Porous Silica Nanoparticles as Carrier for Curcumin Delivery

by Lannie Hadisoewignyo

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Abstract. Mesoporous silica nanoparticles (MSN) with large surface areas and pore volumes show great potential as drug and gene carriers. However, there are still some challenging issues hinders their clinical application. Many types of research in the use of mesoporous silica material for drug and gene delivery involving complex and rigorous procedures. A facile and reproducible procedure to prepare combined drug carrier is required. We investigated the effect of physiochemical parameters of mesoporous silica, including structural symmetry (cubic and hexagonal), particles size (micro size: 1-2 μm and nano size: 100 -300 nm), on the solubility and release profile of curcumin. Transmission Electron Microscopy, X-Ray Powder Diffraction, and Nitrogen sorption were used to confirm the synthesis of the mesoporous silica materials. Mesoporous silica materials with different mesostructures and size have been synthesized successfully. Curcumin has anti-oxidant, anti-inflammation and anti-virus properties which are beneficial to fight various diseases such as diabetic, cancer, allergic, arthritis and Alzheimer. Curcumin has low solubility which minimizes its therapeutic effect. The use of nanoporous material to carry and release the loaded molecules is expected to enhance curcumin solubility. Mesoporous silica materials with a cubic mesostructure had a higher release profile and curcumin solubility, while mesoporous silica materials with a particle size in the range of nano meter (100-300) nm also show better release profile and solubility.

Keywords. Mesoporous silica materials, nanoparticles, curcumin, solubility and release profile.

INTRODUCTION

In recent decades, there are a large number of researches in exploring the use of mesoporous silica materials in drug and gene delivery (1, 2). Mesoporous silica materials are silica based materials with a pore size between 2 to 50 nm. Based on International Union of Pure and Applied Chemistry (IUPAC) there are three types of porous materials: microporous, mesoporous and macroporous materials. Microporous has a pore size below 2 nm, while macroporous has pore size larger than 50 nm. The very high surface area and pore volume of mesoporous silica materials create much application based on this porous material such as catalysis, chemical synthesis, enzyme immobilization and drug delivery (3). Mesoporous silica materials have also been used to improve the solubility of the drug with low bioavailability such as doxorubicin and paclitaxel (4, 5).

Curcumin has long been known for its anti-oxidant, anti-inflammation and anti-viral properties. These properties are very beneficial for medication of different illness such as diabetes, cancer, allergies, arthritis and Alzheimer's disease. Curcumin has a very low bioavailability which becomes a major concern for its application as medicine (6, 7). Mesoporous silica materials can be used to enhance curcumin solubility. Various approaches have been explored

to use mesoporous silica materials as curcumin carrier (8-10). The approaches are quite complex which make them less practical.

We can simplify the method and make the use of mesoporous silica as carrier more practical, by optimizing the physicochemical properties of mesoporous silica. These properties include surface area, pore size, and particle size. These properties can be adjusted through modification of synthesis parameters. Based on the particle size, MS can be divided into two groups: Mesoporous Silica Micro-particle with size in the range of 1 – 8 μm and Mesoporous Silica Nanoparticle with size below 300 nm (11-13). Zhang *et al*. showed that both silica particles could be used as oral drug carrier or parenteral drug carrier (14).

Herein, we report our study on the effect of physiochemical parameters of mesoporous silica, including structural symmetry (cubic and hexagonal), particles size (micro size: 1-2 μm and nano size: 100 -300 nm), on the solubility and release profile of curcumin.

MATERIALS AND METHODS

Chemicals: Triblock poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) copolymer $EO_{106}PO_{70}EO_{106}$ (Pluronic F127, MW=13400), copolymer $EO_{20}PO_{70}EO_{20}$ Pluronic 123, tetraethoxysilane (TEOS, 99%), 1,3,5-trimethylbenzene (TMB), 3-aminopropyl triethoxysilane (APTES 99%), potassium chloride (KCl), phosphate buffer tablet and Tween 80 were purchased from Aldrich. A fluorocarbon surfactant (FC-4) was purchased from Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd. All chemicals were used as received without purification.

Synthesis of Mesoporous silica material with cubic mesostructured in two different particle sizes: Micro size (M-1) and Nano size (N-1)

Micro size (M-1)

Micro size mesoporous silica materials with a cubic mesostructure were synthesized following the previous method by Fan *et al*.(15) with some modification. 1 g of pluronic F127 and 5 g of KCl were mixed in 60 mL of 2 M HCl at 20° C (*synthesis temperature*) and stirred for 30 min. Then, add 1.6 g of TMB and stirring was continued for 6 hours at synthesis temperature. 4 g of TEOS was added and continued stirring for 24 h at 20° C. The solutions after were synthesized then removed to an autoclave and heated at 130° C (*hydrothermal temperature*) for 24 h of hydrothermal treatment. The product was separated, washed and dried. The surfactant is removed by using calcination.

Nano size (N-1)

Nano size mesoporous silica materials with a cubic mesostructure were synthesized following the previous method by Ying *et al*. (13) with some modification. 0.5 g of F127 and 1.4 of FC_4 were mixed in the solutions of 60 mL of 0.02 M HCl for 24 h before 0.5 g of TMB was added and stirring continued for four h, then 3 g of TEOS was added into the solutions and was stirred for 24 h at 20°C. The solutions after were synthesized then removed to an autoclave and heated at 130° (*hydrothermal temperature*) for 24 h of hydrothermal treatment. The product was separated, washed and dried. The surfactant was removed by using calcination

Synthesis of Mesoporous silica material with channel like mesostructured in two different particle sizes: Micro size (M-2) and Nano size (N-2)

Micro size (M-2)

Micro size mesoporous silica materials with a hexagonal mesostructure were synthesized following the previous method by Zhao *et al*. (12) with some modification. 4 g of P123 was added to 100 g water and 7.87 g HCl 37%. The solution is stirred at 35°C overnight. Then, 8.53 g of TEOS was added to solution and stirring was continued for 20 hours. The solution was then placed in an oven at 130°C for 24 hours. The product was separated, washed and dried. The surfactant is removed by using calcination.

Nano size (N-2)

Nano size mesoporous silica materials with a hexagonal mesostructure were synthesized following the previous method by Yang *et al.*(13) with some modification. 0.5 g of P123 and 1.47 g of FC4 were dissolved in 80 mL 0.02 M HCl. 2 g of TEOS was added to the solution and stirred at 35°C for 20 hours. The solution was then placed in an oven at 130°C for 24 hours. The product was separated, washed and dried. The surfactant is removed by using calcination.

APTES modification

Amine functionalization of MS was conducted via grafting method. 0.6 g of mesoporous silica materials was added into 30 ml of Toluene. The mixture was stirred and heated to 70°C. 1.2 ml of APTES was added into the mixture, and the stirring was continued for 20 hours. The product was centrifuged and dried. The products were denoted **M-1A, N-1A, M-2A, and N-2A.**

Curcumin loading, *in vitro* release and solubility test

The loading, release, and solubility test were performed based on the previous method by Jambhrunkar *et al.* with slight modification (1). At first 200 mg of mesoporous silica materials, 50 mg of curcumin and 20 ml of ethanol were mixed and sonicated for 2 min using a bath sonicator. The solution was then placed in a rotary evaporation flask. The temperature of the evaporator was set at 55 °C. At this temperature, ethanol was evaporated slowly under vacuum. Finally, the dry powder was obtained. The *in vitro* release test was conducted by using a dialysis bag method. A mixture of 25 mg of curcumin loaded silica particles, and 5 ml of release solution (phosphate buffered saline (PBS) buffer + 0.8% Tween 80) was placed in the dialysis bag with 14 kDa molecular weight cutoff. The mixture was immersed in 200 ml release solution. At certain interval time, a 1ml of the solution was collected and immediately replaced with 1 ml of release solution. The sample concentration was determined by using a UV–vis spectrophotometer at 432 nm. For the solubility test, an excess of curcumin loaded MS was added into 2 ml of water. The mixture was kept under stirring for 48 h at 37 °C. A supernatant was collected and checked with a UV–vis spectrophotometer at 432 nm.

Characterization

Transmission electron microscopy (TEM) images were obtained by a JEOL 1010 electron microscope with an acceleration voltage 100 kV. Nitrogen sorption isotherms of the samples were obtained using a Quantachrome's Quadrasorb SI analyzer at 77 K. Before the measurements; the samples were degassed overnight at 110 °C in vacuum. The Brumauer-Emmett-Teller (BET) surface area was calculated using experimental points at a relative pressure of P/P0 = 0.05-0.25. The total pore volume was calculated from the N_2 amount adsorbed at the highest P/P_0 (P/P_0 = 0.99). For cubic structures, the cavity pore size and entrance pore size are determined from the adsorption and desorption branches, respectively. XRD patterns were collected on a German Bruker D8 Advanced X-Ray Diffractometer with Ni filtered Cu Kα radiation (40 kV, 30 mA).

RESULTS AND DISCUSSION

Mesoporous silica materials with different mesostructures (cubic/3D and channel like/2D) and different particle sizes (micro size and nano size) were synthesized. The materials were observed by using TEM. The results can be seen in Figure 1. Fig. 1 A and 1B show material with a cubic mesostructure, while Fig. 1C and 1D display material with a channel like mesostructure. Figure 1A and 1C represent micro size particle. The particle size was around 1- 2 μm. The size of nanoparticles was around 100 nm for N-1 and around 300 nm for N-2 (Fig. 1B and 1D). These sizes are considerably smaller compared to micro size. The TEM images indicate the formation of ordered mesostructures. The typically interconnected pores can be seen from Fig. 1A (15). Fig. 1 C shows a typical pore alignment of a long channel like structures (12). The cubic and channel like structures in nano size silica particles are also obvious (Fig. 1 B and D).

For the nitrogen sorption and XRD analysis of M-1 and N-1, TGA and FTIR analysis of amine functionalized silica, we have reported in our recently published journal (16). Both M-1 and N-1 had a hysteresis of type-H2 that belongs to cubic mesostructure. The pore sizes are similar at 10 nm. Fig. 2 shows the nitrogen sorption analysis for M-2 and N-2. Both materials had a type-H1 hysteresis loop with pore size around 6 nm. The XRD pattern of M-1 and N-1 confirm the formation of cubic structures. The XRD spectra show peaks that can be indexed as 111, 220 and 311 (1 These peaks belong to cubic symmetry. Fig. 3 shows the XRD spectra of M-2 and N-2. There are three peaks that can be indexed as 100,110 and 200. These peaks are associated with hexagonal symmetry.

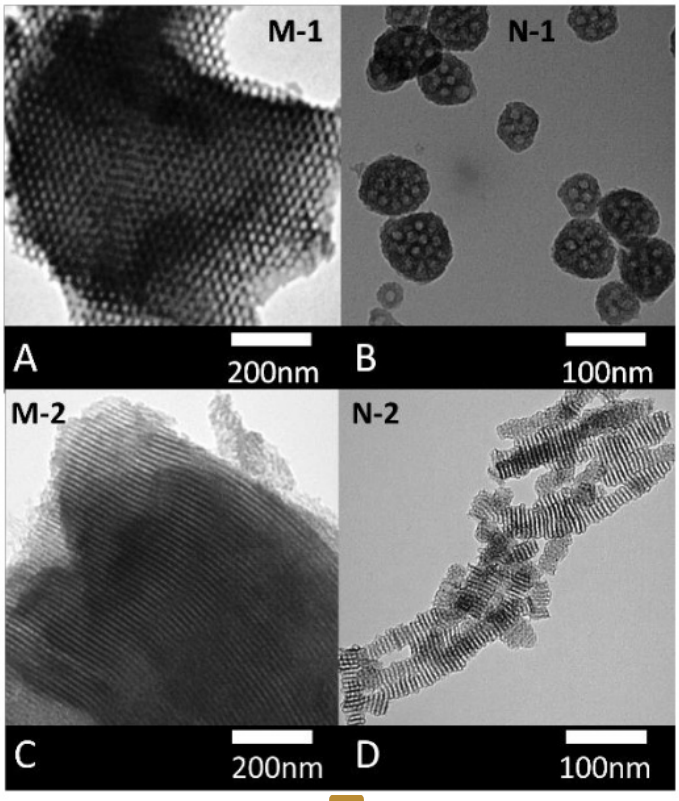

FIGURE 1. TEM images of M-1, N-1, M-2, and N-2.

Amine modified iron nanoparticles have been studied as a carrier of curcumin by Sundar *et al.*(17). However, this study showed that amine functionalized iron oxide nanoparticles had only limited controlled release effect. The system had an issue with a major release of curcumin at an early stage which was caused by the excessive diffusion of curcumin. The main difference between amine-iron oxide nanoparticles and amine-mesoporous silica materials is the presence of the porous network. The porous structure minimizes drug diffusion into the solution. The nanospaces within the porous network limits the formation of big particles (aggregates) thus omit the possibilities of excessive drug release. Many studies show the effectiveness of amine functionalization creating a controlled release profile (18, 19) from mesoporous silica materials. For this reason, the four samples (M-1, N-1, M-2, and N-2) were grafted with amine moieties from APTE

The amine functionalization materials were characterized by using a Fourier Transform Infrared Spectroscopy (FTIR) and Thermogravimetric Analysis (16). The FTIR analysis confirmed the formation of hydrogen bonding between amine groups and the phenolic hydroxyl group of curcumin. On the basis of TGA analysis, a weight loss of around 18% was found after APTES functionalization.

The loading of curcumin into silica pores was conducted by using the rotary evaporator method. Jambrunkar *et al.* showed (1) that the rotary evaporator method was far more efficient compared to the conventional "physical

mixtures". The method allows better encapsulation of curcumin which causes significant solubility. Fig. 4 shows mesoporous silica nanoparticles and curcumin loaded mesoporous silica materials.

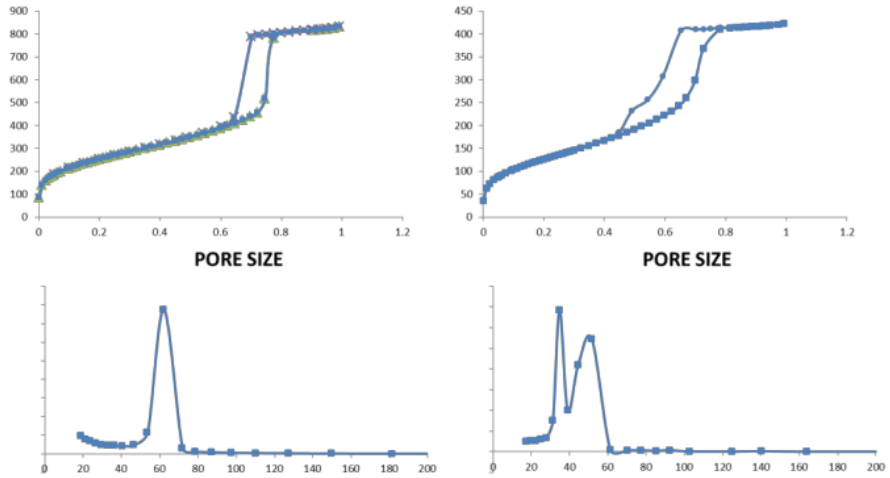

FIGURE 2. Nitrogen sorption analysis and Pore size distribution of M-2 (left) and N-2 (Right)

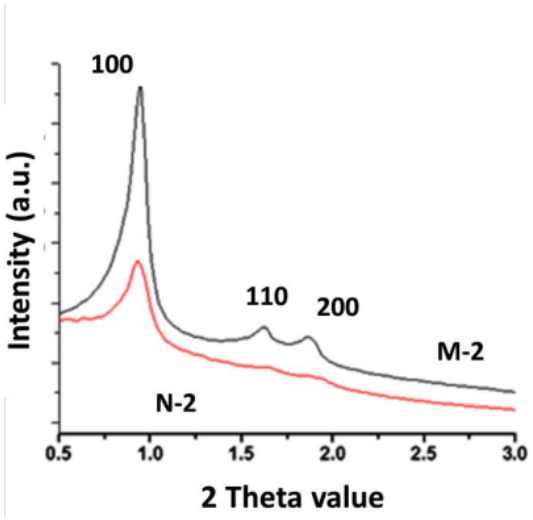

FIGURE 3. XRD spectra of M-2 and N-2.

Fig. 5 shows the *in vitro* release profile for amine functionalized samples (M-2A, N-2A) and free curcumin. Each silica samples had a prolonged release profile. The amount of curcumin release to the media was gradually increased. At the same period, curcumin release from N-2A reached 7% as compared to 5% and 4% for M-2A and free curcumin, respectively. Previously we have reported curcumin release and solubility test results of M-1A and N-1A. The curcumin release from N-1A and M-1A were at around 12% and 9% (16). In general, porous material with cubic structures had a higher release amount of curcumin. In comparison, previous studies by Bollu *et al*. (20) found the release amount of curcumin from amine functionalized MSU-2 (pore size 4.7 nm), and amine functionalized MCM-41 (1.8 nm) were around 8.8% and 1.5%.

The solubility test confirmed that the solubility of curcumin release from N-2A was higher than M-2A and free curcumin. It can be seen that the solubility of curcumin from N-2A was almost four times higher than free curcumin

(Fig. 6). Similar to the *in vitro* release tests, the solubility of curcumin loaded in N-1A and M-1A were higher compared to N-2A and M-2A. The solubility of curcumin from N-1A was ten times as high as the solubility of free curcumin(16). Both tests (release and solubility) informed the superiority of cubic structures samples against channel like structures.

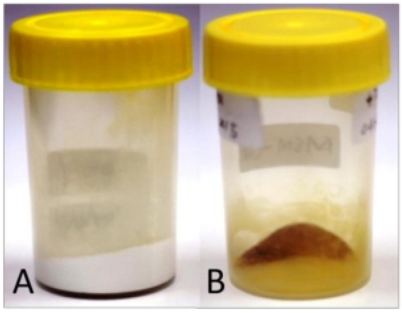

FIGURE 4. Mesoporous silica materials (left) and curcumin loaded mesoporous silica materials (right)

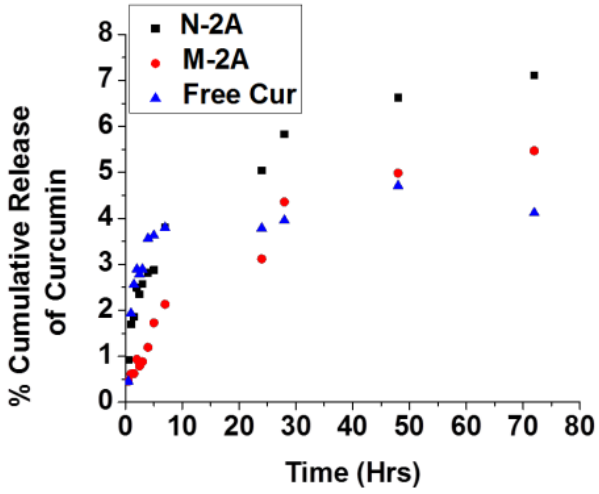

FIGURE 5. The release profile of curcumin from M-2A and N-2A.

Mesostructures (cubic or channel like) and particle size (micro or nano) affect curcumin diffusion within the pores and ultimately influence curcumin release profiles. Firstly, porous materials with three dimension interconnected pores have a better mass transfer and more resistant to pore blockage compared two dimension channel like structures. This is mainly due to its structures in which one main cavity pore is connected with many entrance pores or windows. These entrances guarantee continuing flow of cargo molecules passing through main pores, without having major limitation caused by pore blocking. The pore blocking frequently occurs due to cargo aggregates. Drug powder tends to form aggregates especially at high concentration (4).

Secondly, the particle size determines the effectiveness of mass diffusion. The nano size particles have similar structures with the micro size, but almost ten times smaller in particle size. This short channel determines the distance of drug to move from internal pores to surface. The short channel reduces the steric hindrance from silica walls and enhances the particle release.

The other important factors for interactions between drug molecules and silica particles are the surface functionality. Amine functionalization has been reported effective for a controlled release of curcumin (18, 19). Amine moieties on the silica surface improve the interactions between silica and curcumin. This strong binding

avoids the occurrence of "burst release" of curcumin. The combination of the suitable porous structures and surface functionalization of MSN-A is the underlying reason for the highest solubility of curcumin from N-1A (16).

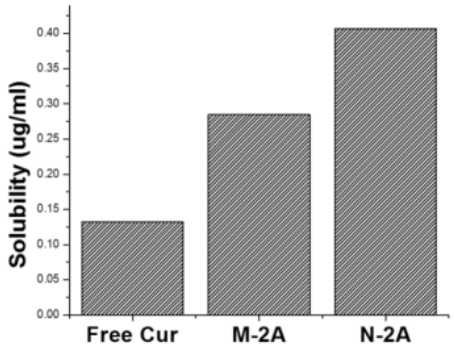

FIGURE 6. The solubility of curcumin from M-2A and N-2A.

CONCLUSION

Despite the obvious benefit from curcumin, the low solubility of these compounds hinders the maximum benefit from curcumin to cure various diseases. Porous silica material with large surface area and pore volume and also tunable pore size is highly effective to increase the solubility of many hydrophobic molecules like curcumin. In summary, a combined curcumin-amine mesoporous silica nanoparticle has been prepared by using a simple approach. This approach improved curcumin in vitro solubility. The improvement of curcumin solubility is very important to enhance its bioavailability which ultimately increases its therapeutic effects that can be very beneficial for treating various diseases such as diabetic and cancer.

ACKNOWLEDGMENTS

We acknowledge the support from Indonesian Directorate General of Higher Education for providing a research grant under the national competition scheme (HIKOM 2015). We are thankful to Prof. Michael Yu and Anand Kumar Meka, Ph.D. from Australian Institute for Bioengineering and Nanotechnology for their general help in the material characterizations including TEM, nitrogen sorption, and XRD analysis. We also thank the Australian Microscopy and Microanalysis Research Facility at the Centre for Microscopy and Microanalysis, The University of Queensland

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