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IMPACT OF TEXTURAL PROPERTIES OF DOUBLE MESOPOROUS CORE-SHELL SILICA NANOSPHERES ON DRUG LOADING AND IN VITRO RELEASE

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Mesoporous silica shell based nanoarchitectures as hollow, solid and rattle type core-mesoporous shell have recently received attentions for their versatile applications in drug delivery, and drug controlled release. Recently we have developed double mesoporous core-shell silica nanospheres by anionic surfactant. However, in this work shell thickness, BET surface area, pore volume and pore size can be tuned by varying synthetic affected accordingly. Double mesoporous core-shell nanospheres were characterized by small angle X-ray Scattering (SAXS), transmission electron microscopy (TEM), and N_2 adsorption–desorption analysis. In that regards, variation of synthetic parameters lead to increment of shell thickness and pore volume from 28 nm to 55 nm and 0.301 to 0.371 cm^3/g, respectively, which finally caused a drug encapsulation efficiency to be promoted from 10.71 to 20.8%. Furthermore, the drug encapsulation efficiency and release rate were found to be release rate tended to be more controlled with increasing the shell thickness and pore volume.

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1. Introduction

The era of controlled drug delivery systems represent a constantly growing resource of drug candidates. The application of nanotechnology to the controlled drug delivery systems is expected to have a major impact leading to the development and targeting of new types of diagnostic and therapeutic tools [1]. The choice of nanoparticle drug carrier is of great importance in the optimization of both drug loading and release profiles as well.

The mesoporous materials are one of the most important nanoparticles carrier materials, due to their large surface areas, ordered mesoporous structure, tunable pore sizes and volumes, and well-defined surface properties for modification [2].

However, these controlled release carriers are mostly formulated from polymer in which the therapeutic agent is entrapped in, adsorbed or chemically coupled onto the polymer matrix [3]. Therefore these methods, particularly the crosslinking agents, temperature and pH during the hydrogel preparation, may have side effects on the loaded drugs, hence limiting the clinical use of silicate as a base of drug delivery system preparation.

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Nanotechnology approaches where a constant dose of chemotherapy is delivered directly to cancer cells over an extended period may result in alternative or complementary therapeutic options for patients with early-stage cancer [4].

In addition, it has the potential to offer solutions to these current obstacles in cancer therapies, because of its unique size (1-100nm) and large surface to- the volume ratios [5]. Nanotechnologies may have properties of self-assembly, stability, specificity, drug encapsulation and biocompatibility as a result of the composition of their material [6].

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 [8]. Increasing the surface hydrophobicity of carrier materials was also shown to reduce the drug release rate by preventing water from entering pores [7].

Docetaxel is a clinically well established anti-mitotic form of chemotherapy used mainly for the treatment of breast, ovarian and non-small cell lung cancer [9]. It is a semi-synthetic analogue of paclitaxel and has significantly higher cytotoxic activity than paclitaxel against human ovarian, endometrial, colon and breast cancer cell lines [10-11].

The clinical efficacy of Docetaxel is limited due to its poor solubility, low selective distribution, fast elimination in vivo, etc. [12]. In addition, despite the recently reported promising outcome of docetaxel, the drug is associated with systemic toxicity that limits the dose and duration of therapy, particularly in the elderly patients [13].

Docetaxel clinical application is limited by several parameters. The drug's limited water solubility requires a specific solvent, ethanolic solution containing polysorbate 80, to facilitate its clinical use while the solvent system elicits hypersensitivity reactions that necessitate premedication, again limiting the maximum tolerable dose of the drug [14]. Another limitation is the non-specific distribution throughout the body, which contributes to drug related side effects, such as neurotoxicity, musculoskeletal toxicity and neutropenia [15]. Thus, novel formulation of Doc that is less toxic and better targets tumor site is desirable.

Ketoprofen is a slightly acidic non-steroidal anti-inflammatory drug belonging to class of propionic acid derivative. It is recommended for the treatment Rheumatic diseases and other inflammatory disorders [16]. Ketoprofen has a plasma half about 2 hours. As like other NSAIDs, ketoprofen history also reveals gastrointestinal inflammatory disorder or ulceration in stomach. Thus the development and clinical use of sustained or controlled release dosage forms of NSAIDs may have several advantages over the use of conventional formulations, e.g. reduction of the side effect, prolongation of drug action and improvement of bioavailability and patient compliance [17].

The present study aims at the formulation of hollow mesoporous core shell nanoparticles loaded with a slightly basic drug, Docetaxel, and a slightly acidic one, Ketoprofen. Also, the effect of nanoparticles' surface area, pore volume, pore diameter and shell thickness on drug loading and release will be investigated.

2. Experimental

Materials

N-lauroylsarcosine sodium (Sar-Na), 3-aminopropyltrimethoxysilane (APMS), polyvinylpyrrolidone (PVP, average Mw ~ 29,000), ammonium hydroxide (30-33 %) and tetraethoxysilane (TEOS) were purchased from Sigma-Aldrich. All chemicals were used without further purification. Ketoprofen (Ket) was generously donated from Amriya Pharmaceuticals Ind. (Alexandria, Egypt). Docetaxel (DOC) anhydrous (MWt = 807.9) was purchased from Knowshine

(Shanghai) Pharmachemicals Inc. Other chemicals were of reagent grade and were used as received.

Methodology

Synthesis

Synthesis of Dense silica core

The dense core silica particles were synthesized by the Stöber method. For a typical synthesis procedure, 0.875 ml of aqueous ammonia was added to a solution containing 18 ml of ethanol and 2.6 ml of deionized water, followed by the addition of 1.5 ml of TEOS to the solution with vigorous stirring. The resulting mixture was then heated at 30 °C for 1 h and the silica precipitate was collected by centrifugation and washed for two times with water. Synthesis parameters of the solid silica core were investigated, as shown in Table S1. The molar composition of the suspension was as follows: TEOS: EtOH: NH3: H2O = 1: 45.8: 3.3: 21.5.

Synthesis of Double mesoporous core-shell nanospheres

The double mesoporous core-shell silica (DMCSS) spheres were prepared by a two-pot synthesis route.49 The mesoporous silica shell was coated around the dense silica cores by using an anionic surfactant as a tempalet and APMS as a co-structure directing agent. To form the mesoporous silica shells, the dense SiO2 particles obtained by Stöber method above as a core were dispersed in 25 ml of H2O by ultrasonication for 10 min. For suppressing the agglomeration of the silica cores, 1.0 g/L of PVP was added with continuous stirring for 60 min. Thereafter, 0.10 ml of APMS, 1.4667 g (5 mmol) of N-lauroylsarcosine sodium (acidified solution) and 1.5 ml of TEOS were added to the reaction mixture with subsequent stirring at 50 °C for 2 h. The final solid product was recovered by centrifugation, washed with deionized water and dried in an oven at 60 °C for 12 h. Template removal was done by heat-treatment in an air stream at 550 °C for 6 h. The resulting molar ratio was TEOS: H2O: APMS: Sar-Na: HCl: PVP = 1:331.6: 0.08: 0.14: 0.06: 5×10-3.

Characterization

Transmission electron microscopy (TEM) images were obtained using a JEOL JSM-2100F electron microscope (Japan) operated at 200 kV. Powder X-ray diffraction (XRD) patterns were recorded on a PANalytical X'Pert PRO MPD (Netherlands) with Ni-filtered Cu Kα radiation (45 kV, 40 mA). Nitrogen sorption isotherms were measured at 77 K with a Quantachrome NOVA 4200 analyzer (USA). Before measurements, the samples were degassed in a vacuum at 200 °C for at least 18 h. The Brunauer-Emmett-Teller (BET) method was utilized to calculate the specific surface areas using adsorption data at the relative pressure range from 0.02 to 0.20. By using the Barrett-Joyner-Halenda (BJH) model, the pore volumes and size distributions were derived from the adsorption branches of isotherms and the total pore volumes (Vt) were estimated from the adsorbed amount at a relative pressure P/P0 of 0.995. The UV/Vis absorbance spectra were measured with a Shimadzu UV-2550 UV-Vis Spectrophotometer. Particle size distributions of the solid silica cores and DMCSS nanospheres were measured by dynamic light scattering on Malvern Nanosizer ZS instrument. 29Si magic angle spinning nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV600 (SB) spectrometer under a π/2 pulse width of 6 μs, recycle delay of 30 s, and 1500 scans. The Fourier transform infrared (FT-IR) spectra were recorded using a Bruker Vertex-80 spectrometer.

Ketoprofen and docetaxel loading efficiency and In vitro release study

Three ml of ethanol was added to 25 mg of the loaded drug in tightly-closed vials and 25 mg of core-shell mesoporous silica (CSMS) sample was added. The dispersion was stirred for 2 h while the evaporation of ethanol was prevented. The CSMS with drug loaded were separated by high-speed centrifugation at 5000 rpm and dried in a vacuum oven at 60 °C.

For the determination of entrapment efficiency, 1 ml of ethanol was added to about 10 mg of the drug-loaded CSMS in a volumetric flask and the volume was complete to 10 mL with phosphate buffer solution (ph 6.8) or 0.1 hydrochloric acid solution (pH 1.2) in case of ketoprofen

and docetaxel, respectively . The dispersion was sonicated for 15 min. Thereafter, the supernatant was filtered and the drug was analyzed spectrophotometrically at 1.0 ml filtrate was extracted with a vial, suitably diluted and then analyzed by UV/vis spectroscopy at 265 and 273 nm for ketoprofen and docetaxel, respectively. Calibration curves for ketoprofen and docetaxel were created by plotting absorbance versus drug concentration between 0 and 50 μg/ml. Drug EE% was calculated using the following formula:

$$E\% = \frac{\text{actual amount of drug in nanoparticles}}{\text{theoretical amount of drug in nanoparticles}} \times 100$$

For the in vitro release studies, Approximately 20 mg of KBU/CSMS and 10 mg Dox/ CSMS nanoparticles were suspended in 10 mL phosphate buffered (pH 6.8) in 50 ml capped test tubes. The tubes were kept under constant shaking (100 rpm) in a shaking water bath (SW22 – JULABO, Germany) at 37°C. At predetermined time intervals, 5 ml was withdrawn from each tube and replaced with 5 ml of fresh buffer (kept at the same temperature). The drug concentration was determined spectrophotometrically in the withdrawn samples at mentioned previously.

3. Results and discussion

Loading ketoprofen and docetaxel into double mesoporous core-shell silica spheres

Optimization of drug loading parameters on entrapment efficiency and release rate

To determine the proper loading conditions of ketoprofen into double mesoporous core-shell silica spheres, the effects of DMCSS: drug ratio, mixing method, washing solvent type and stirring time have been investigated. Fig. 1A shows effect of DMCSS: drug ratio on the in vitro drug release. It is clear that there is no significant difference between different DMCSS: drug ratio except 4:1 ratio that show slower release rate. The drug entrapment efficiency was 42, 33 and 46 % for DMCSS: drug ratio 1:1, 1:2, and 1:4, respectively. Stirring method, whether stirring or shaking, was also studied to elaborate its impact on ketoprofen release rate. Fig. 1B shows that both stirring and shaking has similar release rate up to 3 h that differ at higher release time. The drug loading capacity was 3.2 and 1.6 % for stirring and shaking mixing method, respectively. The type of washing solvent plays an important role in controlling the release rate of ketoprofen from the mesochannels of double mesoporous core-shell silica spheres. When no washing solvent was used, the ketoprofen was rapidly released from the mesopores. Spheres that were washed with water and ethanol prior to centrifugation show a closer release rate but the simulated body fluid buffer solution has the slowest release rate amongst the used solvents. The calculated entrapment efficiencies were 46, 8, 3, and 10% for no washing, buffer washing, ethanol washing and water washing, respectively. Finally, mixing time was also significant in controlling the release of ketoprofen from DMCSS. Long loading time has no impact in controlling the in vitro release of ketoprofen. On the other hand, 2h reaction time resulted in slow release of the loaded ketoprofen. The loading efficiencies were 8% and 53 % for spheres prepared by 2h and 24h stirring, respectively. Based on the previous results, loading parameter that will be considered during drug loading should accomplish reasonable entrapment efficiency together with slow release rate.

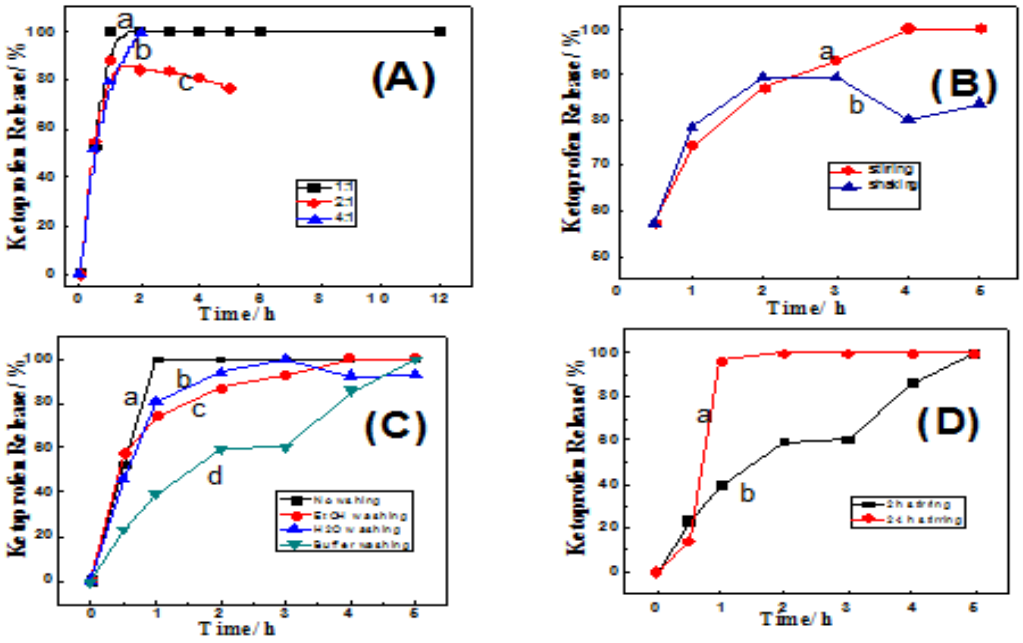

Fig. 1. Impact of loading parameters on ketoprofen loading rate (A) effect of DMCSS: drug ratio (a) 1:1, (b) 1:2, and (c) 1:4., (B) effect of mixing method (a) stirring and (b) shaking., (C) effect of washing solvent (a) no washing solvent, (b) water, (c) ethanol, and (d) buffer., and (D) effect of stirring time (a) 24h and (b) 2h.

The enhanced loading efficiency of docetaxel (the slightly basic drug) might be due to its affinity toward the negatively charged surface of the silica nanoparticles. This finding was also observed by Prokopowicz and Przyjazny [18], who showed that doxorubicin has a great affinity for the negatively charged surface of the silica nanoparticles, which enhances loading into the MSNP pores.

Impact of textural properties of double mesoporous core-shell silica nanospheres on entrapment efficiency and release rate of ketoprofen and docetaxel

To evaluate the impact of textural properties of double mesoporous core-shell silica nanospheres on the entrapment efficiency and release rate, the synthesis conditions of DMCSS spheres were fine tuned. On other words, the synthesis parameters were tuned so as to provide control over their textural properties as BET, pore volume, shell thickness and pore diameter. The fine tuning of synthesis conditions was done by controlling the concentration of ammonia, water, and TEOS in the first and also TEOS concentration in the second step.

Effect of BET on drug loading and in vitro release profiles of Ket and DOC

Fine control over ammonia concentration in the first step (Stöber method) and TEOS concentration in the second step resulted in formation of double mesoporous core-shell silica spheres with different BET surface area as shown in Table 1. Samples that have constant pore volume, shell thickness and total pore volume were selected for the study, while the only variable is BET specific surface area. The drug entrapment efficiency for ketoprofen and docetaxel are also presented in Table 2. BET surface area has no pronounceable effect on ketoprofen storage capacity with low entrapment efficiency around 4%. On the other hand, the anti cancer drug (docetaxel) has comparative high storage capacity 29-68 %. Double mesoporous core-shell silica spheres with different specific surface area are shown in Fig. 2. It is clear that core-shell structure was obtained with mesoporous shell character.

Table 1: double mesoporous core-shell silica spheres with variable BET surface area by tuning synthesis conditions

No	Amm g/ml	TEOS-1st g/ml	Water g/ml	Core nm	TEOS-2nd g/ml	Shell nm	BET cm^2/g	Vp $cc.g^{-1}$	Rp nm	%EE	
										Ket	DOC
81	0.029	0.046	0.068	285	0.021	30	129.8	0.269	3.91	3.24	68.07
80	0.031	0.046	0.068	280	0.021	31	137.9	0.222	3.90	4.70	29.15
82	0.026	0.046	0.068	250	0.019	33	148.9	0.432	3.88	4.74	45.44

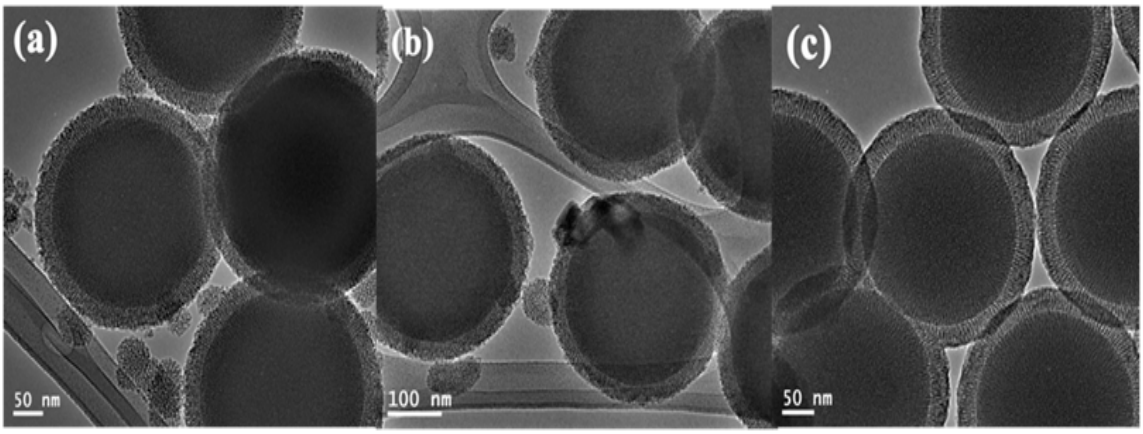

Fig. 2. TEM images of double mesoporous core-shell silica nanospheres with different BET surface area of (a) 129.8, (b) 137.9, and (c) 148.9 cm^2/g.

The in *vitro* release profiles of ketoprofen and docetaxel from their-loaded double mesoporous core-shell silica spheres are shown in Fig. 3. The release rate of ketoprofen was not significantly affected by changing the specific surface area of double mesoporous core-shell silica spheres. The release of ketoprofen has burst release within first 3h, thereafter, a slow release was observed until the complete drug release within 6 hours. On the other hand, the release of DOC from its-loaded spheres did not exhibit the burst release observed with Ket. In addition, the drug showed a very slow release rate compared to ketoprofen, i.e., only about 22% of the loaded DOC was released from the tested spheres formulations along the release period (one week or 168 hr). DMCSS with low surface area showed fast release rather than the high BET surface area. This finding is according to Li et al. [19], who observed an inverse relationship between the in vitro release of Brilliant Blue and the BET of porous hollow silica nanoparticles. Nevertheless, no correlation could be observed between the entrapment efficiency and specific surface area. It could be also attributed to that at high surface area; more drug will be contained with DMCSS spheres. The slow release of docetaxel compared to ketoprofen can be attributed to that docetaxel is a slightly basic drug while ketoprofen is an acidic one. Therefore when the release experiment is done at SPF buffer solution (pH 7.4), it is expected that the slightly basic drug, docetaxel, has slower dissolution and release from mesochannels compared to slightly acidic one, ketoprofen [20].

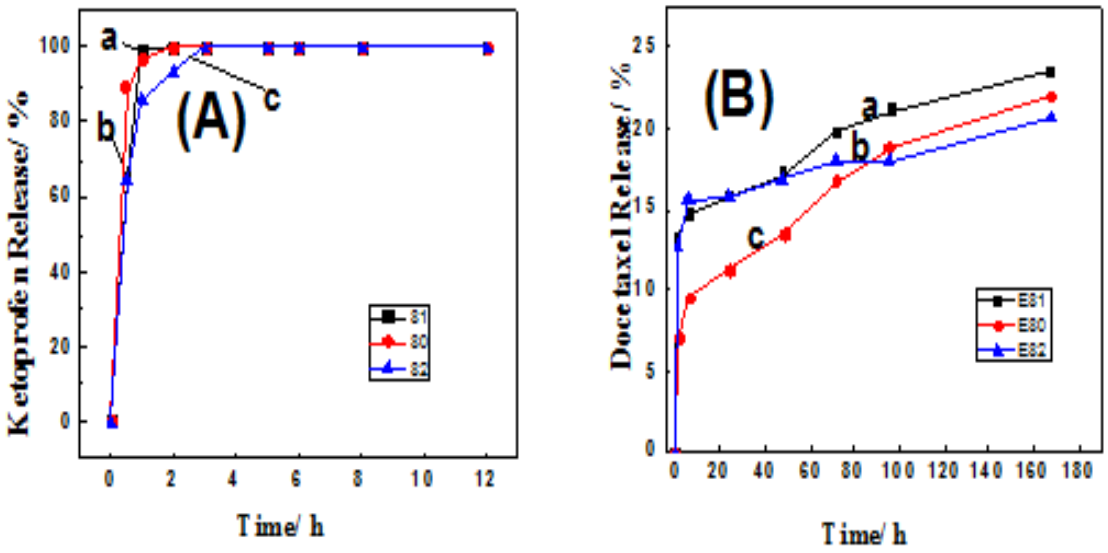

Fig. 3. In-vitro release study of (A) ketoprofen and (B) docetaxel loaded within double mesoporous core-shell silica spheres with different BET surface area of (a) 129.8, (b) 137.9, and (c) 148.9 cm^2/g.

Effect of shell thickness and total pore volume

Fine control of TEOS concentration in the second step caused the variation of shell thickness and relevant total pore volume of double mesoporous core-shell silica spheres. TEM images of DMCSS with different shell thickness and pore volume are shown in Fig. 4. TEM images indicate that the shell thickness increased with tuning synthesis parameters. Moreover, all the images show that core-shell structure can be clearly seen with monodispersity in particle size. Table 2 shows the synthesis parameters of DMCSS, corresponding shell thickness and total pore volume at constant surface area and pore size. Ketoprofen entrapment efficiency was enhanced with the concomitant increase in shell thickness and total pore volume. This could be attributed to the increase of shell thickness and total pore volume that allows more space for storage of ketoprofen molecules. In contrast, docetaxel entrapment efficiency decreased with increasing both shell thickness (from 28 nm to 45 nm) and total pore volume. Such unexpected behavior of docetaxel is difficult to be explained and need to study the reason behind. The high molecular weight of Docetaxel (807.9) may hinder its entrapment into the double mesoporous core shell spheres, compared to the low molecular weight of Ketoprofen (254.3). In addition, the nature of the loaded drugs (acidic Ketoprofen and basic docetaxel) may play a role in controlling their loading to DMCSS.

Table 2: double mesoporous core-shell silica spheres with variable shell thickness and total pore volume by tuning synthesis conditions.

No	Amm g/ml	TEOS-1st g/ml	Water g/ml	Core nm	TEOS-2nd g/ml	Shell nm	BET cm^2/g	Vp $cc.g^{-1}$	Rp nm	%EE	
										Ket	DOC
76	0.025	0.046	0.087	190	0.021	28	137.4	0.301	5	10.71	35.02
78	0.026	0.046	0.087	260	0.022	45	149.8	0.343	4.99	18.15	16.86
79	0.026	0.046	0.087	360	0.019	55	136.5	0.371	4.97	20.80	17.93

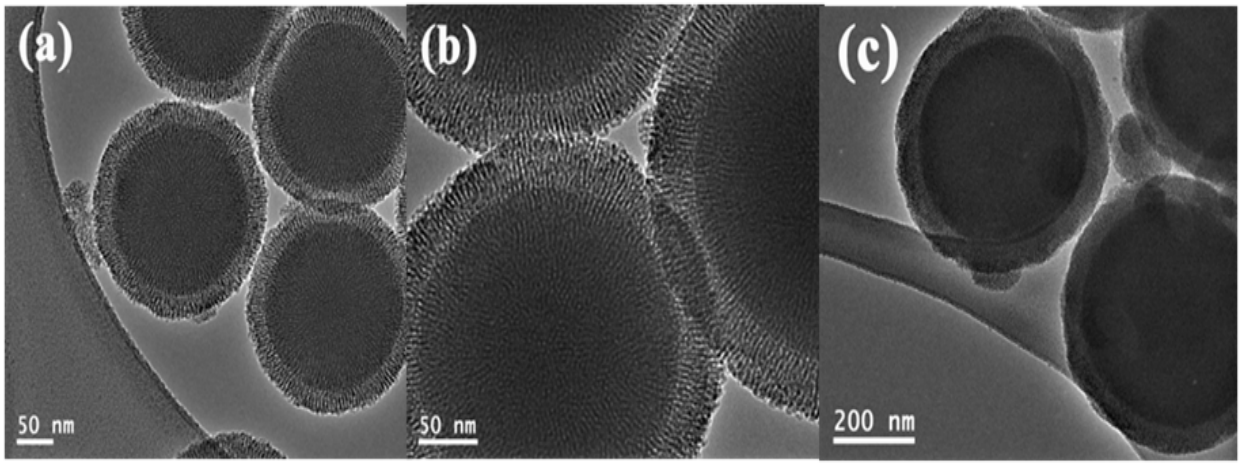

Fig. 4. TEM images of double mesoporous core-shell silica nanospheres with different shell thickness (a) 28 nm, (b) 45 nm, (c) 55 nm and total pore volume of (a) 0.301, (b) 0.343, and (c) 0.371 cc/g.

The in-*vitro* release patterns of ketoprofen and docetaxel at different shell thickness and pore volume are shown in Fig. 5. Ksetoprofen showed more slow release with increasing shell thickness and total pore volume. In addition, the burst release was reduced to about 40% in case of formulae 78 and 79. It is expected that higher pore volume would allow more space for ketoprofen to be contained. On the other hand, docetaxel showed different release profiles. First, the initial burst was prompted with increasing the shell thickness and total pore volume of DMCSS spheres. Second, by increasing the shell thickness and pore volume, the release rate became faster.

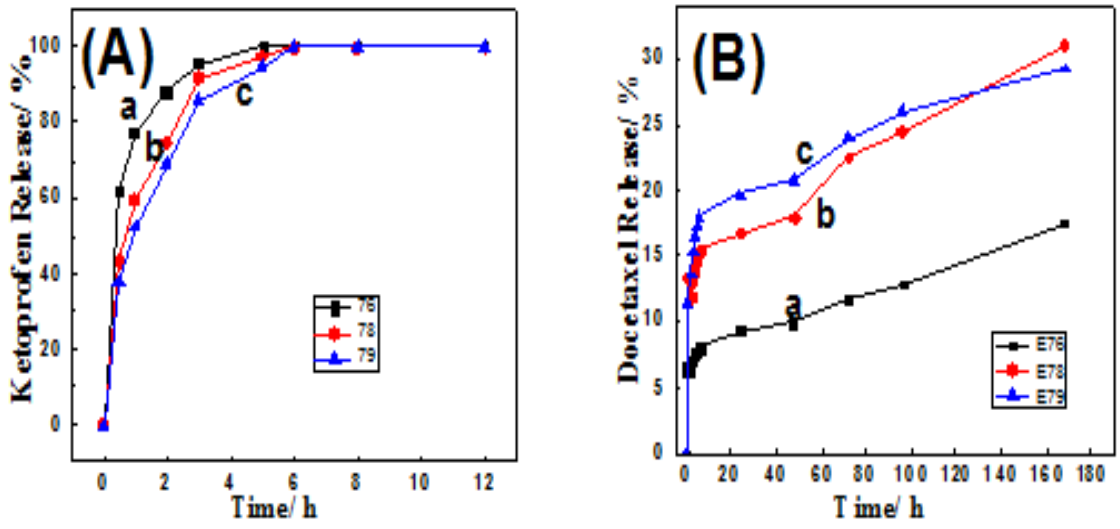

Fig. 5. In-vitro release study of (A) ketoprofen and (B) docetaxel loaded within double mesoporous core-shell silica spheres with different shell thickness (a) 28 nm, (b) 45 nm, (c) 55 nm and total pore volume of (a) 0.301, (b) 0.343, and (c) 0.371 cc/g.

Effect of pore diameter

To tune the pore size of mesoporous silica shell, the concentration of ammonia and water during first step (Stöber method) should be controlled. Control over these concentrations allowed the formation of mesoporous shell with pore diameter of 3.9 and 5 nm, table 3. Conventional mesoporous shell prepared by cationic surfactant (CTAB) provides pore size around 2.2 nm. Therefore anionic surfactant provides mesopores that is as double size as cationic surfactant pore size. Moreover, this increase in pore size will affect total pore volume. However, the entrapment

efficiencies of both Ket and Doc were increased with increasing the pore size of mesoporous silica shell of DMCSS. TEM images for DMCSS with variable pore size are presented in Fig. 6. No pronounceable difference can be observed in the TEM images. However, monodisperse core-shell silica spheres were obtained regardless the pore size of the mesoporous shell.

Table 3: double mesoporous core-shell silica spheres with variable pore size by tuning synthesis conditions

No	Amm g/ml	TEOS-1st g/ml	Water g/ml	Core nm	TEOS-2nd g/ml	Shell Nm	BET cm^2/g	Vp $cc.g^{-1}$	Rp nm	%EE	
										Ket	DOC
76	0.025	0.046	0.087	190	0.021	28	137.4	0.301	5	10.71	35.02
80	0.031	0.046	0.068	280	0.021	31	137.9	0.222	3.90	4.70	29.15

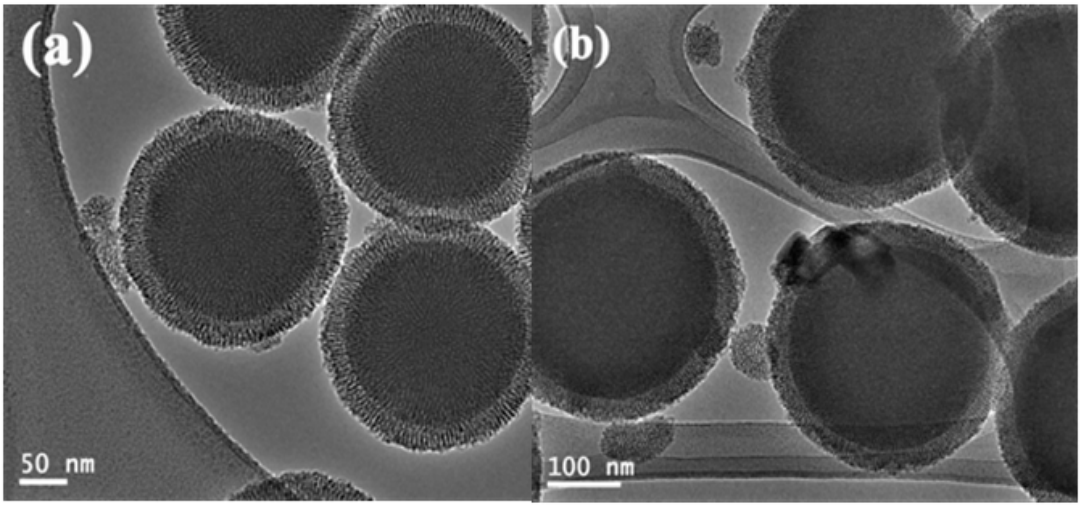

Fig. 6. TEM images of double mesoporous core-shell silica nanospheres with different pore volume of (a) 5 nm, and (b) 3.9 nm.

The in-*vitro* release data of ketoprofen and docetaxel at different pore size of double mesoporous core-shell silica spheres are displayed in Fig. 7. A slight decrease in the release rate of ketoprofen was observed in case of increasing pore size of silica shell. However, the loaded ketoprofen has been completely released from the mesochannels of all nanospheres after 4 h, Fig. 7 A. On the other hand, docetaxel showed a reduction of the initial burst by decreasing pore volume from 5 (E76) to 3.9 nm (E 80), Fig. 7 B. However the drug exhibited a higher release rate from by increasing pore size, formula E 80.

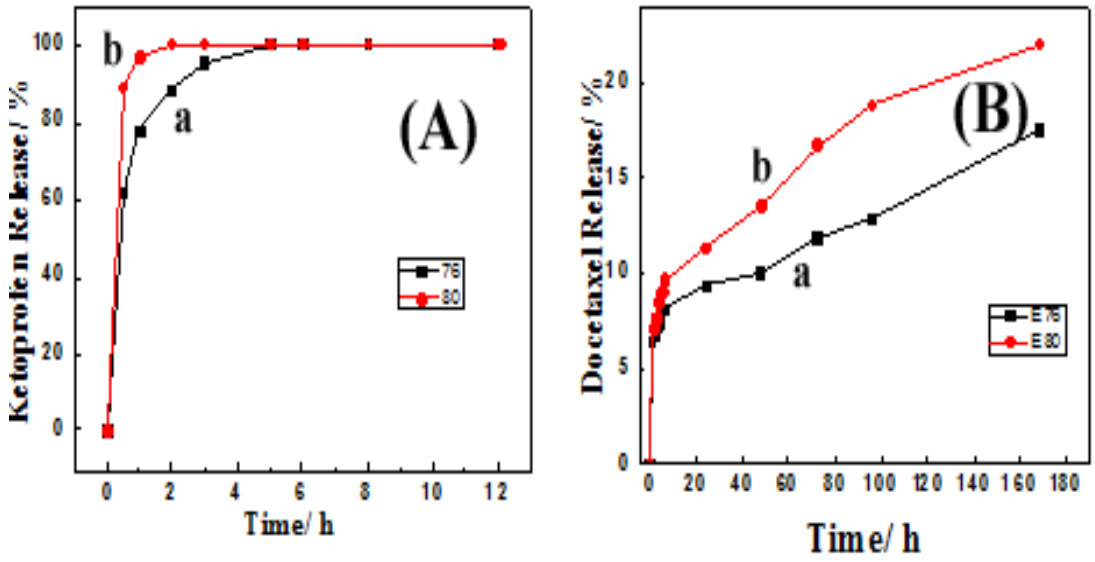

Fig. 7. In-vitro release study of (A) ketoprofen and (B) docetaxel loaded within double mesoporous core-shell silica spheres with different with different pore volume of (a) 5 nm, and (b) 3.9 nm.

Grafting ketoprofen into amino-functionalized double mesoporous core-shell silica spheres

The previous drug loading experiments were based on adsorption techniques. In adsorption technique, drug can be linked for instance through weak hydrogen bonds between its carboxylic acid group and the silanol groups inside the mesochannels. Another way for enhancing loading the drug molecules into mesochannels is the grafting technique [21]. In the grafting techniques, pore's wall will be functionalized for instance with amino group that form stronger ionic bonds between drug's carboxylate group and ammonium groups. Silica pores surface functionalization with amino group can be accomplished through surfactant removal by acid-extraction method or grafting with amino group containing organic silane.

It is worth noting that most of the amino groups would reside on the surface of the mesochannels because the formation of the mesostructured silica follows the $S^-N^+I^-$ pathway in this study. All these results clearly indicate that after surfactant extraction, the surface amino-functionalized DMCSS were obtained.

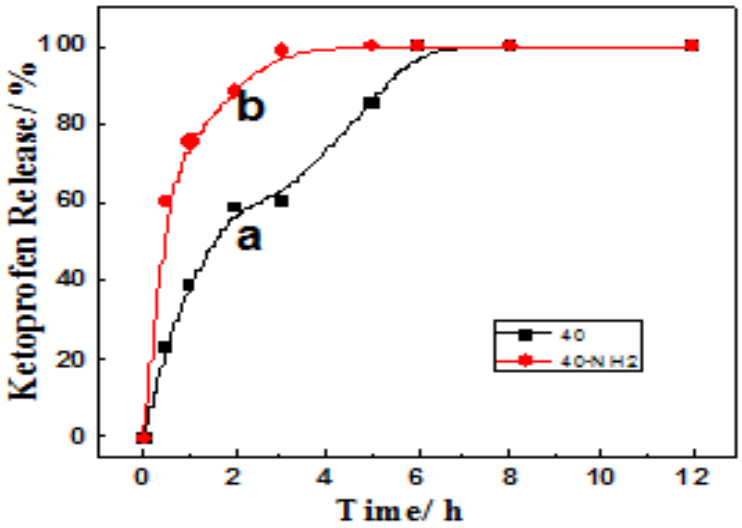

Fig. 8. In-vitro release study of ketoprofen loaded within double mesoporous core-shell silica spheres with (a) no fictionalization, and (b) amino-functionlization.

Table 4: Textural properties for double mesoporous core-shell silica spheres with and without amino-functionaliztion

No.	Shell nm	BET cm^2/g	Vp $cc.g^{-1}$	Rp Nm	%EE
DMCSS	41	274.4	0.268	3.6	8.59
DMCSS-NH_2	41	240.2	0.248	3.6	3.06

To prepare the amino-functionalized mesoporous silica (denoted as DMCSS-NH_2), the surfactant was removed by an acid extraction in the acetonitrile. The textural properties of DMCSS and amino-functionlized DMCSS are presented in Table 4. It can be seen that the prepared DMCSS-NH_2 spheres have surface area and total pore lower than that obtained with DMCSS which can be attributed to the fact that surfactant is not fully removed by acid extraction compared to heat treatment method. On the other hand, ketoprofen entrapment efficiency in case of DMCSS-NH_2 is about half of that obtained in case of DMCSS spheres. This unexpected low entrapment efficiency of DMCSS-NH_2 indicates that despite the presence of NH_2 group remained inside the mesochannels but the grafting interaction between the amino groups and ketoprofen molecules did not take place. The absence of such interaction can be attributed to that acid extraction for surfactant molecules resulted in acid ionization of NH2 resulting in the formation of negative charges that in turn cause some repulsion with negatively charged acidic ketoprofen molecules and leads to failing of grafting ketoprofen inside amino-functionalized mesochannels. Expectedly, in-*vitro* release of ketoprofen from DMCSS-NH_2 was found much faster than the corresponding DMCSS. The in-vitro release rate of DMCSS and DMCSS-NH_2 are shown in Fig. 8.

4. Conclusion

It could be concluded from the study that, in the synsthesis of double mesoporous core-shell nanospheres, surface area (BET), pore volume and pore size can be tuned by varying synthetic parameters. Controlling the synthetic parameters lead to increasing shell thickness and

pore volume, that was followed by enhanced encapsulation efficiency of the tested drugs; Ketoprofen and docetaxel.

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References

[1] Y. Liu, H. Miyoshi, M. Nakamura. Colloids Surf. B: Biointerfaces **58**, 180–187 (2007).
[2] Y. Zhu, I. Shi, W. Shen, H. Chen, X. Dong, M. Ruan M. Nanotechnology **16**, 2633–2638 (2005).
[3] V. Labhasetwar.. Pharm. News **4**, 28–31 (1997).
[4] O. C. Farokhzad, J. Cheng, B. A. Teply, I. Sherifi, I. Jon, P. W. Kantoff. Proc. Nat. Acad. Sci. USA (PNAS) **103**, 6315–6320 (2006).
[5] S. E. McNeil. J. Leuko. Biol. **78**, 585-594 (2005).
[6] P. Grodzinski, M. Silver, L. K. Molnar. Expert Rev. Mol. Diagn. **6**, 307-318 (2006).
[7] M. Vallet-Regí, F. Balas, D. Arcos. Angew. Chem. Int. Edit. **46**, 7548–7558 (2007).
[8] D. H. Hwang, D. Lee, H. Lee, D. Choe, S. H. Lee, K. Lee. Kor. J. Chem. Eng. **27**, 1087-1092 (2010).
[9] S. J. Clarke, L. P. Rivory. Clin. Pharmacokinet. **36**, 99-114 (1999).
[10] M. C. Bissery. Eur. J. Cancer **31**, S1-S6 (1995).
[11] U. Vanhoefer, S. Cao, A. Harstrick, S. Seeber, Y. M. Rustum. Ann. Oncol. **8**, 1221-1228 (1997).
[12] D. Zheng, X. Li, H. Xu, X. Lu, Y. Hu, W. Fan. Acta Biochim. Biophys. Sin. **41**, 578-587 (2009).
[13] V. Sanna, A. M. Roggio, A. M. Posadino, A. Cossu, S. Marceddu, A. Mariani et al. Nanoscale Res. Lett. **6**, 260-269 (2011).
[14] J. Baker, J. Ajani, F. Scotte, D. Winther, M. Martin, M. S. Aapro, G. Von Minckwitz. Eur. J. Oncol. Nurs. **12**, 253-268 (2008).
[15] M. Markman. Supp. Care Cancer **11**, 144-147 (2003).
[16] S. C. Sweetman, Martindale 'The complete drug reference' 34th edition; Pharmaceutical press 51.2 (2005).
[17] J. S. Rowe, J. E. Carless. J. Pham. Phamarcol. **33**, 561-464 (1981).
[18] M. Prokopowicz, A. Przyjazny. J. Microencaps. **24**, 694-713 (2007).
[19] Z-Z. Li, L-X. Wen, L. Shao, J-F. Chen. J. Control. Release **98**, 245– 254 (2004).
[20] Y. Chen, H. Chen, S. Zhang, F. Chen, L, Zhang, J. Zhang et al. Adv. Funct. Mater. **21**, 270–278 (2011).
[21] B. J. Trewyn, I. I. Slowing, S. Giri, H-T. Chen, V. S-Y. Lin. Acc. Chem. Res. **40**, 846–853 (2007).