OPTIMIZATION OF NANO- AND SUBMICRO-SCALED MESOPOROUS SILICA PARTICLES WITH TUNABLE SURFACE PROPERTIES FOR ADVANCED DRUG DELIVERY

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Abstract

The Si-based submicro- and nanoparticles were prepared using a template sol-gel approach in the presence of cationic surfactants with different length of alkyl chains and alkaline catalysts that allowed a modulation of pore size and surface area of particles in the synthesis mixture to obtain materials with a wide range of size (25-1000 nm) and variable textural characteristics. Mesoporous materials were prepared with the aim to optimize and adapt different synthetic routs for further use of SP as reservoirs for carrying and advanced delivery of therapeutics.

Keywords: Mesoporous silica particles synthesis, Stöber method, drug delivery

1. INTRODUCTION

Si-based nano- and submicron-sized carriers have gained a substantial and deserved place among another perspective nanotherapeutic materials due to the wide range of advantages: uniform and tunable particle size and morphology, high surface area and large pore volume, efficient encapsulation and high loading capacity, high thermal and chemical stability compared to other polymer-based carriers, good biocompatibility, high loading capacity and protection of the desired guest molecules, zero premature release before reaching its target, efficient cellular uptake, effective endosomal escape, controllable rate of release to achieve an effective local concentration, cell and tissue targeting [1-3].

Although various synthetic strategies to produce silica particles (SP) with different sizes, shapes, pore structures, and other characteristics have already appeared among the major achievements in the field of material chemistry over the last decades, an implementation of the advanced Si-based carriers into industrial pharmaceutical area is hampered. It is caused by the fact that they cannot withstand an assessment of the benefit obtained from the possible practical implementation of these systems and the availability of obtaining such sophisticated systems in comparison with the already approved pharmaceuticals. In addition, their synthesis procedure is complex and time consuming, resulting in that the advanced Si-based carriers are still on the scientific research level [4-7].

To overcome these drawbacks, in the present work basic sol-gel method based on Stöber approach that utilizes a reaction of simultaneous hydrolysis and condensation of silica source and organotrialkoxysilanes at the high alkaline pH for large-scale SP preparation with sufficient outcome was implemented. While comparing with previously reported results, reaction conditions were improved with the aim to reach homogenous particles of smaller size and higher total surface area that is of crucial importance for small organic molecules loading.

2. EXPERIMENTAL PART

Silica particles were synthesized from the following raw materials: tetraethyl orthosilicate (TEOS) as the silica source, cetyltrimethylammonium bromide (CTAB), dodecyltrymethylammonium bromide (DTAB), tetradecyltrymethylammonium bromide (TTAB) as a template and/or surfactant, L-lysine, N', N', N', N'-tetrakis (2-hydroxypropyl)ethylenediamine (THEEDA), imidazole, 1-(2-pyridyl) piperazine (PP), ammonia (28% water solution), diethanolamine (DEA), triethanolamine (TEA) as the catalysts, all chemicals were obtained from Sigma Aldrich, Czech Republic.

The solvents - acetone, acetic acid (99.5% purity), anhydrous ethanol (99.7%), diethyl ether (99.5% purity) ethanol, methanol, sodium hydroxide, potassium phosphate, hydrochloric acid (HCl) (36-38%), aqueous ammonia (25), chloroform (95% purity), - were bought from IPL Lukes, Uhersky Brod, Czech Republic, chloroform (HPLC grade) and acetic acid (HPLC grade) were purchased from Chromspec, Brno, Czech Republic. Distilled water was used in all our experiments. All the chemicals were used as received without further purification.

The morphology and particle size of the prepared carriers were observed by using a field emission scanning electron microscope (Scanning electron microscope Nova NanoSEM 450 (FEI, The Netherlands). Specific surface area and pore volume were determined from the low-temperature adsorption data (automatic sorption high precision surface area and pore size analyzer BELSORP-mini II, USA) by volumetric gas adsorption method. The samples were degassed at 230C (Si carrier) for 6 hours to remove all water vapor.

3. RESULTS AND DISCUSSION

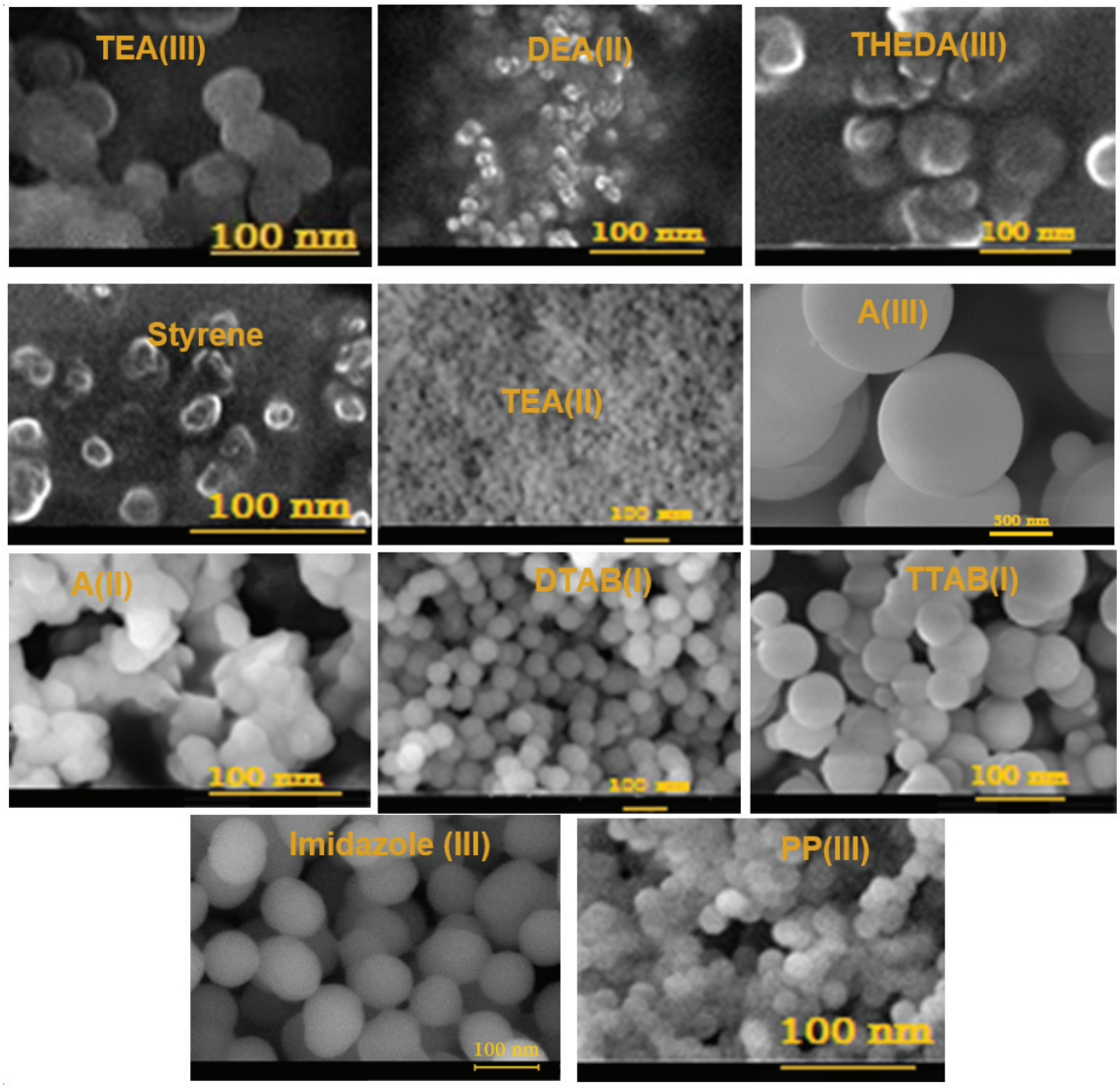

Figure 1 SEM micrographs of obtained SP

Recent advances in silica particles synthesis have enabled the precise control of its morphology, size, and composition which afford its applications in drug delivery. However, a general method for the large-scale

synthesis of SP with uniform size distribution in the range convenient for its biomedical application and different surface properties still remains challenging. For drugs that are mostly small organic molecules delivery, the size of more than 100 nm is preferable to avoid detrimental effect on living tissues. On the other hand, SP bigger than 300 but less than 1000 nm are strictly appreciated in of cosmetology and topical (transdermal, transbuccal) drug delivery.

Stöber approach is a very convenient for SP preparation due to its simplicity. Herein, a general method was developed to synthesize a group of uniform spherical silica particles with uniform size both less than 300 nm and between 300 and 10000 nm through three different approaches by utilizing a number of additive agents to adjust hydrolysis and condensation process:

1) Template-based sol-gel method with different cationic quaternary ammonium salts (Dodecyltrimethylammonium bromide (DTAB_A), trimethyl tetradecylammonium bromide (TTAB_A), hexadecyltrimethylammonium bromide ((CTAB_A)) as organic templates and NH4OH as alkaline catalyst.
2) Template-free sol-gel method with secondary (diethanolamine (DEA), tertiary (triethanolamine (TEA) alkanolamines and NH_4OH (A) as catalysts
3) Template-based sol-gel method with small organic amines (N, N, N, N-tetrakis(2-hydroxyethyl)ethylenediamine (CTAB_THEEDA) or N- heterocyclic compounds (imidazole (CTAB_Imidazole), 1-(2-pyridyl)piperazine (CTAB_PP) or secondary (diethanolamine (CTAB_DEA), tertiary (triethanolamine (CTAB_TEA) alkanolamines and NH4OH (CTAB_A) as alkaline catalysts.

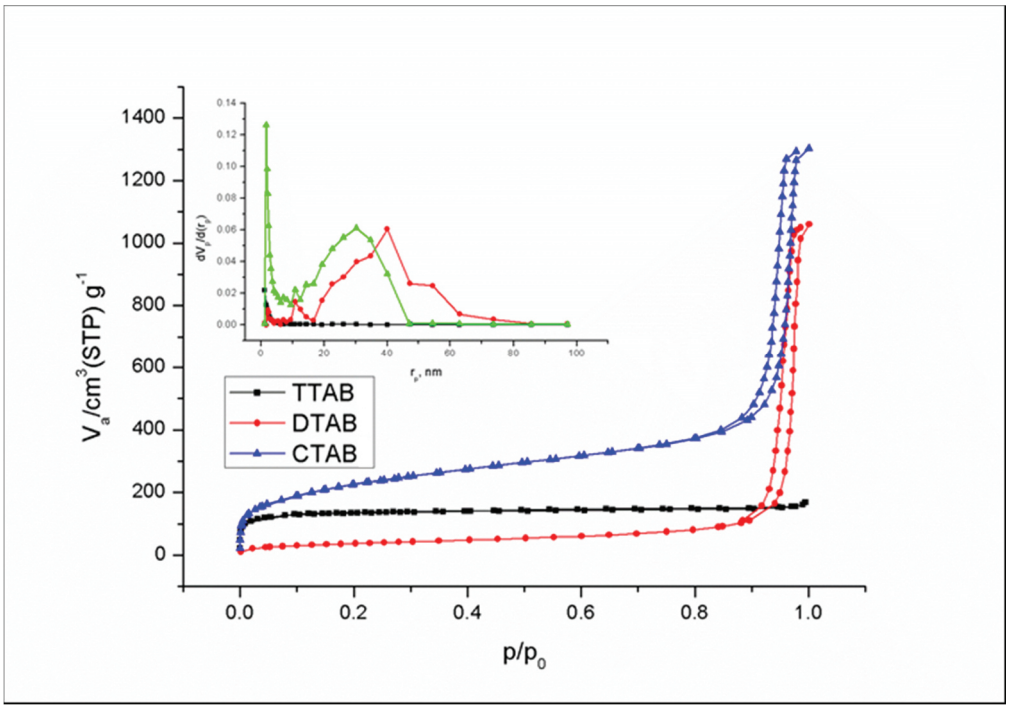

Figure 2 Nitrogen adsorption/desorption isotherms of the SP obtained by the Method I. An insert represents pore size distribution of SP

Table 1 and **Figure 2** represent textural properties of SP obtained by the Method I and their nitrogen adsorption/desorption isotherms**.** As can be seen, size of particles as well as their surface properties were influenced by different cationic quaternary ammonium salts as surfactants, resulting in a decrease of particles size with a decrease of alkyl chain length [4]. Due to precise control of the reaction compounds and appropriate solvents size of particles was significantly decreased comparing with previously described results [4].

Table 1 Textural properties of SP obtained by the Method I. The upper number express data obtained in our syntheses and the lower range shows the reference results [4, 6]

Samples	Pore diameter, MPD, nm	Total surface area, a_s, m^2g^{-1}	Total pore volume, TPV, cm3g-1
TTAB-THEDA	9	738	1.66
	2	545	0.83
CTAB-THEDA	10	855	2.22
	2	431	0.49
DTAB-THEDA	2	497	0.25
	2	527	0.77

Table 2 Textural properties of SP obtained by the Method II. The upper number express data obtained in our syntheses and the lower shows the reference results [4, 6]

Samples	Pore diameter, MPD, nm	Total surface area, a_s, m^2g^{-1}	Total pore volume, TPV, cm^3g^{-1}	Size, nm
DEA	20.1	557	2.80	75
	24.2	41	0.43	100
TEA	15.9	673	2.67	88
	3.5	140	0.66	180
A	3.6	521	0.47	200
	3.1	30	0.36	230

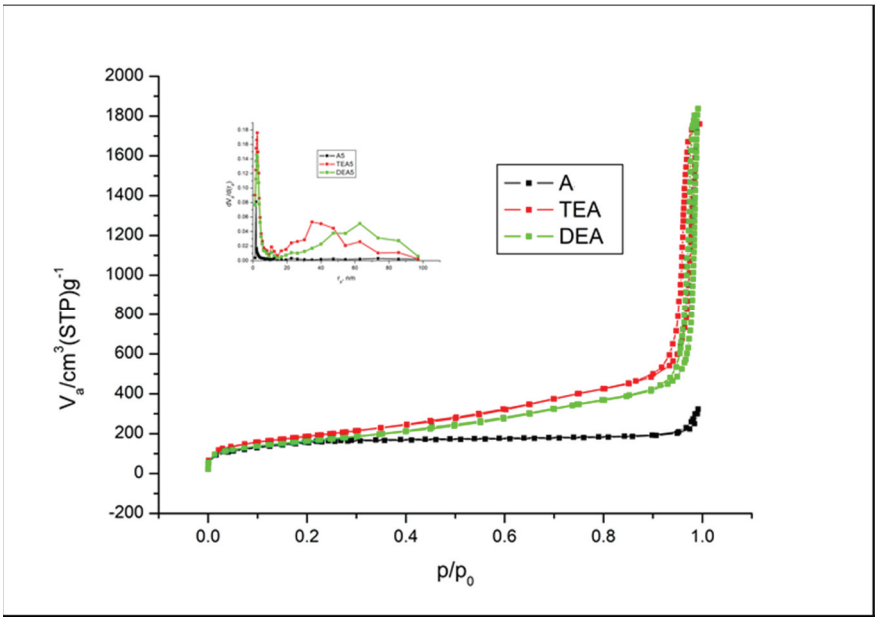

Figure 3 Nitrogen adsorption/desorption isotherms of the SP obtained by the Method II. An insert represents pore size distribution of SP

Although surfactants play an important role in SP formation also as a template source, there are reports about SP formation without any surfactants. Alkaline catalysts have major influence on the hydrolysis and subsequent condensation of Si source resulting in variable size and porosity of obtained particles while Stöber

approach is applying. As can be seen from **Figure 1**, cationic quaternary ammonium salts removal resulted in formation of well-shaped homogenous spherical particles. Nevertheless, they are different in size and surface properties (**Table 2**), with increase of the particle size and decrease of the size of pores in a range TEA, DEA, A, which could be due to their different alkalinity (pK_a(TEA)=9.2, pK_a(DEA)=8.9, pK_a(A)=7.8). For instance, addition of the equal amount of NH_4OH to the reaction will result in drastic change of pH comparing with triethanolamine and fast hydrolysis and further condensation of the Si species resulting in bigger particles with smaller pores. Comparing with template-based method, template-free approach enables preparation of SP with relatively large diametres (**Tables 2, 3, Figures 2, 3**).

Table 3 Textural properties of SP obtained by the Method III. The upper number express data obtained in our syntheses and the lower range shows the reference results [4, 6]

Samples	Pore diameter, MPD, nm	Total surface area, a_s, m^2g^{-1}	Total pore volume, TPV, cm^3g^{-1}	Size, nm
CTAB-THEEDA	9.0	738.2	1.66	30 100
CTAB-Imidazol	6.6	483.5	0.8	70 79
CTAB-PP	2.9	1019	0.76	100
CTAB-DEA	10.0	1005	2.68	169
CTAB-TEA	7.8	104	2.03	25
CTAB-A	2.7	765	0.52	640

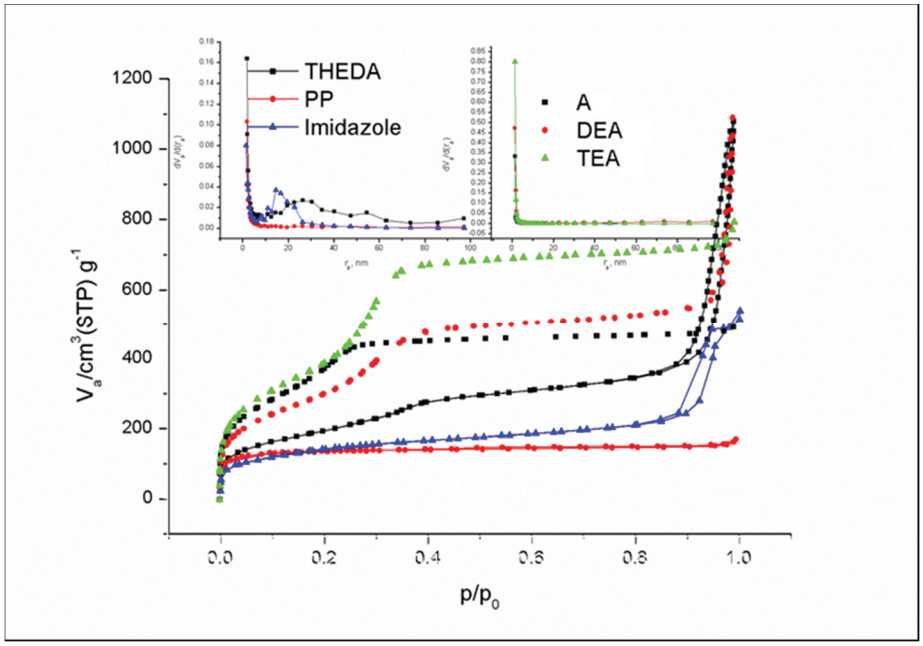

Figure 4 Nitrogen adsorption/desorption isotherms of the SP obtained by the Method III. An insert represents pore size distribution of SP

Small organic amines or nitrogen-containing heterocyclic compounds due to their alkaline properties are suitable to be used as catalysts during SP synthesis. Precise control of reaction conditions and adjustment concentration of catalysts resulted in particles less than 100 nm that is less than was reported before.

Necessity to apply different synthetic routs that allowed preparation of the particles with overlapping size and surface properties is based on further evaluation of biocompatibility and the assumption that synthetic routs might have impact on SP toxicity.

CONCLUSIONS

Uniform and monodisperse mesoporous silica particles have been prepared successfully in a moderate condition using a template-free or template-based sol-gel approach in the presence of various additive agents as catalysts. Formation of SP occurred through self-assembly of silica species with/without cationic surfactants (DTAB, TTAB, CTAB) with following hydrolysis and condensation of Si precursor in solution. The particle size (from 25 nm to 1000 nm) as well as texture properties of SP including pore diameter and surface area can be controlled by adding suitable agents (small organic amines, N- heterocyclic compounds, secondary and tertiary alkanolamines) that affect the hydrolysis and condensation of Si species. Yield of reactions is achieved not less than 77% of the initial Si concentration. Current investigation of optimization of the large-scale room-temperature synthesis of mesoporous silica particles with tunable surface properties allowed us to hypothesize that those materials could serve as active substituents of current fillers in pharmaceutical formulations for advanced delivery of therapeutics.

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