and 40 mA. Data were obtained in the 2θ range of 0.6–3.0 degrees and 5–50 degrees

at a scanning rate of 0.12 degrees and 4 degrees per minute, respectively. A powder sample was applied on a glass plate to form a flat surface for measurement.

Adsorption–desorption of nitrogen

The pore characteristics of the silica samples were studied using a surface area and pore size analyzer (ASAP™ 2020C, Micromeritics, Norcross, GA) at −196°C. Prior to characterization, the SBA-15 samples were degassed under vacuum at 300°C for 12 hours, while the drug-loaded samples were degassed at 40°C for 12 hours in order to avoid sublimation of carbamazepine. The specific surface area of the sample was calculated from the adsorption data obtained at P/P_0 of nitrogen according to the multiple-point Brunauer–Emmett–Teller (BET) method. The pore volume was determined from the adsorption branch of the nitrogen adsorption–desorption isotherm curve at the $P/P_0 = 0.975$ signal point. The pore diameter was calculated from the adsorption branch of the isotherms using the Barrett–Joyner–Halenda method.

Characterization by differential scanning calorimetry

The thermal behavior of the samples was examined by differential scanning calorimetry (DSC 200 F3 Maia, Netzsch, Germany). Samples weighing 5–10 mg were put into open aluminum pans and heated from 30°C to 220°C. Nitrogen at a flow rate of 30 mL per minute was used as the purge gas, while the temperature ramp rate was 10°C per minute. The instrument was calibrated using indium and the data were analyzed using Proteus analysis software.

Physical properties of powders and pellets

Bulk and tapped densities, together with the angle of repose of the powdered materials and pellets, were determined using a BT1000 powder testing instrument (DanDong Bettersize Instruments Ltd, Dandong, China). The mean of three tests is reported. To understand the wettability of the powders, the contact angles were measured using the sessile drop method with a Dataphysics OCA-20 contact angle analyzer (DataPhysics Instruments, Filderstadt, Germany). This instrument consists of a charge-coupled device video camera with a resolution of 768 × 576 pixels and up to 50 images per second, an electronic syringe unit, and a temperature controlled environmental chamber. Prior to measurement, the samples were evaporated under vacuum at 50°C overnight to avoid the impact of moisture. A sample was put into an aluminum pan and pressed with a cover glass under a weight of 50 g for 60 seconds to minimize the impact of rough surface. A drop of water (4.5 μL) was placed onto the flat surface of the sample using a micropipette and images of the drop were captured by the digital camera assembly at a rate of 30 frames per second. With the aid of SCA20 software (DataPhysics), the left and right contact angles and dimension parameters of the drop were calculated from the contours using an ellipsoidal fitting model with an accuracy of ±0.01 degrees.

In vitro dissolution

In vitro dissolution testing was undertaken using the USP II paddle method (75 rpm, 37°C ± 0.5°C, 900 mL dissolution medium) with a ZRS-8G dissolution tester (Tianda Tianfa Technology Co, Ltd, Tianjin, China). The dissolution medium was deionized and degassed water, and the amount of test sample was adjusted to obtain sink conditions. Next, 5 mL samples were withdrawn from the dissolution vessel at 5, 10, 15, 30, 45, and 60 minutes, and filtered through a 0.22 μm Millipore filter (Millipore, Billerica, MA) and measured by ultraviolet spectrophotometry (TU-1901, Beijing Purkinje General Instrument Co, Ltd, Beijing, China) at λ 284 nm. An equivalent amount of fresh medium was added to the dissolution vessel after each sample was withdrawn to maintain a constant volume. Each dissolution study was performed in triplicate.

In order to compare the release profiles for the SBA-15-CBZ powder and SBA-15-CBZ pellets, the similarity factor (f_2)[28] was calculated according to the following equation:

$$f_2 = 50 \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} | R_t - T_t |^2 \right]^{-0.5} \times 100 \right\}$$

where n is the number of dissolution sampling time points, and R_t and T_t are the percentages of drug dissolved for the reference and test samples at time t, respectively. An f_2 value larger than 50 indicates that the two dissolution profiles are similar.

In vivo study

Six healthy female beagle dogs (1.2–2.0 years of age) weighing 14 ± 0.7 kg were used in this randomized crossover study, with a washout period of 2 weeks between the two study periods. The experiment was approved by the animal ethics committee of Sun Yat-sen University and performed in accordance with the National Institute of Health and Nutrition Guidelines for the Care and Use of Laboratory Animals. The dogs were fasted overnight prior to oral administration of the drug but allowed to drink water ad libitum. The treatment

consisted of a single oral administration of one commercially available fast-release carbamazepine 100 mg tablet or four capsules containing SBA-15-CBZ pellets equivalent to a dose of 100 mg carbamazepine, together with 40 mL of water. At 0, 10, 20, 30, 45, 60, 75, 90, 120, 180, 240, 300, and 360 minutes after administration, 4.0 mL blood samples were withdrawn from the cephalic vein of the hind leg and centrifuged for 15 minutes at 3000 rpm. The plasma samples were stored at −20°C until analysis.

Analysis of plasma carbamazepine concentration

Carbamazepine was assayed using a high-performance liquid chromatography method, which was validated following international guidelines and performed as per our previous report.[9] A Waters model 1525 pump equipped with a 2487 ultraviolet detector, a 717 autosample system, and Empower software was used for the analysis. Carbamazepine separation was completed on a Symmetry® C18 column (4.6 × 250 mm, 5 µm) with a guard column (4.6 × 12.5 mm, 5 µm) using a mobile phase consisting of acetonitrile and water (40:60, v/v) at a flow rate of 1.0 mL per minute. The detection wavelength was set at 230 nm.

A 500 µL aliquot of plasma was spiked with 20 µL of methanol containing an internal standard (pentobarbital 10 µg/mL) and vortexed for 30 seconds. Next, 2 mL of acetoacetate was added as the extraction solvent and vortexed for an additional 3 minutes. After centrifugation at 10,000 rpm for 3 minutes, the supernatant was separated and the organic solvent was evaporated overnight under vacuum at room temperature. The residue was reconstituted in 150 µL of mobile phase and 50 µL aliquot was injected for high-performance liquid chromatography analysis.

Pharmacokinetic and statistical analysis

The following pharmacokinetic parameters were calculated: C_{max} (highest observed concentration during the study period), T_{max} (the time at which C_{max} occurred), K_e (slope of the logarithm concentration-time plot estimated from the elimination segment), $t_{1/2}$ (half-life calculated as $0.693/K_e$), and $AUC_{(0\rightarrow\infty)}$ (area under the plasma concentration-time curve calculated by the linear trapezoidal rule from time 0 to infinity). The relative bioavailability was calculated by $[(AUC_{test} \times D_{ref})/(AUC_{ref} \times D_{test})] \times 100$, where D is the dose, and "test" and "ref" correspond to the pellet formulation and commercial tablet, respectively.

The significance of the differences observed for the mean pharmacokinetic parameters of the test pellets and reference tablets was evaluated using the Student's *t*-test and Mann–Whitney rank sum test after normality and equal variance tests. The data were analyzed using SPSS for Windows (version 11.5, SPSS Inc, Chicago, IL). P values < 0.05 were considered to be statistically significant.

Results and discussion

Morphological, structural, and textural properties of SBA-15 materials

SEM and TEM were used to determine the particle morphology, particle size, and pore structure of the mesoporous materials. As shown in SEM images (Figure 1B), SBA-15 consisted of rod-like subparticles with a relatively uniform length of about 0.5–1.5 µm, which aggregated into wheat-like macrostructures. Similar SEM images were reported by Katiyar et al.[29] However, due to the limitations of SEM, TEM was used to reveal the mesoporous structure of SBA-15 in more detail. TEM images of SBA-15 at a parallel orientation (Figure 2A) and at a vertical orientation (Figure 2B) clearly show well ordered hexagonal arrays of mesopores and straight lattice fringes viewed along and perpendicular to the pore axis, confirming the existence of a two-dimensional hexagonal structure of *p*6mm symmetry.[30] The mean pore size was approximately 6.5 nm when measured by analySIS 5.0 software.

The small-angle x-ray diffraction patterns for SBA-15 (Figure 3A) show three well resolved peaks, which could be indexed as (100), (110), and (200) diffractions of highly ordered two-dimensional hexagonal mesoporous structure (p6 mm), suggesting a good long-range order within this material.[31] In order to obtain more precise information about the structure of SBA-15, nitrogen adsorption–desorption measurements were performed, which allowed determination of specific surface area, pore volume, and mesopore size distribution. The nitrogen adsorption–desorption isotherms for SBA-15 (Figure 4A) can be classified as the typical IV-type containing the H1 hysteresis loop associated with mesoporous materials, according to the International Union of Pure and Applied Chemistry classification.[7] Further, SBA-15 showed a narrow pore size distribution (insert of Figure 4A). BET specific surface area (S_{BET}), total pore volume (V_t), and Barrett–Joyner–Halenda pore diameter (w_{BJH}) were calculated (Table 1), and the mean pore size of 6.5 nm is consistent with the value measured from the TEM images. It can be seen that SBA-15 has a very high BET specific surface area and a large pore volume, indicating its potential application as a host to store drug molecules in a drug-release system.

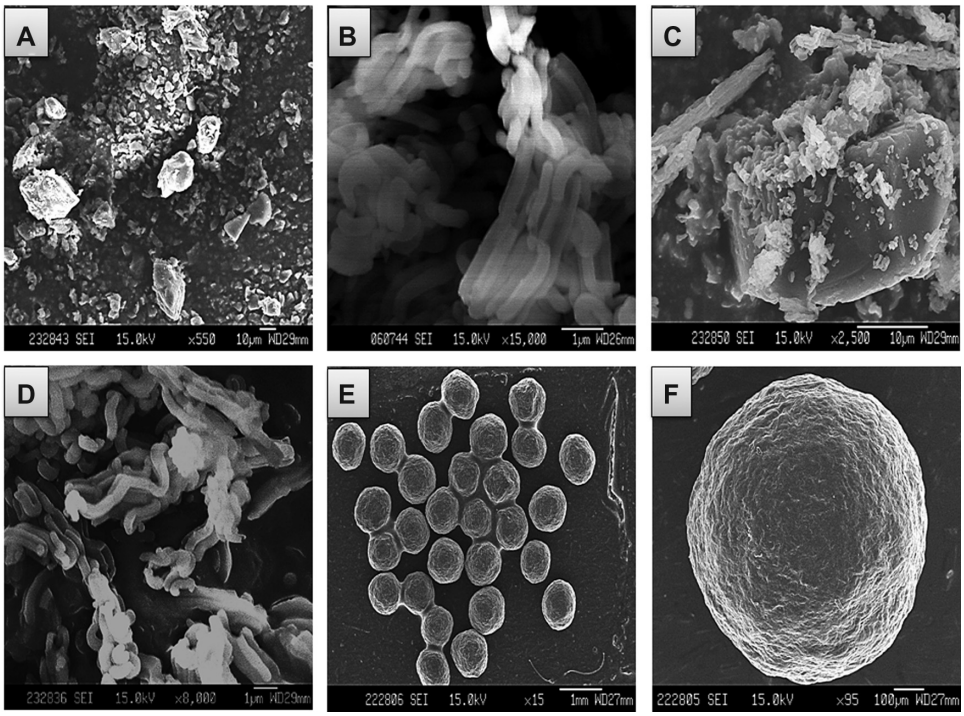

Figure 1 Scanning electron microscopic images of (**A**) crystalline carbamazepine, (**B**) SBA-15, (**C**) physical mixture of 20% carbamazepine and SBA-15, (**D**) 20% SBA-15-CBZ, (**E**) SBA-15-CBZ pellets (15×), and (**F**) SBA-15-CBZ pellet (95×).
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

Drug-loading capacity

In order to investigate the physical state of carbamazepine within SBA-15, silica with 10%, 20%, and 30% drug loading was prepared with drug to carrier ratios of 1:9, 1:4, and 1:2.3 (w/w) in the loading solution. Wide-angle x-ray diffraction patterns were recorded for the drug-loaded samples to determine whether a crystalline carbamazepine phase would exist.[32] The diffraction pattern for pure carbamazepine indicated a highly crystalline substance, with sharp distinct peaks observed at 2θ diffraction angles of 13.10, 15.31, 19.50, and 24.94 degrees (Figure 5A), as reported in our previous study.[9] Numerous peaks in the wide-angle x-ray diffraction pattern were seen for the physical mixture of carbamazepine and SBA-15, and attributed to crystalline carbamazepine (Figure 5B). However, no characteristic peaks of carbamazepine were detected in the patterns for 10% and 20% drug-loaded silica SBA-15-CBZ (Figure 5C and D), indicating that carbamazepine was almost completely converted from a crystalline

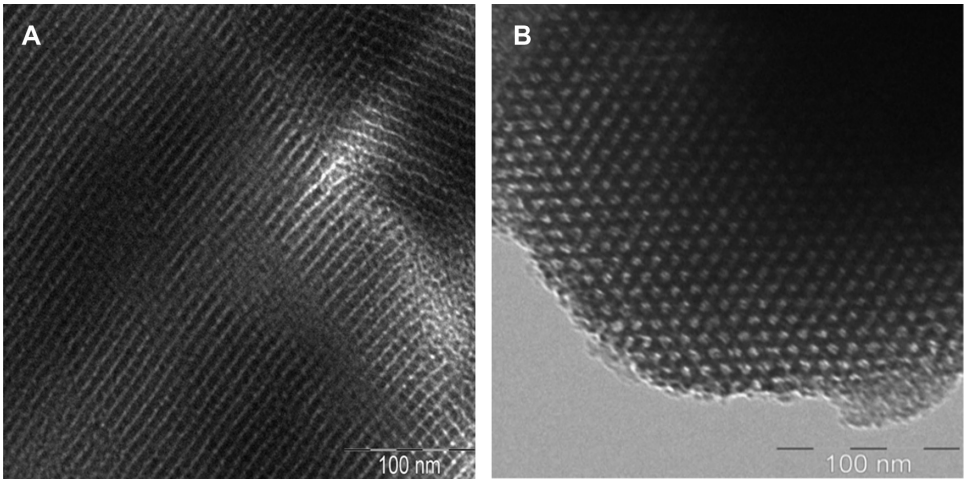

Figure 2 Transmission electron microscopic images of SBA-15 (**A**) at parallel orientation and (**B**) at vertical orientation.
Abbreviation: SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

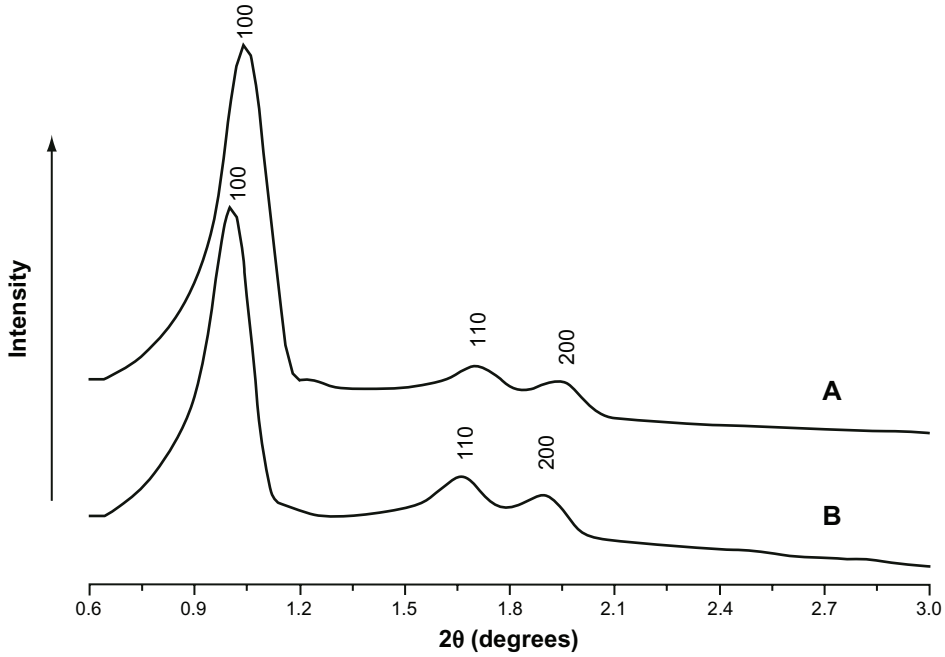

Figure 3 Small-angle x-ray diffraction patterns of (**A**) SBA-15 and (**B**) 20% SBA-15-CBZ.
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

to an amorphous state after loading into SBA-15. In addition, it was noted that some characteristic peaks of carbamazepine appeared in 30% SBA-15-CBZ (Figure 5E), indicating crystalline carbamazepine located on the surface of SBA-15 that was detected by x-ray diffraction. As a result, 20% carbamazepine in SBA-15-CBZ was determined as the maximum drug-loading capacity. Carbamazepine dispersed in an amorphous state inside pores coordinated with silanol groups could contribute to improvement in the dissolution rate.

The presence or absence of crystalline drug was also confirmed by differential scanning calorimetric analysis using the drug melting peak in the thermograms as an

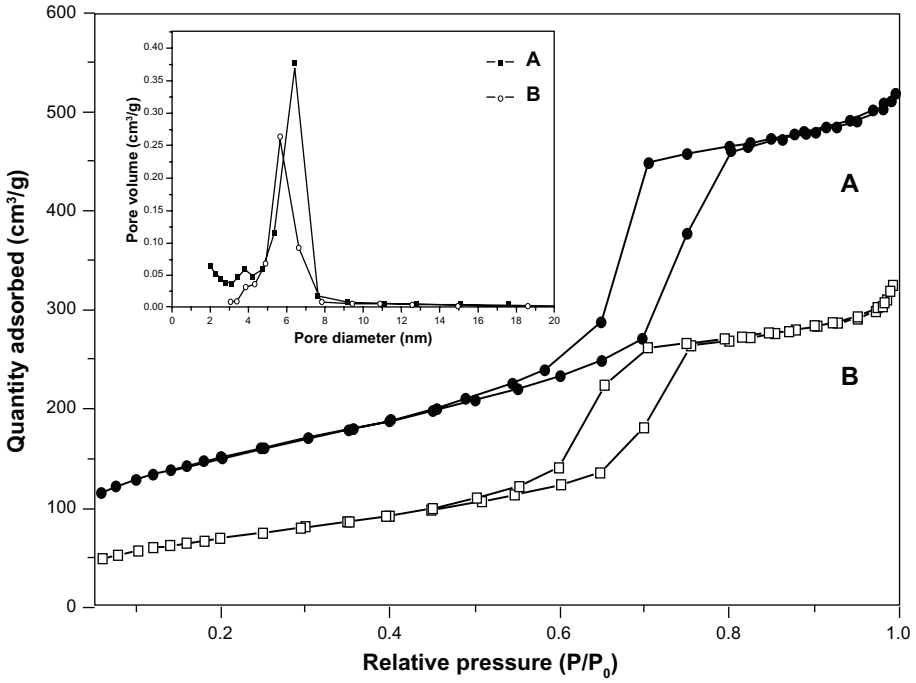

Figure 4 Nitrogen adsorption/desorption isotherms of (**A**) SBA-15 and (**B**) 20% SBA-15-CBZ. Pore size distributions of (**A**) SBA-15 and (**B**) 20% SBA-15-CBZ in the insert.
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

Table 1 Structural parameters of SBA-15 before and after loading CBZ

Sample	BET surface area (m^2/g)	Pore volume (cm^3/g)	Pore size (nm)
SBA-15	648	0.62	6.5
20% SBA-15-CBZ	325	0.39	5.6

Abbreviations: BET, Brunauer–Emmett–Teller; CBZ, carbamazepine; SBA, Santa Barbara Amorphous-15 mesoporous silica.

indication of crystalline carbamazepine.[33] The differential scanning calorimetric thermogram for crystalline carbamazepine shows a single sharp endothermic peak at 190°C[34] (Figure 6A), corresponding to its intrinsic melting point. In turn, in the thermograms for 10% and 20% SBA-15-CBZ (Figure 6C and D), no peak relative to drug melting was observed, confirming the absence of carbamazepine crystals in the drug-loaded silica. Not surprisingly, an endothermic peak appeared at 190°C in the thermogram of 30% SBA-15-CBZ (Figure 6E) due to the partial existence of crystalline carbamazepine. Both the results of wide-angle x-ray diffraction and differential scanning calorimetry demonstrated the maximum amount of drug incorporated in the SBA-15 matrices to be 20% in weight. In contrast, the melting peak of carbamazepine was observed at 190°C for a physical mixture of carbamazepine and SBA-15 (Figure 6B).

Confirmation of drug loading in SBA-15

As shown in SEM images, the morphology of 20% SBA-15-CBZ (Figure 1D) was distinctly different from that of pure carbamazepine (Figure 1A) and the corresponding physical mixture (Figure 1C). No drug particles were found on the surface or each side of the SBA-15 in SBA-15-CBZ (Figure 1D), but both carbamazepine and SBA-15 particles were observed in the physical mixture (Figure 1C). However, the morphology of 20% SBA-15-CBZ was similar to that of SBA-15 (Figure 1B).

Figure 3B shows that 20% SBA-15-CBZ has the same peaks as SBA-15, indicating that the pristine hexagonal mesoporous array of SBA-15 was conserved after inclusion of carbamazepine. However, compared with the unloaded SBA-15, the intensity of the x-ray diffractive reflection of SBA-15-CBZ was slightly weaker, which might be attributed to a change in pore density after loading drug molecules inside the channels.[35]

Adsorption of drug into mesoporous material is a surface phenomenon that is governed by adsorption properties. Therefore, surface area is expected to be the main factor determining the amount of adsorbed drug. As shown in Table 1, after drug loading, the BET surface, pore volume, and average pore diameter of 20% SBA-15-CBZ were all decreased as compared with SBA-15. As expected, incorporation of carbamazepine led to a decrease in pore diameter, pore volume, and surface area of SBA-15, indicating that carbamazepine molecules were successfully loaded inside the mesopores of SBA-15.

Physical properties of drug-loaded SBA-15

Powder characteristics were studied in order to evaluate the practicality of processing SBA-15-CBZ powder into

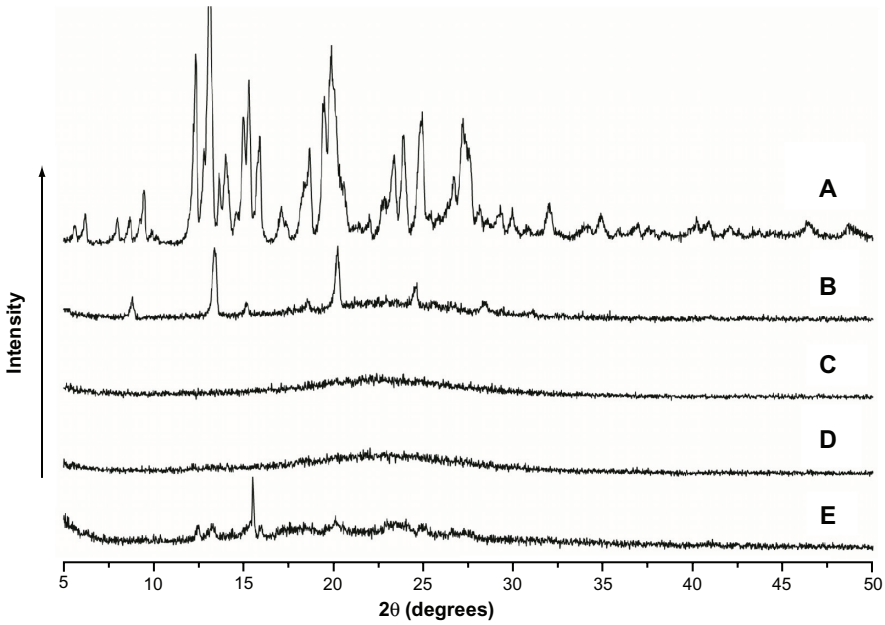

Figure 5 Wide-angle x-ray diffraction patterns of (**A**) crystalline carbamazepine, (**B**) physical mixture of 20% carbamazepine and SBA-15, (**C**) 10% SBA-15-CBZ, (**D**) 20% SBA-15-CBZ, and (**E**) 30% SBA-15-CBZ.
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

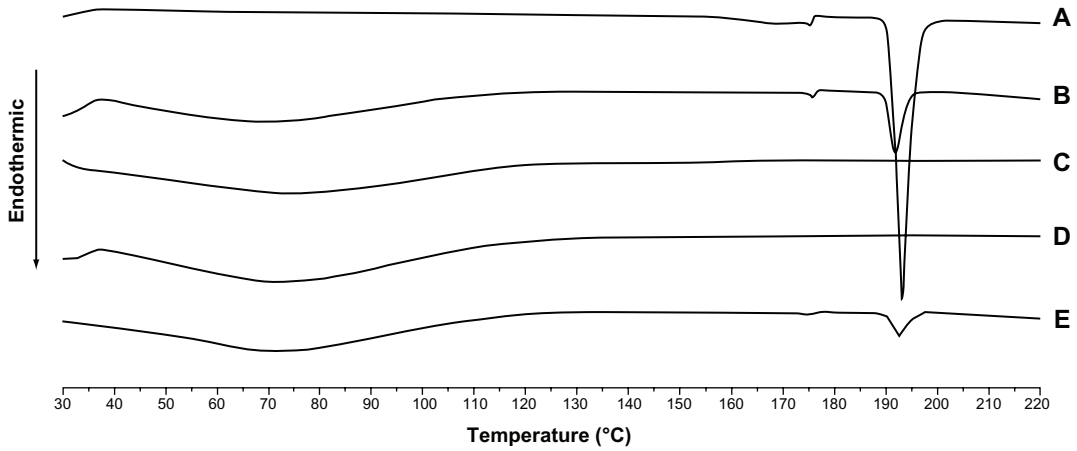

Figure 6 Thermal behavior of (**A**) pure carbamazepine, (**B**) physical mixture of 20% carbamazepine and SBA-15, (**C**) 10% SBA-15-CBZ, (**D**) 20% SBA-15-CBZ, and (**E**) 30% SBA-15-CBZ.
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

SBA-15-CBZ pellets. The angle of repose of SBA-15 and SBA-15-CBZ was nearly 50 degrees (Table 2), indicating poor flowability, and it is well known that an angle of repose ≤ 30 degrees indicates excellent flowability and an angle of repose ≤ 40 degrees indicates that the powder meets the needs of production processes in the pharmaceutical industry. After addition of some excipients (microcrystalline cellulose, sorbitol, and sodium carboxymethyl starch), the angle of repose of the mixed powder decreased to 36.9 ± 1.25 degrees. After preparation into pellets, the angle of repose of SBA-15-CBZ decreased further to 23.8 ± 0.8 degrees. The bulk and tapped densities along with the change in the angle of repose confirmed that the flowability of SBA-15-CBZ powder improved markedly when prepared as a pellet formulation with suitable excipients.

Other general properties of a powder formulation, such as wettability and contact angle, were also evaluated. A large contact angle typically means that distilled water cannot wet the surface of the powder, indicating poor wettability.[36] From the video included in the Supplementary materials section, the contact angle for pure carbamazepine can be seen to be as large as 139.2 ± 1.00 degrees, and distilled water did not permeate into the carbamazepine powder within 105 frames and 3.469 seconds, indicating the hydrophobic nature of the drug. The hydrophobicity of carbamazepine was also obvious during dissolution testing where the drug particles were floating on the surface of the dissolution medium. However, different phenomena were observed for SBA-15, 20% SBA-15-CBZ, and the corresponding physical mixture of carbamazepine and SBA-15, because distilled water permeated into the powders quickly, within 0.235–0.732 seconds. Surprisingly, even the physical mixture containing 80% of carbamazepine with SBA-15 could absorb water rapidly. From the video, it can be seen that distilled water permeated into the SBA-15-CBZ powder and the physical mixtures so quickly that the instrument could not measure the contact angle accurately. However, the SBA-15-CBZ powder and the physical mixture showed a reduced contact angle in the presence of SBA-15, suggesting that SBA-15 improved the wettability of the hydrophobic drug. Upon contact with water, an amorphous drug loaded into SBA-15 would easily dissolve and diffuse out of the pores, thus enhancing the dissolution rate.

Table 2 Powder properties of 20% SBA-15-CBZ powder and pellets (n = 3)

Sample	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (degrees)
SBA-15	0.223 ± 0.02	0.321 ± 0.02	48.9 ± 0.58
SBA-15-CBZ powder	0.210 ± 0.01	0.301 ± 0.02	49.8 ± 1.16
SBA-15-CBZ + excipients	0.325 ± 0.01	0.494 ± 0.02	36.9 ± 1.25
SBA-15-CBZ pellets	0.718 ± 0.03	0.758 ± 0.01	23.8 ± 0.8

Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

Preparation of pellets

The extrusion/spheronization process, consisting of five unit operations, ie, blending, wet massing, extrusion, spheronization, and drying, is an accepted method of producing spherical pellets with a homogeneous surface.[37] In the first stage of extrusion, a wet mass is extruded to form a strip-like extrudate, while in the second stage of spheronization, the extrudate is spheronized. SEM images (Figure 1E and F at magnitudes of 15× and 95×, respectively) show formation of spherical pellets with a smooth surface at a mean size of about 0.8 mm. The remarkable reduction in angle of repose and increased bulk and tapped densities (Table 2) demonstrate

that the flowability of the pellets is excellent and suitable for industrial production.

In vitro drug release study

In order to carry out the dissolution test in sink conditions, samples equivalent to 20 mg of carbamazepine were used, which is a very low amount in comparison with the approximately 100 mg doses used in therapy. Drug-release profiles for the SBA-15-CBZ powder and SBA-15-CBZ pellets were compared with those from the corresponding physical mixture and pure crystalline carbamazepine (Figure 7). The pellets disintegrated quickly over 30 seconds in the dissolution medium. After 30 minutes, drug release from the SBA-15-CBZ powder and SBA-15-CBZ pellets reached 88.58% and 85.83%, respectively, versus only 34.23% and 57.00% from crystalline carbamazepine and the physical mixture, respectively. The similarity factor (f_2) for the release profiles of SBA-15-CBZ powder and SBA-15-CBZ pellets was 70.61, indicating that incorporation into pellets did not change the release behavior of carbamazepine from the SBA-15 carrier.

The remarkable improvement in dissolution rate for carbamazepine through incorporating with SBA-15 is due to the following:

- the high BET specific surface area of SBA-15-CBZ improved the wettability of the hydrophobic drug
- incorporation into the pore channels of SBA-15 changed carbamazepine from a crystalline state to an amorphous state, thus improving drug solubility and dissolution rate[33]
- particle sizes for the amorphous drug incorporated in the pore channels (nanometer range) were significantly reduced as compared with micron-sized crystalline carbamazepine particles (Figure 1C and D), and it is known that a decrease in particle size down to the nanometer scale accelerates the dissolution rate.[33]

A slight increment in dissolution rate was observed for the physical mixture, probably because the hydrophilic SBA-15 decreased the hydrophobicity of carbamazepine. Overall, the improved in vitro release rate for carbamazepine upon application of SBA-15 suggests an increase in absorption and bioavailability of this poorly soluble drug.

Pharmacokinetics of SBA-15-CBZ pellets

In our previous report,[9] a standard with good linearity ($r^2 > 0.99$) had been established for carbamazepine over a concentration range of 0.05–3.0 μg/mL. By evaluating a series of method-performance characteristics, including accuracy, precision, recovery, and limit of quantification, the results of our method validation ensured that the detection method was reliable.

Generally, the bioavailability of carbamazepine, a class II drug according to the Biopharmaceutic Classification System, is limited by its poor dissolution, and an increase in dissolution rate would result in an improvement in its bioavailability.[38] Through incorporation with ordered mesoporous silica SBA-15, the dissolution rate of SBA-15-CBZ pellets was remarkably improved, so significantly increased drug bioavailability would be expected in beagle dogs.

Mean carbamazepine plasma concentration-time profiles following oral administration of the commercial carbamazepine tablets and the prepared SBA-15-CBZ pellets are compared in Figure 8. The relevant pharmacokinetic parameters, including mean peak plasma concentration (C_{max}, T_{max}), AUC, K_e, and $t_{1/2}$, are summarized in Table 3. Based on these parameters, the relative bioavailability was calculated to be

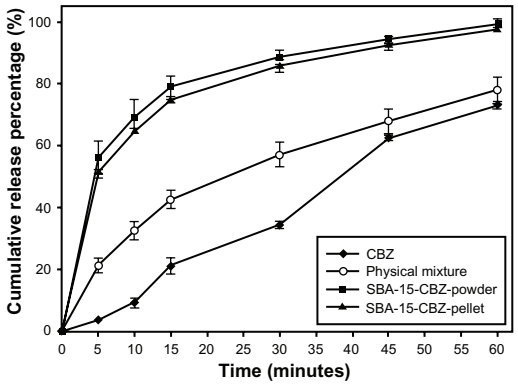

Figure 7 Release profiles of carbamazepine from crystalline carbamazepine, a physical mixture of 20% CBZ and SBA-15, and the corresponding SBA-15-CBZ powder and SBA-15-CBZ pellets in deionized water. Each datum point represents the mean ± standard deviation of three determinations.
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

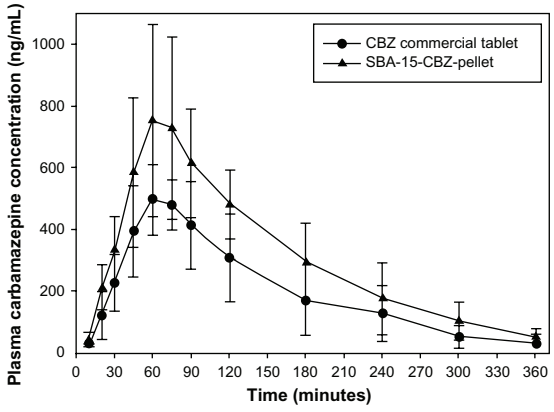

Figure 8 Mean carbamazepine plasma profiles following a single dose, crossover bioavailability study comparing SBA-15-CBZ pellets with commercial carbamazepine tablets (n = 6).
Abbreviations: CBZ, carbamazepine; SBA-15, Santa Barbara Amorphous-15 mesoporous silica.

Table 3 Pharmacokinetic parameters (mean ± SD) of carbamazepine following oral administration of a single 100 mg dose of commercial tablets and prepared SBA-15-CBZ pellets (n = 6)

PK parameter	Commercial tablet	SBA-15-CBZ pellet	*P* value
C_{max} (ng/mL)	528.83 ± 106.85	803.70 ± 296.78	0.059
T_{max} (min)	65.00 ± 15.49	65.00 ± 12.25	0.865
K_e (min^{-1})	0.01 ± 0.00	0.01 ± 0.00	0.317
$t_{1/2}$ (min)	59.24 ± 39.19	57.37 ± 24.21	0.200
$AUC_{(0\to\infty)}$ (ng·h/mL)	72580.30 ± 25283.90	113709.91 ± 17150.92	0.007

Abbreviations: $AUC_{(0\to\infty)}$, area under the plasma concentration-time curve calculated by the linear trapezoidal rule from time 0 to infinity; CBZ, carbamazepine; PK, pharmacokinetic; SBA-15, Santa Barbara Amorphous-15 mesoporous silica; SD, standard deviation; $t_{1/2}$, elimination half-life; C_{max}, peak plasma concentration; T_{max}, time to reach peak plasma concentration; K_e, slope of the logarithm concentration-time plot estimated from the elimination segment.

156.67% for SBA-15-CBZ immediate-release pellets as compared with the commercial carbamazepine tablets. By Student's *t*-test, the results show that there is a significant difference in AUC between the SBA-15-CBZ pellets and commercial tablets ($P < 0.05$), but no significant difference was observed in C_{max} ($P > 0.05$). By Mann–Whitney rank sum test, there is no significant difference to be observed in T_{max}, K_e, or $t_{1/2}$.

Overall, our in vitro and in vivo studies confirm that the immediate-release SBA-15-CBZ pellet formulation supported on ordered mesoporous silica not only increases the drug dissolution rate but also leads to a faster absorption rate. Moreover, compared with the commercial tablet, enhancement of the oral bioavailability of carbamazepine via the immediate-release pellet formulation suggests that a lower drug dose can be administered to achieve a similar clinical effect but with fewer associated adverse effects.

Conclusion

In the present study, novel immediate-release carbamazepine pellets supported by mesoporous silica SBA-15 were prepared successfully. Characterization demonstrated the outstanding features of SBA-15, including a high surface area, large pore volumes, a well defined pore size distribution, making it an excellent drug carrier. Drug-loaded SBA-15-CBZ pellets showed markedly improved dissolution compared with crystalline carbamazepine in vitro, and significantly enhanced the oral bioavailability of carbamazepine in vivo as compared with commercially available carbamazepine tablets. This study indicates that ordered mesoporous silica SBA-15 is a promising carrier which enhances the oral bioavailability of poorly water-soluble drugs. Preparing drug-loaded silica into immediate-release pellets may represent a new approach to development of rapidly acting and better absorbed oral formulations for poorly soluble drugs.

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Disclosure

The authors report no conflicts of interest in this work.

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