Multiscale Colloidal Assembly of Silica Nanoparticles into Microspheres with Tunable Mesopores

Citation for published version (APA):
Fijneman, A. J., Högbom, J., Palmlöf, M., de With, G., Persson, M., & Friedrich, H. (2020). Multiscale Colloidal Assembly of Silica Nanoparticles into Microspheres with Tunable Mesopores. Advanced Functional Materials, 30(27), [2002725]. https://doi.org/10.1002/adfm.202002725

DOI:
10.1002/adfm.202002725

Document status and date:
Published: 01/07/2020

Document Version:
Accepted manuscript including changes made at the peer-review stage

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

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Download date: 12. Jun. 2022
Colloidal assembly of silica (nano)particles is a powerful method to design functional materials across multiple length scales. Although this method has enabled the fabrication of a wide range of silica-based materials, attempts to design and synthesize porous materials with a high level of tuneability and control over pore dimensions have remained relatively unsuccessful. Here, we report the colloidal assembly of mesoporous silica microspheres (MSMs) using a set of discrete, silica sol nanoparticles as building blocks within the confinement of a water-in-oil emulsion system. By studying the independent manipulation of different assembly parameters during the sol-gel process, we outline a design strategy to synthesize MSMs with excellent reproducibility and independent control over pore size and overall porosity, which does not require additional ageing or post-treatment steps to reach pore sizes as large as 50 nm. The strategy as presented here can provide the necessary tools for the microstructural design of the next generation of tailor-made silica microspheres for use in separation applications and beyond.
1. Introduction
Mesoporous silica microspheres (MSMs) have long been used as the stationary phase in high performance liquid chromatography (HPLC) for the separation and purification of molecules due to their versatile and tunable properties.\[^{1,2}\] Silica microspheres have good mechanical strength, high thermal and chemical stability and they can easily be modified with many different surface-active groups.\[^{3}\] However, not all types of molecules can be separated efficiently with the MSMs that are commercially available today. An important yet notoriously difficult class of molecules to separate are biomacromolecules such as peptides and antibodies, mainly due to their large size and diverse properties.\[^{4,5}\] Separation of this class of molecules depends upon the availability of MSMs that can be specifically tuned to the size and shape of the macromolecule of interest, thus, requiring new technologically scalable approaches for manufacturing.

To this end, we focus on creating MSMs with highly tunable porosity characteristics, i.e., pore size, pore volume and surface area, by sol-gel emulsion chemistry that is both versatile, easily reproducible and scalable. The sol-gel reaction, i.e., the transformation of a suspension of silica nanoparticles (sols) into gels, can easily be triggered upon change of pH, temperature or ionic strength.\[^{6,7}\] Typical precursor solutions include tetraethyl orthosilicate (TEOS)\[^{8–13}\] or sodium silicate (waterglass)\[^{14,15}\], but in this work discrete silica nanoparticles are used as building blocks to form the gel. There are several benefits of using well-defined nanoparticles to form a gel. Gels made from particles do not need additional template molecules to guide the formation of a porous network, have great flexibility in terms of microstructural design and process scalability and most importantly, allow a high level of control over the reaction.

To attain MSMs, the sol-gel reaction is confined within emulsion droplets. Emulsions are ideal systems to synthesize particles with a well-defined shape and an internal composition defined by the confined nanoparticle building blocks. There are various approaches to use emulsions to create higher order assemblies which can be roughly divided into methods that are dominated by: 1) the
external confinement and process conditions, i.e., evaporation-driven colloidal assembly\textsuperscript{[16–24]}, and 2) by the interaction forces between the nanoparticles, i.e., entropy-driven or gelation-driven colloidal assembly\textsuperscript{[25–29]}. In evaporation-driven assembly the nanoparticles are forced into close contact by gradually removing the carrier liquid until the (nano)particles assemble into larger assemblies, which are sometimes called supraparticles, supracolloids or supraballs.\textsuperscript{[22,24]} In gelation-driven assembly the nanoparticles are assembled into supraparticles by screening of the nanoparticle surface charges and by increasing the frequency of nanoparticle-nanoparticle collisions. The main difference between the two methods is that evaporation-driven assembly usually leads to densely packed supraparticles, whereas gelation-driven assembly usually leads to porous supraparticles such as MSMs.

Due to current limitations in tuning the porosity characteristics during MSM synthesis, in many conventionally applied industrially relevant processes the as-gelled silica microspheres have to undergo one or multiple ageing or post-treatment steps.\textsuperscript{[30,31]} A common ageing step that is frequently used is Ostwald ripening. In Ostwald ripening the gelled microspheres are immersed in a liquid in which they are soluble and are heated to high temperatures for prolonged times in a sealed reactor. Material on the surface is then slowly dissolved and precipitated into regions of negative curvature, i.e., in between the necks between the nanoparticles and inside small pores. The result is a decrease in surface area and an increase in average pore size.\textsuperscript{[32,33]} This is a time consuming process and although successful, it also leads to significantly wider pore size distributions as compared to MSMs that have been directly synthesized.\textsuperscript{[34]}

In this work, we describe how to create MSMs with a highly tunable porosity characteristics using a limited set of discrete silica sol particles as building blocks confined within water-in-oil (W/O) emulsion droplets. We show that, by the choice of silica sol and mixtures thereof, careful manipulation of the gelation rate of the sol nanoparticles and the processing conditions, we can vary
the surface area, pore volume and average pore diameter of the MSMs over a much wider range than has been shown so far in literature. The presented approach does not require additional post-treatment steps such as ageing and is expected to ensure availability of MSMs for efficient separation of a wide variety of biomacromolecules in future.

2 Results and Discussion
2.1. General Mechanisms of Microsphere Formation
Perfectly spherical MSMs were synthesized via a protocol inspired by literature.\textsuperscript{[10,35–37]} In general, a W/O emulsion was prepared by adding a colloidal silica sol to an external oil phase containing emulsifier under rapid stirring. After emulsification the gelation of the sol particles into MSMs was induced by either shrinking the emulsion droplets (dewatering) under vacuum conditions (evaporation-driven assembly) or by minimizing the water uptake of the oil phase and greatly increasing the reaction temperature in combination with high concentrations of salt (gelation-driven assembly). In this work water uptake is defined as the increase in storage capacity of the oil phase as a function of temperature above its saturation point at room temperature. After gelation the microspheres were removed from the oil phase via filtration and were subsequently dried and calcined to remove any organic residue still present in the MSMs. More detailed information can be found in the materials and methods section and Supplementary Information section 1.

We hypothesize that MSM formation is dependent on two main parameters: (1) the rate of sol particle gelation $r_{gel}$ modulated by the sol particles used as building blocks and by the reaction conditions and (2) the rate of emulsion droplet shrinkage $r_{shrink}$ due to dewatering of the droplets. A proposed mechanism is shown in Figure 1.
Figure 1. Proposed mechanism for the formation of MSMs. (a) cryoTEM image of an aqueous colloidal silica sol. (b) Schematic representation of the pore structure that is formed inside the emulsion droplet during the gelation process. The microsphere porosity can be modulated by the gelation rate of the particles $r_{gel}$ and the shrinkage rate of the droplets $r_{shrink}$. (c) SEM image of a MSM after calcination.

At the start of the process, the colloidal silica particles are randomly distributed throughout the emulsion droplets. Then, depending on how quickly the sol particles within these droplets gel and how quickly water is transported out of the droplets, the resulting microspheres can either become very porous, very dense or anywhere in between. If the gelation of the sol particles occurs significantly faster than the shrinking of the droplets ($r_{gel} \gg r_{shrink}$), i.e., when there is no shrinkage of the droplets and the assembly process is completely gelation-driven, the resulting microspheres can be very porous with a porosity as high as high as $\phi_{p} = 0.70$ and in theory as high as the total fraction of water in the sol. If the droplet shrinkage rate is significantly faster than the gelation rate ($r_{gel} \ll r_{shrink}$), i.e., evaporation-driven assembly, the sol particles are compressed into dense spheres, with a porosity as low as $\phi_{p} = 0.30$. Microsphere porosities in-between these two values are achieved by a careful balance between the gelation rate and droplet shrinkage rate. Regardless of the chosen pathway, all microspheres are perfectly spherical. SEM images of the surface of the microspheres reveal that the microspheres are completely assembled of smaller sol particles (Figure S4). A representative size distribution of the spheres is show in Figure S5.

2.2. Synthesis of Mesoporous Silica Microspheres
Our design strategy is based on three parameters that will be addressed below: (1) choice of the silica building blocks, (2) control over the water uptake of the oil phase, and (3) control over the sol
particle mobility and stickiness. Full control over all three parameters is key to tailor the porosity characteristics of the resulting MSMs for different applications (e.g. separation of macromolecules).

2.2.1. Choice of the colloidal silica building blocks

The first design principle obtained in this work, which will be employed throughout the following sections, is the choice of the colloidal silica sol as building blocks. The choice of the sol has a direct influence on the internal morphology (size of the pores and struts) as well as the external morphology (specific surface area) of the microspheres. To build a large variety of microspheres, five colloidal silica sols with different particle sizes varying from 4 nm up to 100 nm were used (see also Supplementary Information section 2.1-2.3 and Figure S1-S2). With these five sols microspheres were synthesized with specific surface areas (SSA) varying from 38 m²/g up to 560 m²/g, and, most notably, independent of the size or the porosity of the microspheres (Figure S6).

All sols used in this work are negatively charged and are highly stable, i.e., they do not settle or aggregate spontaneously for up to several months.[6,7] The stability of a sol can be described using the DLVO theory. The DLVO theory provides a theoretical framework that describes the interaction potential between two charged surfaces in a liquid medium.[38] For a short summary on the DLVO theory we refer to Supplementary Information section 2.4 and Figure S3.

On first sight it appears that the smaller the size of the sol particles that are used as building blocks, the higher the porosity of the synthesized microspheres (Figure 2a). Smaller sol particles have a higher mobility due to Brownian motion. The frequency that two particles will collide and rapidly form a loose gel network (high porosity) is therefore higher for smaller particles. Moreover, smaller sol particles have a higher areal density of isolated silanol groups on the nanoparticle surface that can easily be deprotonated and react to form siloxane bridges.[6,39] The number of deprotonated silanol groups is directly related to the number of charges per nanoparticle.[40] To quantify the
charge density of the different sols, the elektrokinetic charge density versus the average sol particle size is shown in Figure 2b. The electrokinetic charge density is the charge density normalized at the shear plane, which can be derived from the zeta-potential (see also Supplementary Information section 2.5).[41,42]

**Figure 2.** (a) Effect of sol particle size and reaction pressure on porosity. (b) Electrokinetic charge density as a function of the particle size. Below a particle size of ~30 nm the charge density is strongly dependent on the particle size. Above ~30 nm the charge density becomes independent of the particle size.

Figure 2b shows that the charge density clearly depends on the particle size.\textsuperscript{[40]} The larger the nanoparticle, the lower the charge density. Our results are in good agreement with a theoretical study by Barisik et al.\textsuperscript{[43]} and an experimental study by Shi et al.\textsuperscript{[44]}, who showed that the charge density decreases significantly for silica nanoparticles from 4 to 30 nm in size and becomes constant for nanoparticles above 30 nm. This behavior can be attributed to a difference in the type of surface silanol groups that are present on the nanoparticles. Nanoparticles with a diameter less than 30 have relatively high amount of isolated silanol groups that are far apart from each other due to the large particle curvature. These isolated silanol groups can be easily deprotonated, causing a steep drop in the charge density. Nanoparticles with a diameter larger than 30 nm have a relatively high amount of vicinal silanol groups, i.e., H-bridged silanol groups, which are not easily deprotonated.\textsuperscript{[39]}
These results show that the choice of the silica sol used as building block has important implications for the assembly behavior of the microspheres and thereby the microsphere porosity. In order to tailor the microsphere properties, it is, however, desirable to be able to tune the microsphere porosity without changing the silica building blocks, as shown in the next two sections.

2.2.2. Evaporation-driven assembly

One way of manipulating the microsphere porosity is by controlled shrinkage of the emulsion droplets at elevated temperature and reduced pressure, i.e., evaporation-driven assembly. To illustrate this point, the porosity was compared for microspheres synthesized from the different sols at two different reaction pressures at a constant reaction temperature of \( T_R = 65 \, ^\circ \text{C} \) (Figure 2a). Here, one can clearly see that the lower the reaction pressure during the evaporation step, the lower the microsphere porosity.

Following the classical Clausius-Clapeyron equation:

\[
\ln \left( \frac{P_1}{P_2} \right) = -\frac{\Delta H_{\text{vap}}}{R} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)
\]  

(1)

a lower absolute pressure equals a lower boiling point of water. Here \( P_1 \) is the atmospheric pressure (1013 mbar), \( P_2 \) the reduced pressure, \( T_1 \) the standard boiling point of water, \( T_2 \) the boiling point of water at reduced pressure, \( R \) the universal gas constant, and \( \Delta H_{\text{vap}} \) the enthalpy of vaporization, which can be calculated from:

\[
\Delta H_{\text{vap}} = A \left( 1 - \frac{T_2}{T_c} \right)^n
\]

(2)

in which \( A, T_c \) and \( n \) are regression coefficients depending on the chemical compound. For water, \( A = 54 \, \text{kJ}\cdot\text{mol}^{-1}, T_c = 647.13 \, \text{K} \) and \( n = 0.34 \).
At $P_2 = 200 \text{ mbar}, T_2 = 60^\circ \text{C}$. At $P_2 = 100 \text{ mbar}, T_2 = 45^\circ \text{C}$. Therefore, at a lower absolute pressure and at constant reaction temperature $T_R$, more thermal energy $\Delta T = T_R - T_2$ is available for the evaporation process. The result is that the larger evaporation rate, the faster droplet shrinkage and, hence, more densely packed microspheres are obtained. To confirm, the amount of evaporated water over time was measured at both pressures and at a constant reaction temperature $T_R = 65^\circ \text{C}$ (Figure S7). It can be seen that at $P = 100 \text{ mbar}$ ($\Delta T = 20^\circ \text{C}$), the evaporation rate is roughly two times larger than at $P = 200 \text{ mbar}$ ($\Delta T = 5^\circ \text{C}$).

2.2.3. Gelation-driven assembly

While it is easy to synthesize microspheres with a low porosity by simply shrinking the emulsion droplets, it is not as straightforward to synthesize microspheres with a high porosity, especially if the sol particles are relatively large, i.e., larger than 20 nm. Therefore, in the next section, we do not shrink the droplets, but instead control the microsphere porosity via the reaction temperature and addition of salt. To illustrate this point, the resulting porosity for sol 3 is plotted at different reaction temperatures at atmospheric pressure and at a salt concentration of $C_{\text{salt}} = 0.19 \pm 0.02 \text{ M}$ (Figure 3a). It can be seen that the porosity of the MSMs increases with an increasing temperature, which can be explained by an increased particle mobility. However, above $T_R = 65^\circ \text{C}$ the porosity no longer increases even though the mobility of the sol particles still increases. The reason for this is that water uptake in the oil phase, phenethyl alcohol (PEA), also increases with increasing temperature (Figure 3b – inset).[47] This causes a shrinkage of the emulsion droplets during the gelation process and subsequently leads to more densely packed microspheres than one would expect based solely on the increased particle mobility.

To minimize the effect of water uptake, i.e., to minimize the droplet shrinkage during the gelation process, a mixed organic phase was used containing a non-polar organic compound that has no affinity to water, i.e., mesitylene (MST). By adding a non-polar organic compound to the oil phase,
the uptake of water becomes adjustable (Figure 3b). Note that if the concentration of MST is too high, i.e., \( \geq 75\% \) of the total mixture, the emulsifier precipitates and no stable emulsion can be formed. The addition of a non-polar organic compound, reducing water uptake and minimizing shrinkage of the aqueous droplets during gelling, allows the synthesis of MSM with significantly higher levels of porosity and pore sizes.

**Figure 3.** (a) Effect of the reaction temperature on the microsphere porosity. Black squares: porosity for the PEA system. Green stars: porosity when MST is added. (b) Effect of MST on the relative water uptake in the mixed organic phase. Inset: water uptake for PEA and MST as function of temperature.

A high reaction temperature by itself is, however, not enough to access the whole range of microsphere porosities, especially if the particles are forced into close contact due to shrinkage of the droplets. If the electric double layer around each sol particle is too large, i.e., the particles are too negatively charged, the particles will not stick together and instead repel each other upon collision. A small amount of salt is required to reduce repulsion of the sol particles and to induce spontaneous gelation over time.\(^{[48,49]}\) Higher concentrations of salt lead to a more compressed double layer (shorter Debye screening length) and therefore faster gelation of the sol particles (more stickiness). To illustrate this effect, the concentration of added salt was plotted versus the porosity of microspheres synthesized from sol 4 (**Figure 4a**).
Figure 4. (a) Effect of the salt concentration on the microsphere porosity at elevated temperature $T_R = 65$-$85 \degree$C. Black squares: porosity for the PEA system. Green stars: porosity when MST is added. (b) Macroscopic gelation experiments of the sols at room temperature. The optimal salt concentration can be estimated by matching the macroscopic gelation time with the duration of the experimental procedure. The solid lines are calculated using DLVO theory.

Figure 4 shows that the microsphere porosity initially increases rapidly with an increasing salt concentration. Above a certain salt concentration, in this case $C_{\text{salt}} > 0.20$ M, the microsphere porosity no longer increases significantly. We hypothesize that once the majority of the electrical charges are shielded, additional salt has no effect on the probability that particles will successfully stick together upon particle-particle collision. Moreover, above $C_{\text{salt}} > 0.40$ M the emulsion itself will become unstable and particles start to precipitate out of solution and form large aggregated structures.\[^{50}\]

The optimum salt concentration is dependent on the sol used as building blocks and requires some experimental optimization. The order of magnitude can, however, be estimated from, macroscopic gelation experiments of the sols at room temperature or calculated using DLVO theory (Figure 4b).
The best results are obtained when the macroscopic gelation time of the sol particles is roughly equal to the duration of the experimental procedure, which is typically a few hours.

2.3. Evaluation of the pore network
The specific surface area of the MSMs together with the porosity determines the average pore diameter of the microspheres and, therefore, the potential application of the synthesized MSMs. In Figure 5a the average pore diameter of all synthesized MSMs from the five silica sols versus the microsphere porosity are shown. It can be clearly seen that the higher the porosity, the larger the average pore diameter. In addition, the larger the size of the sol nanoparticles used as building block, the larger is also the average pore diameter of the microspheres. From an application point of view the width of the pore size distribution is, however, just as important as the average pore diameter. For example in chromatography, the narrower the spread of the pore size distribution, the higher the peak resolution that can be obtained.[51] The obtained width of the pore size distribution always had a coefficient of variation of $\text{CV} = \sigma/\mu = 0.4$, regardless of the total porosity or the silica sol used (Figure S8), indicating good reproducibility and control during synthesis.

To evaluate the gas adsorption behavior between samples, microspheres with the same porosity ($\phi_p = 0.67$) but constructed from different sols were compared. The results are shown in Figure 5b. Every sample displayed IUPAC type IVa isotherms, which is characteristic for adsorption behavior inside mesoporous adsorbents.[52] At low pressure $p/p^o$ there is a region of mono-multilayer adsorption on the mesopore walls, followed by pore condensation and finally a horizontal saturation plateau, indicating completely filled mesopores. The onset of the condensation increases, and the length of the saturation plateau decreases, for microspheres synthesized from sol 1 to sol 4. This is logical because the average pore diameter of the microspheres of sol 1 is smaller than that of sol 4, resulting in earlier and faster saturation of the complete pore network. The pore condensation regions of samples 2 to 4 have a partially common pressure range ($p/p^o = 0.85-0.90$) and partially
overlapping pore size distributions (5-15 nm). This is because pores of the same size have the same condensation pressure.\textsuperscript{[53]} Pore condensation is followed by a hysteresis loop where the desorption branch becomes parallel to the adsorption branch. The hysteresis loops become sharper and steeper ranging from sol 1 to sol 4. In general, the steeper the loop, the faster nitrogen can evaporate from the pore network. Interpretation of the shape of a hysteresis loop is, however, not straightforward because the desorption branch is dependent on various network effects and pore blocking.\textsuperscript{[52]}

The pore size distributions of the compared samples show some overlap at the base of the profiles because the silica nanoparticles used as building blocks are not monodisperse and share partially similar size fractions (Figure 5c). Each sample, however, displays a narrow pore size distribution, which is significantly smaller than pore size distributions that can be obtained when additional ageing steps such as Ostwald ripening are used.\textsuperscript{[34]} SEM shows that microspheres that were treated with an Ostwald ripening process have a much more uneven distribution of pores over the surface (Figure S9). MSMs that have been formed via direct nanoparticle assembly have an even distribution of pores across the surface.

These results clearly show that microspheres obtained via the presented method have better defined porosity characteristics and that the process in general is significantly more controllable than comparable process that require post-treatment steps, e.g., to tune pore sizes.
Figure 5. (a) Relationship between the average BET pore diameter and porosity of MSMs for the different silica sols. (b) Representative N₂ adsorption/desorption isotherms for MSMs from sols 1-4 with a porosity of \( \phi_p = 0.67 \). The isotherms display IUPAC type IVA behaviour. (c) Corresponding pore size distributions calculated from the desorption branch of the isotherm shown in panel b. Overlap in the PSD’s result from polydispersity of the sol particle sizes. A comparable sample obtained from an Ostwald ripening process is added for comparison.

2.4. Fine tuning via sol particle mixing
In above sections the general principles of tuning pore size and surface area of MSMs have been discussed. Above methodology can be further extended using mixtures of silica sols to very precisely tune the microsphere properties. By mixing two sols with different particle sizes, the resulting microspheres will have an average surface area based on the ratio of the mixture. By tuning the surface area, the pore size distribution of the microspheres can be shifted without
changing the total porosity. As an example, microspheres from a 1:2 mixture of sol 2 and sol 3 were synthesized. The resulting pore size distribution of the mixture is located precisely in between the two original sols (Figure 6a). The distribution profile overlaps at the base with the two original sols because the microspheres are build-up from both particle size fractions. However, the majority of the pores clearly have a pore diameter in-between that of the two original sols.

Figure 6. Effect of mixing two sol species. Based on the choice of the sols and the ratio of the mixture, MSMs with properties that fall in-between microspheres synthesized from the individual sol species or with properties beyond what is otherwise possible. (a) Pore size distribution of a mixture of sol 2+3, with a SSA of 252 m²/g and a particle porosity of $\phi_p = 0.62$. The SSA for sol 2 is 392 m²/g and for sol 3 is 197 m²/g, (b) Pore size distribution obtained via mercury porosimetry of a mixture of sol 1+5, with a SSA of 49 m²/g and a particle porosity of $\phi_p = 0.52$.

Furthermore, in select cases mixing two sols can yield MSMs with properties that are otherwise unobtainable. The largest average pore diameter that was obtained from one building block, i.e., sol 5, was 35 nm with a microsphere porosity of $\phi_p = 0.42$. Attempts to increase the average pore diameter further have not been successful because the larger the nanoparticle building block, the more difficult it becomes to obtain high porosities. By adding a small portion of another sol, microspheres can be obtained with higher porosities and subsequently larger pore sizes. To illustrate this point, 2wt% of sol 1 was mixed with sol 5. The resulting microspheres have a porosity of $\phi_p = 0.52$ and an average pore diameter of 50 nm, which is significantly larger than what could be obtained from just one sol (Figure 6b). The microspheres are still perfectly spherical but are not as
densely packed as without the addition of sol 1 (Figure S10). This shows that, with a limited set of silica nanoparticles, a large variety of MSMs can be synthesized with precise control over pore size, porosity and specific surface area as needed for a specific application.

3. Conclusions
We have shown that the colloidal assembly of silica nanoparticles into MSMs can be precisely manipulated by actively and passively controlling the reaction conditions and environment in which the sol-gel reaction takes place. With these insights in the underlying mechanisms of colloidal assembly in hand, we introduced a strategy to the design of perfectly spherical MSMs with precisely tunable porosity characteristics across multiple length scales that are highly reproducible and scalable using only a limited set of discrete colloidal silica sols as building blocks. In contrast with conventionally applied industrially relevant processes, we demonstrated that we can synthesize MSMs with highly tunable porosity characteristics without the need for additional ageing or post-treatment steps and / or additional template molecules to guide the formation of the porous network. The results shown here are expected to have a significant impact and ensure availability of MSMs for use in different applications in future, e.g., for the separation of a wide variety of biomacromolecules.[54]

4. Experimental Section
Materials
The colloidal silica sols used in this work were provided by Nouryon Pulp and Performance Chemicals AB, Sweden and consist of colloidal silica nanoparticles (sol) of different sizes and concentrations in water (Table 1). All sols are ammonium stabilized, which means they have been brought to a pH of 8 – 10 by the addition of ammonia (25% w/w, Scharlau). The sols 3A, 4A, 4B and 5A were diluted with deionized water that contained sufficient ammonia in order to ensure the concentration of ammonium ions was the same as the pre-diluted sol. A detailed characterization of the nanoparticles is shown in the Supplementary Information section 2.
Table 1. Colloidal silica sols used to synthesize MSMs.

| sol | SiO$_2$ wt% | $D_{[1,0]}$ (nm) | pH  |
|-----|-------------|------------------|-----|
| 1   | 12          | 4.2 ± 1.0        | 10.1|
| 2   | 14          | 8.2 ± 2.5        | 9.2 |
| 3   | 30          | 17.5 ± 4.6       | 8.6 |
| 3A  | 14          | -                | -   |
| 4   | 40          | 25.2 ± 5.8       | 9.1 |
| 4A  | 25          | -                | -   |
| 4B  | 14          | -                | -   |
| 5   | 22          | 95.4 ± 18.3      | 8.6 |
| 5A  | 14          | -                | -   |

Phenethyl alcohol (PEA, 99%) and mesitylene (MST, 97%) as the oil phase and hydroxypropyl cellulose (HPC, average $M_w$ 100.000 g/mol) as a stabilizer and emulsifier were purchased from Acros Organics. A 5 M stock solution of salt was prepared of ammonium acetate (Merck). All chemicals were used as received without further purification. The water used in this work was deionized by a Milli-Q Advantage A10 system (Merck Millipore) and had an electrical resistivity of 18.2 MΩ·cm at 25 °C.

**Water uptake**

The water content in the saturated mixed organic phase was determined by means of the Karl-Fischer volumetric method using a Mettler-Toledo DL38 Karl Fischer titrator. Milli-Q water and organic phase (PEA and MST) were vigorously stirred in a 100 mL glass vial for 12 hours and subsequently settled at room temperature for at least 24 hours. Then the saturated solution was decanted in a separatory funnel and samples were taken for analysis.

**Synthesis route**

Three different experimental protocols were carried out to produce silica microspheres. A detailed description of the protocol, amounts of materials used, and properties of the resulting microspheres are listed in the Supplementary Information section 1.
Microsphere characterization

Specific surface areas, pore volumes and pore size distributions of the synthesized samples were determined from nitrogen sorption isotherms (Micromeritics TriStar 3000). The isotherms were measured at −196 °C. The specific surface area was calculated from the monolayer adsorbed gas quantity in the pressure interval $p/p^0 = 0.05-0.22$ using the Brunauer-Emmett-Teller (BET) equation.[55] The pore volume and pore size distribution were calculated from the desorption isotherm using the Barrett–Joyner–Halenda (BJH) model.[52,56] Every sample displayed IUPAC type IVa isotherms, indicating adsorption behavior inside mesoporous adsorbents.[52] The microsphere porosity was calculated from the total pore volume of the microspheres and the density of amorphous silicon dioxide:[57]

$$\phi = \frac{V_{pore}}{\rho_{SiO_2} + V_{pore}}$$

(3)

where $V_{pore}$ is the total pore volume of the particles and $\rho_{SiO_2}$ is the density of amorphous SiO$_2$, which is assumed as 2.2 g·cm$^{-3}$.[6]

SEM images of select microspheres were obtained using a FEI Quanta 3D equipped with a field emission electron gun operating at 5 kV. The particles were deposited on a SEM-stub and sputter-coated with a 20 nm layer of gold (Emitech K550) to prevent charging.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

Electron microscopy was performed at the Center for Multiscale Electron Microscopy, Eindhoven University of Technology. N$_2$ physisorption experiments were performed at the chemical analysis laboratory of Nouryon Pulp and Performance Chemicals AB.

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 676045.
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Table of Contents (50-60 words)

A strategy is presented for the design and synthesis of mesoporous silica microspheres with precisely tunable porosity characteristics using discrete silica sol nanoparticles as building blocks. The presented strategy gives valuable insight in the underlying mechanisms of colloidal assembly and provides tools for the microstructural design of tailor-made silica microspheres for use in separation applications and beyond.

**Keyword:** colloidal assembly

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**Multiscale Colloidal Assembly of Silica Microspheres with Tunable Mesopores**
Supporting Information

Multiscale Colloidal Assembly of Silica Microspheres with Tunable Mesopores
Andreas Fijneman, Joakim Högbloom, Magnus Palmlöf, Gijsbertus de With, Michael Persson, Heiner Friedrich*

1. Sample preparation
1.1. Experimental protocol
Three different experimental protocols were carried out which are detailed below. Amounts of materials used are provided in Table S1, synthesis conditions in Table S2 and properties of the resulting MSMs are provided in Table S3. For each procedure, a 5 wt% aqueous solution of hydroxypropyl cellulose (HPC) was used as emulsifier and stabilizing agent. It was prepared by dispersing HPC (5 g) in Milli-Q water (95 g) at 60 °C. The mixture was stirred continuously, and allowed to cool to room temperature after one hour. Stirring was continued for 24h. It was then filtered twice over 5 µm pore size filter paper (Munktell), and stored in a plastic container.

Procedure 1: evaporation-driven assembly
An oil phase was prepared by mixing phenethyl alcohol (PEA) and 5wt% HPC solution in a beaker at room temperature, and stirring at 300 RPM for one hour with an overhead mixer (IKA Yellow line OST Basic), after which the mixture was fully transparent.

Colloidal silica (and where applicable – see Table S1 - 5 M aqueous ammonium acetate solution) were then added to above mixture under constant stirring (350 RPM) to form a water-in-oil emulsion which had a white/milky appearance. After 60 minutes of stirring, the emulsion was poured in a round bottom flask that was subsequently attached to a rotary evaporator fitted with a water bath (Buchi R-200), and exposed to the temperature and reduced pressure specified in Table S2.

Rotary evaporation was continued for 90 minutes, at which point almost all the water had been removed from the emulsion, resulting in an almost completely clear/transparent mixture. The temperature was then increased to 85 °C for a further 30 minutes, before being allowed to cool to room temperature. The resulting MSMs were separated by filtration over a Pyrex glass filter and dried at 90 °C for 16 hours. Finally, MSMs were calcined in air at 650 °C for 4 hours.

Procedure 2: gelation-driven assembly
Identical to procedure 1, except the flask was rotated in the water bath at atmospheric pressure and heated for the time specified in Table S2. After the time specified in Table S2, after which gelling had occurred, a reduced post-gelling pressure according to Table S2 was applied for a period of approximately 30 minutes. The temperature of the water bath was then raised to 85°C and stirring continued for a further 30 minutes at the same pressure.
Procedure 3: gelation-driven assembly
Identical to procedure 2, except mesitylene (MST) was mixed with PEA prior to emulsification.

Procedure 4: Ostwald ripening
A silica prepared via procedure 1 was subjected to Ostwald ripening to increase the average pore diameter. This was done by adding 31 g of silica to a 1 L steel autoclave, together with 619 g water and 73 g of 25 wt% aqueous ammonia solution. The autoclave was sealed and heated to 120 °C for 116 hours. After cooling to 30 °C, 105 g of 63 wt% nitric acid was added. The silica was then filtered off, washed with 300 g water, followed by 158 g acetone. The silica was then dried in an oven at 90 °C for 16 hours.

1.2 List of samples
Tables S1 to S3 are arranged so that the samples are grouped according to the silica sol that was used as building blocks.

Table S1. Quantities of materials used

| Example | Sol | PEA (g) | MST (g) | HPC (g) | Silica (g) | NH₄Ac (µl) |
|---------|-----|---------|---------|---------|------------|------------|
| 1       | 1   | 50      | 0       | 0.13    | 1.15       | 0          |
| 2       | 1   | 50      | 0       | 0.13    | 1.14       | 0          |
| 3       | 1   | 50      | 0       | 0.13    | 1.15       | 0          |
| 4       | 2   | 50      | 0       | 0.04    | 1.33       | 0          |
| 5       | 2   | 50      | 0       | 0.13    | 1.32       | 0          |
| 6       | 2   | 50      | 0       | 0.13    | 1.32       | 100        |
| 7       | 2   | 50      | 0       | 0.13    | 1.33       | 0          |
| 8       | 2   | 50      | 0       | 0.13    | 1.33       | 100        |
| 9       | 2   | 50      | 0       | 0.13    | 1.32       | 200        |
| 10      | 2   | 50      | 0       | 0.13    | 1.33       | 200        |
| 11      | 2   | 50      | 0       | 0.04    | 1.33       | 200        |
| 12      | 2   | 50      | 0       | 0.13    | 1.33       | 100        |
| 13      | 2   | 50      | 0       | 0.04    | 1.32       | 250        |
| 14      | 2   | 50      | 0       | 0.13    | 4.02       | 750        |
| 15      | 2   | 50      | 0       | 0.13    | 1.33       | 200        |
| 16      | 2   | 50      | 0       | 0.13    | 1.33       | 250        |
| 17      | 2   | 50      | 0       | 0.04    | 1.32       | 200        |
| 18      | 2   | 50      | 0       | 0.21    | 1.33       | 200        |
| 19      | 3A  | 50      | 0       | 0.13    | 1.35       | 0          |
| 20      | 3   | 50      | 0       | 0.13    | 2.88       | 0          |
| 21      | 3A  | 50      | 0       | 0.13    | 1.35       | 0          |
| 22      | 3   | 50      | 0       | 0.13    | 2.88       | 0          |
| 23      | 3A  | 50      | 0       | 0.12    | 1.35       | 200        |
| 24      | 3A  | 50      | 0       | 0.13    | 1.34       | 100        |
| 25      | 3A  | 100     | 0       | 0.42    | 2.88       | 200        |
| 26      | 3   | 100     | 0       | 0.25    | 2.89       | 200        |
| 27      | 3   | 50      | 0       | 0.13    | 2.88       | 200        |
| 28      | 3   | 50      | 0       | 0.13    | 2.88       | 200        |
| Example | Sol | PEA (g) | MST (g) | HPC (g) | Silica (g) | NH₄Ac (µl) |
|---------|-----|---------|--------|--------|----------|------------|
| 29      | 3A  | 50      | 0      | 0.13   | 1.35     | 200        |
| 30      | 3A  | 100     | 0      | 0.25   | 1.38     | 122        |
| 31      | 3A  | 100     | 0      | 0.42   | 2.89     | 750        |
| 32      | 3   | 50      | 0      | 0.13   | 2.89     | 200        |
| 33      | 3   | 100     | 0      | 0.25   | 2.89     | 200        |
| 34      | 3A  | 100     | 0      | 0.52   | 2.89     | 750        |
| 35      | 3   | 100     | 0      | 0.25   | 2.90     | 200        |
| 36      | 3A  | 50      | 50     | 0.11   | 2.71     | 650        |
| 37      | 3   | 100     | 0      | 0.25   | 2.89     | 200        |
| 38      | 3A  | 100     | 0      | 0.42   | 2.90     | 650        |
| 39      | 3   | 100     | 0      | 0.25   | 2.90     | 825        |
| 40      | 3   | 100     | 0      | 0.25   | 2.89     | 200        |
| 41      | 3   | 100     | 0      | 0.25   | 2.88     | 300        |
| 42      | 3A  | 100     | 0      | 0.25   | 1.38     | 200        |
| 43      | 3A  | 100     | 100    | 0.42   | 2.85     | 650        |
| 44      | 3A  | 100     | 100    | 0.42   | 2.90     | 650        |
| 45      | 3A  | 100     | 100    | 0.42   | 2.84     | 650        |
| 46      | 3   | 56      | 56     | 0.23   | 2.89     | 200        |
| 47      | 3A  | 100     | 100    | 0.42   | 2.84     | 650        |
| 48      | 4B  | 50      | 0      | 0.13   | 1.36     | 0          |
| 49      | 4B  | 50      | 0      | 0.13   | 1.36     | 70         |
| 50      | 4B  | 50      | 0      | 0.13   | 1.36     | 0          |
| 51      | 4B  | 50      | 0      | 0.13   | 1.36     | 200        |
| 52      | 4   | 50      | 0      | 0.13   | 2.94     | 150        |
| 53      | 4   | 50      | 0      | 0.13   | 2.94     | 200        |
| 54      | 4B  | 100     | 0      | 0.42   | 2.93     | 1050       |
| 55      | 4B  | 100     | 0      | 0.42   | 2.94     | 1200       |
| 56      | 4B  | 100     | 0      | 0.42   | 2.93     | 900        |
| 57      | 4A  | 100     | 0      | 0.25   | 2.46     | 300        |
| 58      | 4B  | 100     | 0      | 0.25   | 2.46     | 1350       |
| 59      | 4   | 50      | 0      | 0.13   | 2.96     | 300        |
| 60      | 4B  | 50      | 50     | 0.21   | 2.93     | 900        |
| 61      | 4   | 100     | 0      | 0.25   | 2.94     | 200        |
| 62      | 4B  | 50      | 50     | 0.21   | 2.94     | 900        |
| 63      | 4A  | 100     | 0      | 0.42   | 1.50     | 250        |
| 64      | 4B  | 100     | 0      | 0.42   | 2.94     | 900        |
| 65      | 4B  | 50      | 50     | 0.21   | 2.94     | 900        |
| 66      | 4   | 100     | 0      | 0.25   | 2.94     | 300        |
| 67      | 4B  | 100     | 0      | 0.25   | 2.94     | 900        |
| 68      | 4B  | 100     | 0      | 0.25   | 1.38     | 200        |
| 69      | 4B  | 501     | 501    | 2.09   | 14.78    | 3000       |
| 70      | 4B  | 501     | 501    | 2.09   | 14.77    | 3000       |
| 71      | 4B  | 100     | 100    | 0.42   | 2.93     | 600        |
| 72      | 4B  | 100     | 100    | 0.42   | 2.94     | 600        |
| 73      | 5A  | 50      | 0      | 0.13   | 1.08     | 0          |
| 74      | 5A  | 50      | 0      | 0.21   | 1.08     | 0          |
| 75      | 5   | 50      | 50     | 0.11   | 2.16     | 0          |
| 76      | 5   | 50      | 50     | 0.11   | 2.17     | 0          |
| 77      | 5A  | 50      | 50     | 0.11   | 2.16     | 0          |
| Example | Sol | PEA (g) | MST (g) | HPC (g) | Silica (g) | NH₄Ac (µl) |
|---------|-----|---------|---------|---------|------------|------------|
| 78      | 5   | 100     | 0       | 0.42    | 1.33       | 60         |
| 79      | 5   | 100     | 0       | 0.25    | 2.17       | 50         |
| 80      | 5A  | 100     | 0       | 0.25    | 1.33       | 50         |
| 81      | 5   | 100     | 0       | 0.25    | 2.17       | 50         |

[a] Amount of HPC expressed on a dry basis.
[b] Amount of silica added on a dry basis (i.e. not including water from the sol).
[c] Volume of 5 M ammonium acetate solution used.

Table S2. Synthesis conditions.

| Example | Synthetic Procedure | Heating Temp (°C) | Heating Pressure (mbar) | Heating Time (min) | Final Pressure (mbar) |
|---------|---------------------|-------------------|-------------------------|--------------------|-----------------------|
| 1       | 1                   | 65                | 100                     | 90                 | 100                   |
| 2       | 1                   | 65                | 160                     | 90                 | 160                   |
| 3       | 1                   | 65                | 200                     | 90                 | 200                   |
| 4       | 1                   | 65                | 100                     | 90                 | 100                   |
| 5       | 1                   | 65                | 160                     | 90                 | 160                   |
| 6       | 1                   | 65                | 200                     | 90                 | 200                   |
| 7       | 1                   | 65                | 200                     | 90                 | 200                   |
| 8       | 1                   | 65                | 160                     | 90                 | 160                   |
| 9       | 1                   | 65                | 100                     | 90                 | 100                   |
| 10      | 1                   | 65                | 100                     | 90                 | 100                   |
| 11      | 1                   | 65                | 100                     | 90                 | 100                   |
| 12      | 1                   | 65                | 124                     | 90                 | 124                   |
| 13      | 1                   | 65                | 160                     | 90                 | 160                   |
| 14      | 1                   | 65                | 200                     | 90                 | 200                   |
| 15      | 1                   | 65                | 124                     | 90                 | 124                   |
| 16      | 1                   | 65                | 180                     | 90                 | 180                   |
| 17      | 1                   | 65                | 160                     | 90                 | 160                   |
| 18      | 1                   | 65                | 160                     | 90                 | 160                   |
| 19      | 1                   | 65                | 200                     | 90                 | 200                   |
| 20      | 1                   | 65                | 200                     | 90                 | 200                   |
| 21      | 1                   | 65                | 200                     | 90                 | 200                   |
| 22      | 1                   | 65                | 200                     | 90                 | 200                   |
| 23      | 1                   | 65                | 100                     | 90                 | 100                   |
| 24      | 1                   | 65                | 100                     | 90                 | 100                   |
| 25      | 2                   | 53                | atm                     | 90                 | 100                   |
| 26      | 2                   | 65                | atm                     | 90                 | atm                   |
| 27      | 2                   | 65                | atm                     | 90                 | atm                   |
| 28      | 1                   | 65                | 100                     | 90                 | 100                   |
| 29      | 1                   | 65                | 200                     | 90                 | 200                   |
| 30      | 2                   | 53                | atm                     | 90                 | 100                   |
| 31      | 2                   | 53                | atm                     | 45                 | 100                   |
| 32      | 1                   | 65                | 200                     | 90                 | 200                   |
| 33      | 2                   | 53                | atm                     | 90                 | 100                   |
| 34      | 1                   | 88                | 500                     | 90                 | 500                   |
| Example | Synthetic Procedure | Heating Temp (°C) | Heating Pressure (mbar) | Heating Time (min) | Final Pressure (mbar) |
|---------|---------------------|------------------|-------------------------|------------------|----------------------|
| 35      | 2                   | 53               | atm                     | 90               | 100                  |
| 36      | 2                   | 88               | atm                     | 90               | 500                  |
| 37      | 3                   | 65               | atm                     | 90               | 200                  |
| 38      | 2                   | 65               | atm                     | 90               | 100                  |
| 39      | 2                   | 53               | atm                     | 60               | 200                  |
| 40      | 2                   | 65               | atm                     | 90               | 200                  |
| 41      | 2                   | 65               | atm                     | 90               | 200                  |
| 42      | 1                   | 88               | 500                     | 90               | 500                  |
| 43      | 3                   | 65               | atm                     | 90               | 400                  |
| 44      | 3                   | 80               | atm                     | 90               | 400                  |
| 45      | 3                   | 88               | atm                     | 90               | 500                  |
| 47      | 3                   | 75               | atm                     | 90               | 400                  |
| 48      | 1                   | 65               | 100                     | 90               | 100                  |
| 49      | 1                   | 65               | 100                     | 90               | 100                  |
| 50      | 1                   | 65               | 200                     | 90               | 200                  |
| 51      | 1                   | 65               | 100                     | 90               | 100                  |
| 52      | 1                   | 65               | 100                     | 90               | 100                  |
| 53      | 1                   | 65               | 100                     | 90               | 100                  |
| 54      | 2                   | 53               | atm                     | 45               | 100                  |
| 55      | 2                   | 53               | atm                     | 45               | 100                  |
| 56      | 2                   | 53               | atm                     | 90               | 100                  |
| 57      | 2                   | 65               | atm                     | 90               | 200                  |
| 58      | 2                   | 53               | atm                     | 45               | 100                  |
| 59      | 1                   | 65               | 200                     | 90               | 200                  |
| 60      | 3                   | 65               | atm                     | 60               | 200                  |
| 61      | 1                   | 88               | 500                     | 90               | 500                  |
| 62      | 3                   | 65               | atm                     | 60               | 200                  |
| 63      | 2                   | 65               | atm                     | 90               | 200                  |
| 64      | 2                   | 53               | atm                     | 30               | 200                  |
| 65      | 3                   | 65               | atm                     | 90               | 200                  |
| 66      | 1                   | 88               | 500                     | 90               | 500                  |
| 67      | 2                   | 65               | atm                     | 60               | 200                  |
| 68      | 1                   | 88               | 500                     | 90               | 500                  |
| 69      | 3                   | 90               | atm                     | 90               | 200                  |
| 70      | 3                   | 88               | atm                     | 90               | 550                  |
| 71      | 3                   | 88               | atm                     | 90               | 500                  |
| 72      | 3                   | 88               | atm                     | 90               | 500                  |
| 73      | 1                   | 65               | 100                     | 90               | 100                  |
| 74      | 1                   | 65               | 50                      | 90               | 50                   |
| 75      | 1                   | 65               | atm                     | 90               | 200                  |
| 76      | 1                   | 65               | atm                     | 90               | 200                  |
| 77      | 1                   | 65               | atm                     | 90               | 200                  |
| 78      | 2                   | 65               | atm                     | 90               | 200                  |
| 79      | 1                   | 88               | 500                     | 90               | 500                  |
| 80      | 2                   | 88               | atm                     | 90               | 500                  |
| 81      | 2                   | 88               | atm                     | 90               | 500                  |
Table S3. MSM properties.

| Example | SSA (m² g⁻¹) | PV (cm³ g⁻¹) | Porosity (-) | µ_BET PD (Å) | µ_BJH PD (Å) | σ_BJH PD (Å) | CV |
|---------|--------------|--------------|--------------|--------------|--------------|-------------|----|
| 1       | 550          | 0.68         | 0.60         | 50           | 41           | 12          | 0.29|
| 2       | 570          | 0.85         | 0.65         | 60           | 48           | 13          | 0.27|
| 3       | 563          | 0.94         | 0.67         | 67           | 53           | 14          | 0.26|
| 4       | 401          | 0.28         | 0.38         | 28           | 28           | 9           | 0.31|
| 5       | 390          | 0.34         | 0.43         | 35           | 31           | 9           | 0.29|
| 6       | 396          | 0.42         | 0.48         | 42           | 37           | 10          | 0.28|
| 7       | 391          | 0.49         | 0.52         | 50           | 40           | 11          | 0.28|
| 8       | 397          | 0.56         | 0.55         | 57           | 48           | 15          | 0.30|
| 9       | 384          | 0.65         | 0.59         | 68           | 60           | 20          | 0.33|
| 10      | 382          | 0.66         | 0.59         | 69           | 60           | 20          | 0.34|
| 11      | 390          | 0.67         | 0.60         | 69           | 59           | 19          | 0.32|
| 12      | 385          | 0.71         | 0.61         | 73           | 61           | 18          | 0.29|
| 13      | 392          | 0.72         | 0.61         | 74           | 64           | 23          | 0.36|
| 14      | 397          | 0.73         | 0.62         | 74           | 63           | 20          | 0.32|
| 15      | 398          | 0.80         | 0.64         | 82           | 69           | 23          | 0.33|
| 16      | 391          | 0.80         | 0.64         | 81           | 72           | 25          | 0.35|
| 17      | 398          | 0.81         | 0.64         | 81           | 71           | 23          | 0.33|
| 18      | 388          | 0.92         | 0.67         | 95           | 82           | 32          | 0.39|
| 19      | 194          | 0.19         | 0.30         | 40           | 33           | 10          | 0.30|
| 20      | 198          | 0.20         | 0.31         | 41           | 33           | 9           | 0.27|
| 21      | 197          | 0.25         | 0.35         | 50           | 40           | 11          | 0.27|
| 22      | 202          | 0.26         | 0.36         | 51           | 41           | 11          | 0.26|
| 23      | 197          | 0.33         | 0.42         | 67           | 57           | 17          | 0.31|
| 24      | 199          | 0.34         | 0.43         | 69           | 58           | 18          | 0.31|
| 25      | 191          | 0.40         | 0.47         | 85           | 71           | 22          | 0.31|
| 26      | 193          | 0.52         | 0.54         | 108          | 95           | 27          | 0.28|
| 27      | 196          | 0.58         | 0.56         | 117          | 102          | 39          | 0.38|
| 28      | 196          | 0.58         | 0.56         | 119          | 104          | 40          | 0.38|
| 29      | 196          | 0.61         | 0.57         | 125          | 113          | 37          | 0.32|
| 30      | 193          | 0.64         | 0.58         | 132          | 115          | 42          | 0.36|
| 31      | 200          | 0.65         | 0.59         | 130          | 115          | 42          | 0.37|
| 32      | 198          | 0.68         | 0.60         | 138          | 122          | 38          | 0.31|
| 33      | 197          | 0.70         | 0.61         | 142          | 125          | 36          | 0.29|
| 34      | 196          | 0.75         | 0.62         | 153          | 132          | 33          | 0.25|
| 35      | 212          | 0.76         | 0.62         | 143          | 125          | 45          | 0.36|
| 36      | 194          | 0.77         | 0.63         | 159          | 133          | 31          | 0.23|
| 37      | 194          | 0.78         | 0.63         | 160          | 157          | 50          | 0.32|
| 38      | 196          | 0.78         | 0.63         | 159          | 137          | 28          | 0.21|
| 39      | 196          | 0.78         | 0.63         | 160          | 165          | 58          | 0.35|
| 40      | 193          | 0.79         | 0.63         | 163          | 137          | 29          | 0.21|
| 41      | 193          | 0.85         | 0.65         | 177          | 177          | 38          | 0.21|
| 42      | 197          | 0.87         | 0.66         | 176          | 176          | 53          | 0.30|
| 43      | 194          | 0.92         | 0.67         | 190          | 199          | 63          | 0.32|
| 44      | 190          | 0.93         | 0.67         | 195          | 196          | 56          | 0.28|
| 45      | 195          | 0.98         | 0.68         | 201          | 208          | 70          | 0.34|
| 46      | 195          | 0.99         | 0.69         | 204          | 204          | 51          | 0.25|
| 47      | 194          | 1.02         | 0.69         | 211          | 216          | 64          | 0.30|
| Example | SSA (m² g⁻¹) | PV (cm³ g⁻¹) | Porosity (-) | µ_BET PD (Å) | µ_BJH PD (Å) | σ_BJH PD (Å) | CV |
|---------|-------------|--------------|--------------|--------------|--------------|--------------|----|
| 48      | 133         | 0.19         | 0.30         | 58           | 49           | 14           | 0.28 |
| 49      | 132         | 0.21         | 0.31         | 63           | 53           | 14           | 0.27 |
| 50      | 135         | 0.22         | 0.33         | 66           | 56           | 15           | 0.28 |
| 51      | 133         | 0.30         | 0.40         | 91           | 80           | 25           | 0.32 |
| 52      | 132         | 0.40         | 0.47         | 123          | 112          | 36           | 0.32 |
| 53      | 132         | 0.44         | 0.49         | 134          | 123          | 34           | 0.27 |
| 54      | 127         | 0.59         | 0.56         | 185          | 199          | 61           | 0.30 |
| 55      | 128         | 0.60         | 0.57         | 188          | 200          | 61           | 0.31 |
| 56      | 131         | 0.61         | 0.57         | 186          | 201          | 63           | 0.31 |
| 57      | 126         | 0.62         | 0.58         | 195          | 210          | 71           | 0.34 |
| 58      | 130         | 0.62         | 0.58         | 191          | 210          | 66           | 0.31 |
| 59      | 132         | 0.62         | 0.58         | 188          | 204          | 56           | 0.27 |
| 60      | 129         | 0.63         | 0.58         | 195          | 208          | 55           | 0.26 |
| 61      | 132         | 0.63         | 0.58         | 191          | 198          | 48           | 0.24 |
| 62      | 129         | 0.63         | 0.58         | 195          | 216          | 59           | 0.27 |
| 63      | 128         | 0.65         | 0.59         | 204          | 216          | 58           | 0.27 |
| 64      | 128         | 0.67         | 0.60         | 208          | 222          | 71           | 0.32 |
| 65      | 134         | 0.68         | 0.60         | 202          | 216          | 59           | 0.27 |
| 66      | 132         | 0.69         | 0.60         | 210          | 221          | 53           | 0.24 |
| 67      | 128         | 0.72         | 0.61         | 223          | 246          | 92           | 0.37 |
| 68      | 132         | 0.76         | 0.63         | 230          | 243          | 80           | 0.33 |
| 69      | 131         | 0.81         | 0.64         | 248          | 264          | 82           | 0.31 |
| 70      | 127         | 0.88         | 0.66         | 277          | 292          | 90           | 0.31 |
| 71      | 126         | 0.93         | 0.67         | 295          | 312          | 98           | 0.31 |
| 72      | 130         | 0.96         | 0.68         | 295          | 317          | 102          | 0.32 |
| 73      | 37          | 0.21         | 0.32         | 231          | 236          | 59           | 0.25 |
| 74      | 38          | 0.22         | 0.32         | 231          | 241          | 71           | 0.29 |
| 75      | 39          | 0.22         | 0.33         | 228          | 233          | 43           | 0.18 |
| 76      | 39          | 0.23         | 0.33         | 233          | 242          | 51           | 0.21 |
| 77      | 38          | 0.24         | 0.34         | 247          | 256          | 63           | 0.25 |
| 78      | 38          | 0.24         | 0.35         | 255          | 270          | 60           | 0.22 |
| 79      | 40          | 0.25         | 0.36         | 255          | 278          | 66           | 0.24 |
| 80      | 38          | 0.26         | 0.36         | 278          | 284          | 70           | 0.25 |
| 81      | 39          | 0.26         | 0.36         | 270          | 281          | 73           | 0.26 |

2. Nanoparticle characterization

2.1. Methods

The particle volume fraction of the sols was determined using X-ray fluorescence spectroscopy (Philips MagiX PW2424), the size distribution was determined via CryoTEM, the pH of the sols was measured using a calibrated pH electrode (Jenway 3510 pH meter) and the bulk ammonia concentration of each sol was determined via titration.

Electrophoretic mobilities were measured using a Malvern Zetasizer Nano ZS equipped with a 4 mW, 633 nm He–Ne laser. Measurements were performed using disposable polycarbonate folded capillary cells (Malvern DTS1070). The cells were rinsed with Milli-Q water prior to use. All measurements were performed at 25 °C and the samples were equilibrated for 120 s. The measurements were
performed using the optimized conditions resulting from the automatic procedure of the equipment and the voltage was fixed at 25 V. Electrophoretic mobilities were converted into zeta potentials post-measurement using the Henry equation.\[1\]

CryoTEM images were obtained using the TU/e CryoTitan (FEI, www.cryotem.com) operating at 300 kV. The images were recorded using a 2k × 2k Gatan CCD camera. The silica sols were diluted to approximately 1wt% with Milli-Q water and applied on copper TEM grids (QUANTIFOIL® R 2/2, Cu 200 mesh - Quantifoil Micro Tools). The grids were surface plasma treated for 40 s using a Cressington 208 carbon coater prior to use. The samples were then vitrified by plunging them into liquid ethane using an automated vitrification robot (FEI Vitrobot Mark III).

Image processing was done in MATLAB R2016 using the DIPlib scientific image processing library V2.8.1 and an in-house developed Matlab script. The script requires the long and short axes of particles to be defined by manually clicking at the corresponding edge of the particle in the image. Subsequently, the pixel positions are converted into distances using the magnification calibration of the corresponding Digital Micrograph image file. Approximately 300 particles were analyzed per sample. The reported values is the geometrical mean between the longest and shortest axes.

2.2 CryoEM characterization
CryoEM images of the five silica sol building blocks are shown in Figure S1.

![Figure S1](image)

**Figure S1.** CryoTEM images of dilute silica nanoparticles (1wt%) imaged at a magnification of 24000x. Images were acquired on a 2k × 2k Gatan CCD camera. (a) 4 nm-diameter silica nanoparticles, (b) 8 nm-diameter silica nanoparticles, (c) 18 nm-diameter silica nanoparticles, (d) 25 nm-diameter silica nanoparticles, (e) 100 nm-diameter silica nanoparticles.
2.3. Nanoparticle size distribution

For size analysis roughly 300 particles of each sample were analyzed manually by measuring the longest and shortest axis using an in-house developed MATLAB script. Only individual distinguishable particles were measured. For the smallest nanoparticles, either discrete nanoparticles were imaged or particles that could easily be identified within the aggregates due to differences in contrast. The values of both axis were then multiplied and the square root was taken to obtain a geometrical mean diameter of each nanoparticle. A number mean diameter $D_{[1,0]}$ and volume mean diameter $D_{[4,3]}$ of the whole population were then calculated from:

$$D_{[1,0]} = \frac{\sum_{i=1}^{n} D_i}{n}$$

(S1)

$$D_{[4,3]} = \frac{\sum_{i=1}^{n} D_i^4}{\sum_{i=1}^{n} D_i^3}$$

(S2)

Additionally, the aspect ratio was calculated by dividing the longest axis over the shortest axis. The results are summed up in Table S4. The number mean and volume mean particle size distributions are shown in Figure S2.

**Table S4.** Nanoparticle size and aspect ratio as determined via cryoTEM.

| sol | number mean $D_{[1,0]}$ (nm) | standard error | volume mean $D_{[4,3]}$ (nm) | standard error | aspect ratio  |
|-----|-------------------------------|----------------|-------------------------------|----------------|--------------|
| 1   | 4.2 ± 1.0                     | 0.06           | 4.9 ± 1.2                     | 0.07           | 1.36 ± 0.31  |
| 2   | 8.2 ± 2.5                     | 0.13           | 10.6 ± 3.5                   | 0.18           | 1.31 ± 0.33  |
| 3   | 17.5 ± 4.6                    | 0.26           | 21.6 ± 6.1                   | 0.34           | 1.20 ± 0.16  |
| 4   | 25.2 ± 5.8                    | 0.32           | 28.8 ± 6.8                   | 0.38           | 1.13 ± 0.10  |
| 5   | 95.4 ± 18.3                   | 2.67           | 102.3 ± 19.6                 | 2.85           | 1.05 ± 0.05  |

**Figure S2.** (a) Number mean $D_{[1,0]}$ particle size distribution and (b) Volume mean $D_{[4,3]}$ particle size distribution of the silica sols, determined via cryoTEM. Roughly 300 particles were analyzed manually per sample.
2.4. DLVO theory

The DLVO theory, named after Derjaguin, Landau, Verwey and Overbeek, provides a theoretical framework that describes the interaction potential between two charged surfaces in a liquid medium.\[^2\] The interaction potential is a combination of attractive van der Waals interactions and repulsive electrostatic interactions.\[^3\] The combination of these interactions leads to a potential energy-distance profile with, at close separation, a deep minimum, called the primary minimum, followed by a maximum, called the energy barrier, and sometimes followed by another minimum, called the secondary minimum. The height of the barrier corresponds directly to the probability that a particle-particle collision will lead to particle aggregation and is determined by physicochemical parameters such as the Hamaker constant, surface potential, electrolyte concentration and the dielectric constant of the solvent.\[^4\]

The classical expression for the interaction potential is given by:\[^3\]

\[
U_{ss}(D) = U_{vdW}(D) + U_{el}(D)
\] (S3)

where \(U_{ss}\) is the interaction potential for two spherical particles at a surface-to-surface separation distance \(D\), \(U_{vdW}\) is the attractive van der Waals interaction potential and \(U_{el}\) is the repulsive electrostatic interaction potential due to the electric double layer of the charged surface.

The electrostatic interaction potential between two spherical particles can be derived from the Poisson–Boltzmann equation.\[^5,6\] Solving the full nonlinear Poisson-Boltzmann equation for spherical particles requires complex numerical analysis, which is beyond the scope of this work. The classical DLVO theory is based on the linearized Poisson-Boltzmann equation (Debye-Hückel approximation), for which an analytical solution exist.\[^7,8\] An often used simplified solution for the electrostatic interaction potential between two identically charged spheres is given by:\[^3\]

\[
U_{el}(D) = 32\pi\varepsilon\varepsilon_0 \left(\frac{k_B T}{z e}\right)^2 \gamma^2 \exp(-\kappa D)
\] (S4)

with \(\gamma = \tanh(\psi_0 / 4)\), and where \(\psi_0 = \frac{e\psi_0}{k_B T}\) is the dimensionless surface potential.

Equation S4 in its current form is, however, too simplified to describe the silica sols used in this work. The Debye-Hückel approximation is only valid for low potentials, \(e|\psi| \ll k_B T\), which is roughly 25 mV at room temperature. In addition, this analytical solution uses the Derjaguin approximation for two spherical particles\[^9\], which is only valid when the particles are much larger than the electric double layer interaction (\(\kappa a > 10\)) and the separation distances are small.\[^7,10\]

Since for most particles in this work \(\kappa a\) is (much) smaller than 10 and the potentials are (much) larger than 25 V, a more complex analytical solution is required. Sader et al.\[^11\] modified equation S4 in order to calculate the electrostatic interaction potential between two identically charged spheres at constant surface potential for any distance regardless of the particle size, and that is valid for moderate to high surface potentials up to approximately 100 mV:

\[
U_{el}(D) = 64\pi \left(\frac{a^2}{2a + D}\right) \varepsilon_0 \left(\frac{k_B T}{z e}\right)^2 Y^2 \ln \left(1 + \exp(-\kappa D)\right)
\] (S5)
where \( Y = \exp(\kappa D / 2) \arctanh\left( \exp(-\kappa D / 2) \tanh(\psi_o / 4) \right) \).

Equation S5 is a good approximation for the exact numerical results of the full Poisson-Boltzmann equation at constant surface potential.\(^{[12]}\)

It is important to mention that both equation S4 and equation S5 are derived for simple symmetrical electrolytes such as [NaCl]. The colloidal particles in this work are ammonia stabilized. Ammonia is not a simple, symmetrical electrolyte but for simplicity reasons we assume that ammonia in water takes the form of [NH\(_4\)OH] of which the ion concentration in the bulk solution is known. Secondly, the electronic double layer interactions in both equations are based on the surface potential. But since the surface potential cannot easily be determined experimentally, we assume that the surface potential is equal to the zeta potential, as is often done in literature.\(^{[13]}\)

The van der Waals interaction between two identical charged spheres at a separation distance \( D \) can be calculated via the Hamaker equation, which is valid at all separation distances regardless of the particle size.\(^{[14]}\)

\[
U_{vdW}(D) = -\frac{A_H}{6} \left[ \frac{2a^2}{(4a + D)^6} + \frac{2a^2}{(2a + D)^2} + \ln\left( \frac{(4a + D)D}{(2a + D)^2} \right) \right]
\]

(S6)

where \( A_H \) is the Hamaker constant, which is \( 4.6 \times 10^{-21} \) for amorphous SiO\(_2\) in water.\(^{[15]}\) The other symbols have their usual meaning.

The particles cannot approach each other indefinitely due to short-range Born-repulsion.\(^{[16]}\) Below a separation distance of \( d_0 \approx 0.158 \) nm, the Born repulsion potential climbs to infinity, which prevents the particles from coming closer than \( D = d_0 \).\(^{[17]}\) By combining equation S5 and equation S6 a potential energy-distance diagram can be drawn for each sol (Figure S3).

**Figure S3.** Calculated DLVO potential energy-distance diagrams for (a) the repulsive electric double layer interaction potential \( U_{el}(D) \) and attractive van der Waals interaction potential \( U_{vdW}(D) \) and (b) the total interaction potential \( U_{SS}(D) = U_{el}(D) + U_{vdW}(D) \) of two silica nanoparticles of radius \( a \) at a separation distance \( D \). \( d_0 = 0.158 \) nm is the minimum equilibrium distance, below which the Born repulsion climbs to infinity.

**2.5. Electrokinetic charge density**

Each nanoparticle has a certain amount of ions near its surface that can interact with the particle: the electric double-layer. The ions closest to the particle surface are bound to the particle surface due to electrostatic interactions (Stern layer). Ions further away from the surface can move around freely
The distribution of the ions in the diffuse layer can be described using the Gouy-Chapman theory, which is based on the Poisson–Boltzmann equation.\(^5,6\) The thickness of the electric double-layer (Debye length, \(1/\kappa\)) can be calculated from the bulk ion concentration:\(^3\)

\[
\kappa = \sqrt{2 I N_A e^2 / \varepsilon \varepsilon_0 k_B T}
\]  
(S7)

where \(I\) is the ionic strength of the solution:

\[
I = \frac{1}{2} \sum_i z_i^2 c_i N_A
\]  
(S8)

where \(N_A\) is Avogadro’s number, \(e\) the elementary charge, \(\varepsilon \varepsilon_0\) the dielectric constant of the solvent, \(k_B\) the Boltzmann constant, \(T\) the temperature, \(z\) is the valence of ion \(i\) and \(c\) the molar concentration of ion \(i\). Equation (2.8) shows that the larger the bulk ion concentration, the shorter the Debye length. This is logical because the more ions are near a charged surface, the more surface charges are shielded and the more compact the diffuse double-layer becomes. The thickness of the double-layer of each sample is listed in Table S5.

The double-layer and rest of the bulk liquid are separated by a shear plane, which has a potential called the zeta-potential. The zeta-potential cannot be measured directly but it can be calculated from electrophoretic mobility measurements via the Henry equation:\(^1\)

\[
\mu_e = \frac{2 \varepsilon \varepsilon_0 \zeta f(\kappa a)}{3 \eta}
\]  
(S9)

where \(\mu_e\) is the electrophoretic mobility, \(\zeta\) the zeta-potential, \(f(\kappa a)\) the Henry function, wherein \(\kappa\) is the inverse Debye length, \(a\) the particle radius, and \(\eta\) the zero shear viscosity of the medium. The other symbols have their usual meaning.

The Henry function depends on the thickness of the Debye length compared to the particle radius. A simple empirical relation for the Henry function with a relative error of less than 0.1% is given by Swan et al.\(^{18}\):

\[
f(\kappa a) = \frac{16 + 18 \kappa a + 3(\kappa a)^2}{16 + 18 \kappa a + 2(\kappa a)^2}
\]  
(S10)

For \(\kappa a \gg 1\), which means a very thin double layer compared to the particle size, \(f(\kappa a) \rightarrow 1.5\), the so-called Smoluchowski approximation. For \(\kappa a \ll 1\), a thick double layer, \(f(\kappa a) \rightarrow 1\), the so-called Hückel approximation.\(^{13}\) For each sample the Henry function was calculated using equation S10 after which two sets of ten zeta-potential measurements were ran for each sample, respectively. The average values and corresponding coefficients of variation are listed in Table S5.

The zeta-potential can be related to the electrokinetic charge density for symmetrical electrolytes via the empirical relationship proposed by Loeb et al.\(^{1,19}\):

\[
\sigma_z = \frac{\varepsilon \varepsilon_0 k_B T \kappa}{e} \left[ 2 \sinh \left( \frac{\zeta}{2} \right) + \frac{4}{\kappa a} \tanh \left( \frac{\zeta}{4} \right) \right]
\]  
(S11)
with \( \bar{\zeta} = \frac{e\zeta}{k_BT} \) as the dimensionless zeta potential.

Note that the electrokinetic charge density is the charge density normalized at the shear plane, unlike the surface charge density which is the charge density at the actual particle surface.\(^{[19]}\) The surface charge density, however, cannot be calculated from the zeta-potential directly because the zeta-potential is not equal to the surface potential. The electrokinetic charge density gives an indication of the amount of charges on a silica nanoparticle, which originates from the amount of deprotonated silanol functional groups. The charge density of each sample was calculated using equation S11 and the results are summed up in Table S5.

Table S5: Calculated Debye length, zeta-potential and electrokinetic charge density of each sample.

| Sol | \(1/\kappa \) (nm) | \( \kappa_a \) | \( f(\kappa_a) \) | \( \zeta \)-potential (mV) | CV (%) | \( \sigma_\zeta \) (mC/m\(^2\)) |
|-----|------------------|-----------|----------------|-------------------|-------|----------------|
| 1   | 1.52             | 1.39      | 1.04           | \(-54.0 \pm 2.4\) | 4.4   | \(-45.7\)     |
| 2   | 1.84             | 2.22      | 1.07           | \(-57.5 \pm 1.5\) | 2.6   | \(-35.5\)     |
| 3   | 1.66             | 5.27      | 1.17           | \(-39.1 \pm 2.3\) | 5.8   | \(-20.9\)     |
| 4   | 1.65             | 7.63      | 1.22           | \(-35.3 \pm 1.5\) | 4.3   | \(-17.9\)     |
| 5   | 3.17             | 16.4      | 1.32           | \(-36.9 \pm 1.4\) | 3.7   | \(-9.3\)      |

3. Microsphere characterization

3.1. Microsphere morphology

Zoomed-in SEM images of the surface of the microspheres reveal that the microspheres are completely assembled of smaller sol particles (Figure S4).

Figure S4. Zoomed-in SEM images of the surface of the synthesized microspheres, revealing that the microspheres are assembled form different sol particle building blocks: (a) sol 1 – 4 nm particles, (b) sol 2 – 8 nm particles, (c) sol 3 – 18 nm particles, (d) sol 4 – 25 nm particles, (e) sol 5 – 100 nm particles. (f) Macroscopic image of the microsphere corresponding to zoomed-in image e.
3.2. Microsphere size distribution
Particle size distributions of select synthesized microspheres were obtained via laser diffraction (Malvern Mastersizer Micro) following the Mie scattering theory with a refractive index of 1.456 and an absorption coefficient of 0.01. A representative distribution is shown in Figure S5.

![Figure S5](image)

**Figure S5.** Particle size distribution of a representative sample, obtained via laser diffraction.

3.3. Microsphere surface area

![Figure S6](image)

**Figure S6.** SSA of the synthesized microspheres versus the mean sol particle size. The SSA of the microspheres is completely independent of the microsphere size or porosity.
3.4. Effect of reaction pressure on the water evaporation rate

![Graph showing effect of absolute pressure on evaporation rate](image)

Figure S7. Effect of the absolute pressure on the evaporation rate at a constant reaction temperature $T_R = 65$ °C. The evaporation rate increases with decreasing absolute pressure.

3.5. Microsphere pore size distribution

Pore size distributions were calculated from the desorption isotherm using the Barrett–Joyner–Halenda (BJH) model.[20,21] The width of the distributions are independent of the silica sol that was used to synthesize the microsphere and independent of the microsphere porosity (Figure S8).

![Graph showing pore size distribution](image)

Figure S8. Width of the pore size distribution. There is no correlation between the spread of the PSD and the microsphere porosity or the silica sol used as building block. The $\sigma_{BJH}/\mu_{BJH}$ is always below 0.4, indicating a relatively narrow pore size distribution.

3.6. Direct assembly vs Ostwald ripening

SEM images of microspheres synthesized via direct assembly vs microspheres obtained via Ostwald ripening have distinct differences (Figure S9). Microspheres obtained via Ostwald ripening have an uneven and less homogeneous surface compared to microspheres obtained via direct nanoparticle assembly. This has negative implications for the pore size distribution and subsequently the potential separation efficiency.
3.7. Effect of silica sol mixing

SEM reveals that microspheres synthesized from a mixture of silica sols are still perfectly spherical (Figure S10). Due to the addition of a fraction of smaller silica sol nanoparticles, the overall porosity of the microspheres increases as well as the average pore diameter. This can be seen by a slightly rougher surface of the microspheres, which indicate a less dense packing fraction.

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