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# Brief review: Effects of textural properties of lamellar silica in drug delivery applications

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**ABSTRACT**

**Background:** Silica-based materials, especially those with lamellar morphology, usually have other names, such as dendritic, nanoflower, and wrinkle are often used in various applications due to their unique textural properties, such as radially centered pore structure, pore channels, and large pore volume.

**Objectives:** To determine the effect of lamellar silica texture properties, such as surface area, porosity, pore size, morphological shape, particle size, and surface charge value, as potential drug delivery material candidates.

**Materials and methods:** The texture properties of silica materials were reviewed in drug delivery applications, and four silica materials with different morphologies were reviewed for their texture properties and potential in drug delivery applications.

**Results:** The literature review revealed the effect of material texture properties on their potential in drug delivery applications. Drug loading in porous carriers can improve their activity, stability, and selectivity, and can reduce the drug dose to inhibit cell viability compared to unencapsulated drugs. Surface modification can also affect the zeta potential value and its performance in drug loading. In vitro drug release properties of the material and drug release rates showed different results related to their different texture properties. Particle size affects particle penetration into cells; the smaller the particle size, will cause deeper the penetration, but it has a tendency for particle aggregation.

**Conclusion:** Lamellar silica-based materials with various unique properties of their texture properties show great potential in drug delivery applications and are expected to be used in the future.

## Introduction

Silica-based nanoparticles are often utilized in various applications, including MCM-41[1,2] and SBA15.[3,4] This is due to their tunable morphology, high surface area, easy modification, and biodegradable.[5-7] Although MCM-41 and SBA-15 have a high surface area, their tubular pore structure causes limited accessibility within the pores. In addition, when these silicas are loaded with guest molecules, there is limited loading of guest molecules and poor accessibility of active sites. Lastly, these materials are unstable at high temperatures and pressures due to their thin walls.[8] A potential candidate as a drug carrier material that has been widely developed is mesoporous silica nanoparticles (MSNs), which have several unique

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features. Recently, dendritic silica-based materials with center-radial pore structures, large pore channels, and highly accessible pore volumes were utilized as promising drug delivery systems.[9-13] The large pore nature of dendritic silica will bring the advantage of loading more drugs to be targeted.

The fibrous surface of dendritic silica allows it to be easily loaded with several ranges of organic groups, organometallic complex ionic liquids, polymers, peptides, enzymes, DNA, genes, drugs, and others.[14-16] The dendritic silica structure having radially distributed fibrous channels usually promotes increased functionalization capacity due to the presence of many accessible sites, which allows easy incorporation of different agents. This allows designing materials with modifications along with targeting systems.[17] The name of the dendritic itself has been a topic of discussion; some have mentioned it as fibrous, wrinkle, nanoflower, and most recently[18] found the fact that the morphological shape of this silica is lamellar morphology, so a new terminology is proposed in the form of biconcentric lamellar silica. In various types of terminology, the use of this material in drug delivery is limited, so it is necessary to optimize the formation of the material to maximize the performance of the material design, especially in drug delivery applications. The initial evaluation process of the potential material as a drug carrier can be done by evaluating its texture properties. By understanding how the texture of the material (such as pore size, surface area, particle shape, zeta potential value) affects the interaction with drugs, especially in biological tissues, the design of a more effective and safe drug delivery system can be carried out for further evaluation.

***Textural properties***

Some things that need to be considered in the formation of materials for drug delivery applications are the textural properties, including porosity and pore distribution,[19,20] surface area,[21] morphology, particle size,[22-24] zeta potential value[25] of the material. These properties will affect the drug loading, release profile, stability, and biocompatibility.[26] Several parameters that have a strong influence on the synthesis conditions, such as surfactants, silica precursors, solvents or cosolvents, pH of the media, reaction variations, or hydrothermal temperatures, will result in the formation of mesoporous silica nanoparticles with pore sizes, as well as the orientation of the formed pores, varied surface areas, and different morphologies.[27] Analysis of the textural properties of materials can be carried out by the absorption of gases such as $N_2$, He, Ar (adsorbate) at various relative pressures on solids (adsorbents), which provides information on textural properties including surface area, pore volume, and pore size.[28] Table 1 shows the analysis of the nature of dendritic silica texture with various morphological terminologies, using the specific method and results in their surface area and pore size.

**Table 1**. Analysis of the nature of dendritic silica texture with various morphological terminologies.

| Material | Method | Surface area ($m^2$/gm) | Pore size (nm) | Type of isotherm and hysteresis | Reference |
|---|---|---|---|---|---|
| Dendritic fibrous silica | Open vessel conventional heating protocol | 397-635 | 2-25 | Type IV isotherm | 31 |
| KCC-1 | Hydrothermal | 435 | 4.56 | Type IV isotherm with H3 hysteresis loop | 32 |
| Dendritic mesoporous silica | Aqueous-based dual-templating | 784-809 | 3.2-9.8 | Type IV isotherm | 33 |
| KCC-1 | Microemulsion hydrothermal method | 501.3 | 3.4 | Type IV isotherm with H4 hysteresis loop | 34 |
| KCC-1 | Microemulsion microwave-assisted | 691 | 4.77 | Type IV isotherm with H1 hysteresis loop | 35 |
| Discontinuous concentric lamellar | Low-pressure solvothermal | 478-782 | 3.66-5.09 | Type IV isotherm with an H3 hysteresis loop | 36 |
| Nanoflower silica | Light-assisted method | 701 | 3.4 | Type IV isotherm | 37 |
| KCC-1 | Sol-gel method | 442 | 2.76 | Type IV with a type of hysteresis loop | 38 |

The pore diameter can be adjusted from 2 to 30 nm depending on the surfactant used as a template and the synthesis conditions.[29] The formation of these pores and morphology will also affect the application of the silica material itself. The morphology of silica can also be affected by the formation of surfactant molecules into liquid micelles, which are often highly dependent on the hydrophobic-hydrophilic balance between the template, precursor material, hydrolysis reagent, and solvent.

In addition, the key to fibrous morphology as well as particle size is the control of the hydrolysis speed of TEOS as silica precursor by the hydrolysis reagent. However, with further increase in the amount of hydrolysis reagents, no change in fibrous morphology was observed except for an increase in particle size distribution, which may be due to the rapid (uncontrolled) hydrolysis of TEOS molecules by excess hydrolysis reagents.[30]

***Porosity and pore size distribution***

Porosity is defined as the ratio of total pore volume to particle or agglomerate volume.[39] In the IUPAC Classification, most silica materials have a mesoporous pore size (2-50 nm). Loading of drugs in porous carriers can improve their activity, stability, and selectivity, and can lower the dose of drugs to inhibit cell viability compared to unencapsulated drugs. This is one of the advantages of drug loading in pores.[40] In addition, drug loading inside a porous material shows an increase in the solubility of the drug because of spatial restriction in nano-sized pores. Crystalline drug molecules usually cannot form highly ordered crystals; instead, remaining in an amorphous or non-crystalline form, which is known to increase the rate of drug dissolution.[41] In addition to drug loading, drug release also depends on the pore size of the carrier. RSV drug release tests conducted by[39] showed materials with large pore size have more drug release percentage than carriers with smaller pores. Drug loaded in the pore can also be beneficial to achieve effective treatment concentrations quickly.[40] Type of pore shapes will also affect drug loading, worm-like pore ones are slightly had lower than hexagonal-porous ones, probably due to the smaller pore size and curved shape of worm-like pores, which makes the entry of drugs into the interior of the pore.[41]

In drug delivery applications, KCC-1, which has a fibrous morphology and a pore size of 4.77 nm, has increased diclofenac adsorption performance. Induction occurs at the beginning of 10 minutes, where the adsorption capacity and diclofenac removal efficiency increase with contact time. After 40 minutes, the diclofenac adsorption performance decreases drastically because the active sites of the composite for adsorption have been saturated with diclofenac.[34] In the work done,[42] the loading of CUR into the pore on the nanocarrier in the form of dendritic silica can enhance the cytotoxic activity because the nanocarrier maintains the optimum concentration of CUR molecules through sustained and controlled drug release and increases the solubility of CUR in PBS media. The formation of larger dendritic silica pore size to improve the performance of the material in drug loading can be done using auxiliary surfactants. One of the auxiliary surfactants used is ferrocene carboxylic acid (FCA) with different mass ratios of FCA to CTAB,[33] DLMSN can be used for selective loading of Dox, IR780, and Hb. The pore sizes of MSN, DLMSNFCA with FCA to CTAB mass ratio of 0.2, and DLMSNFCA with FCA to CTAB mass ratio of 0.3 were 2.6, 6.3, and 12.2 nm, respectively, which showed the highest selective loading content for Dox (34.4%), IR780 (5.7%), and Hb (43.3%).

***Surface area***

High surface area is one of the important things in drug delivery system applications. The drug loading capacity is positively correlated with the specific surface area; a large specific surface area will provide more absorption sites for the drug.[42] Drug loading studies were conducted on several commercial silica mesopores and showed that an increase in surface area (through smaller pore diameters) would not increase drug loading capacity, but rather a decrease, as the entire surface cannot be covered monomolecularly due to the spatial limitations of the narrow pores. Drug molecules cannot access the entire surface area, and the drug will precipitate outside the pores of conventional silica materials.[43] This is one of the advantages of the fibrous surface of lamellar silica that allows for the loading of various types of matrices as well as the ease of modification on its surface. The increase in pore diameter and surface area by the addition of organic functional groups further greatly enhances the loading and release of drug molecules and the kinetics.[40]

Surface functionalization of the material aims to introduce new functional groups in the framework of the carrier material to bind the drug without changing its structure, crystallinity, or morphology.[44] Functionalization on the surface will cause a decrease in the surface area of the material due to the closure of the pore with new functional groups.[45] Mesoporous amine-modified KCC-1 (KCC-1-$NH_2$) can be considered as a promising carrier for drug delivery systems to control the drug release rate influenced by molecular interactions, especially for highly soluble drugs, such as paracetamol.[46]

***Morphology***

As mentioned earlier, the name of this dendritic silica has been a topic of discussion, with some referring to it as dendritic fibrous, wrinkle, nanoflower, and most recently, the fact that the morphological shape of this silica is lamellar, so that a new terminology is proposed in the form of biconcentric lamellar silica.[18]

Here, we will explain some mentions of lamellar silica morphology, how it is formed, and its utilization in drug delivery applications.

***Dendritic fibrous silica (KCC-1)***

DFNS has a unique fibrous morphology (flower-like morphology consisting of thin sheets), unlike the porous structure of various conventional silica spheres. It has a high surface area due to its fibers (thin sheets) and, more importantly, it has improved accessibility to the internal surface and enhanced stability due to its good fiber/sheet thickness.[30] Some obtained DLMSNs had center-radial pore structures, unique open three-dimensional dendritic superstructures with large pore channels, and highly accessible internal surface areas.[32]

The formation mechanism of DFNS is an interaction between various processes, such as surfactant molecular assembly, micelle or microemulsion droplet formation, nucleation, and growth. In the five-step DFNS formation mechanism (Figure 1A), CTAB molecules self-assemble to form a flat phase and are further stabilized, where cosurfactant molecules are inserted between CTAB molecules. This is followed by the formation of Bicontinuous Microemulsion Droplets (BMDs) with water and oil channels. Some of these BMDs (depending on the alcohol chain length of the cosurfactant) are unstable, so their coalescence results in larger BMDs. Silica precursors already present in the oil channel are hydrolyzed at the water-oil interface. After supersaturation, nucleation and growth occur in the BMD channel.[47]

The mechanical stability of DFNS is due to the silica sheets being covalently and hence not mechanically disintegrating due to pressure or friction. The thermal stability is due to the better sheet (fiber) thickness of DFNS compared to the wall thickness of SBA-15 or MCM-41 so that it does not collapse even after heating up to 800 °C. The uniqueness of DFNS is its open dendritic fibrous morphology, which significantly improves its accessibility.[8]

The use of dendritic-based silica materials has been widely used for drug delivery applications.[48-54] In a study conducted,[48] the successful loading of the drug PTX in DMSNs was demonstrated by elemental carbon mapping. No appreciable carbon element was observed in the blank DMSN (Figure 1B, 1C), whereas the carbon 153 element appeared to be homogeneously distributed throughout the DMSN after PTX loading (Figure 1D, 1E).

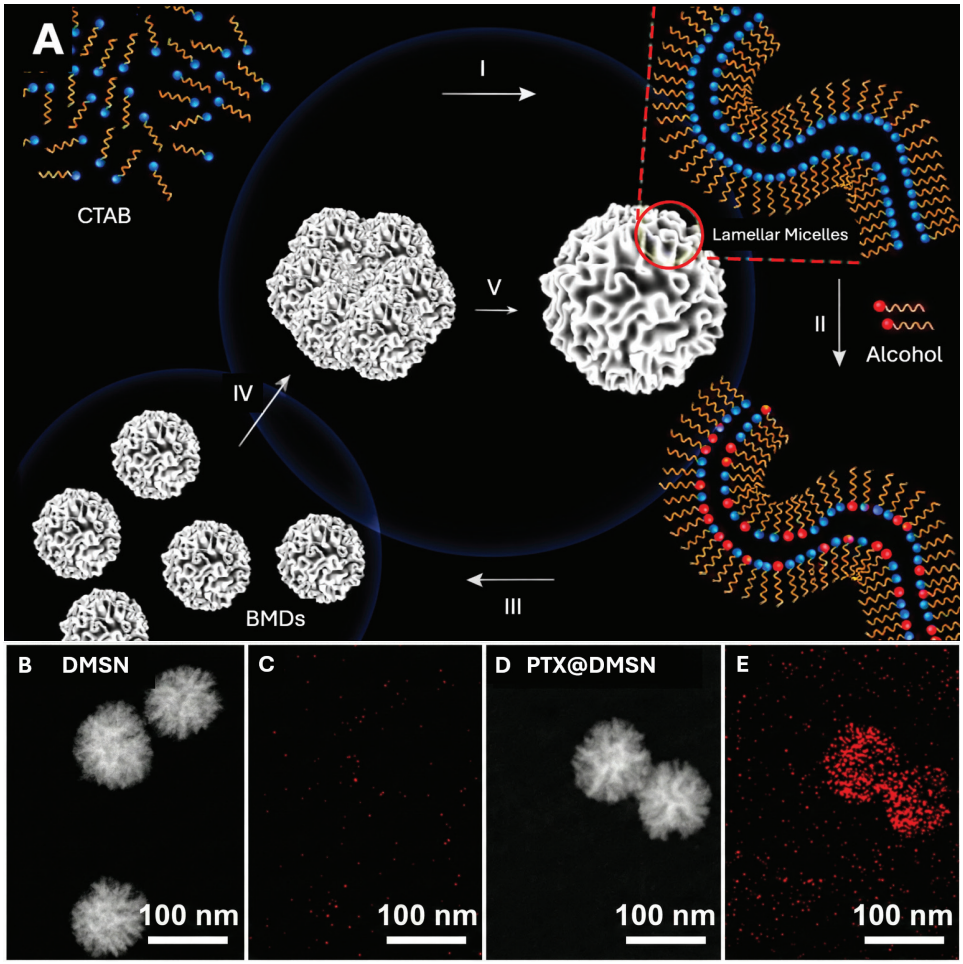


***Figure 1.*** *Formation of DFNS and application of DMNS in drug delivery. A: formation mechanism of DFNS, B-C: carbon elemental mapping and the corresponding TEM images of DMSN, D-E: PTX@DMSN. (Adapted with permission from Deng C, et al.[48] Copyright 2021 Elsevier and Maity A, et al.[47] Copyright 2017 American Chemical Society).*

***Wrinkle silica***

During the synthesis of wrinkle silica nanoparticles, the silica fibers grow and spread radially from the center of the nanostructure, resulting in a cone-shaped pore with progressively larger parts moving outward. This feature helps to accommodate large macromolecules, such as proteins, from clogging the pore.[55] The formation of wrinkle silica is described in Figure 2 (Upper panel), which is formed from a bicontinuous microemulsion. It was confirmed that WSNs were generated in the bicontinuous microemulsion phase of the Winsor III system.[56] By using the phase behavior of the Winsor III system, which depends on the water-surfactant-oil mixing ratio, and by adding various cosolvents, the structure of silica nanoparticles can be precisely controlled from mesoporous shape to wrinkle shape, and the distance between wrinkles can be controlled.

Figure 2 (Lower panel) shows the effect of oil ratio as cosolvent in the formation of wrinkle silica. Based on the typical phase diagram of the Winsor III system, when additional oil is added gradually with a fixed amount of water and surfactant (sometimes including cosolvent) within a certain region of reaction conditions, the equilibrium state of the mixture will be reached.[56] WSM synthesis was carried out using various types of emulsion systems in the multiphase area as the structure-directing template can control the internal morphology and interparticle connecting structure (Figure 2 a-f).[57] The results show that mesoporous silica nanoparticles are interconnected and transformed into a wrinkled structure depending on the amount of oil in the emulsion system, which starts from direct micelles. In addition, it was confirmed that WSNs were interconnected and formed bulk gels interconnected with wrinkle structures as the amount of water in the emulsion system decreased, starting from the composition that resulted in the formation of spherical WSNs. The pores of the synthesized silica mesostructures with varying amounts of oil are interconnected and produce varying wrinkle structures. A few researchers have used this wrinkle-based silica material in drug delivery applications.[58-60] WMS presenting covalently coupled curcumin (WMS-Curc) demonstrates the flexibility of this methodology for the design and synthesis of new DDS, tailoring the surface functionalization of silica nanomaterials.[60]

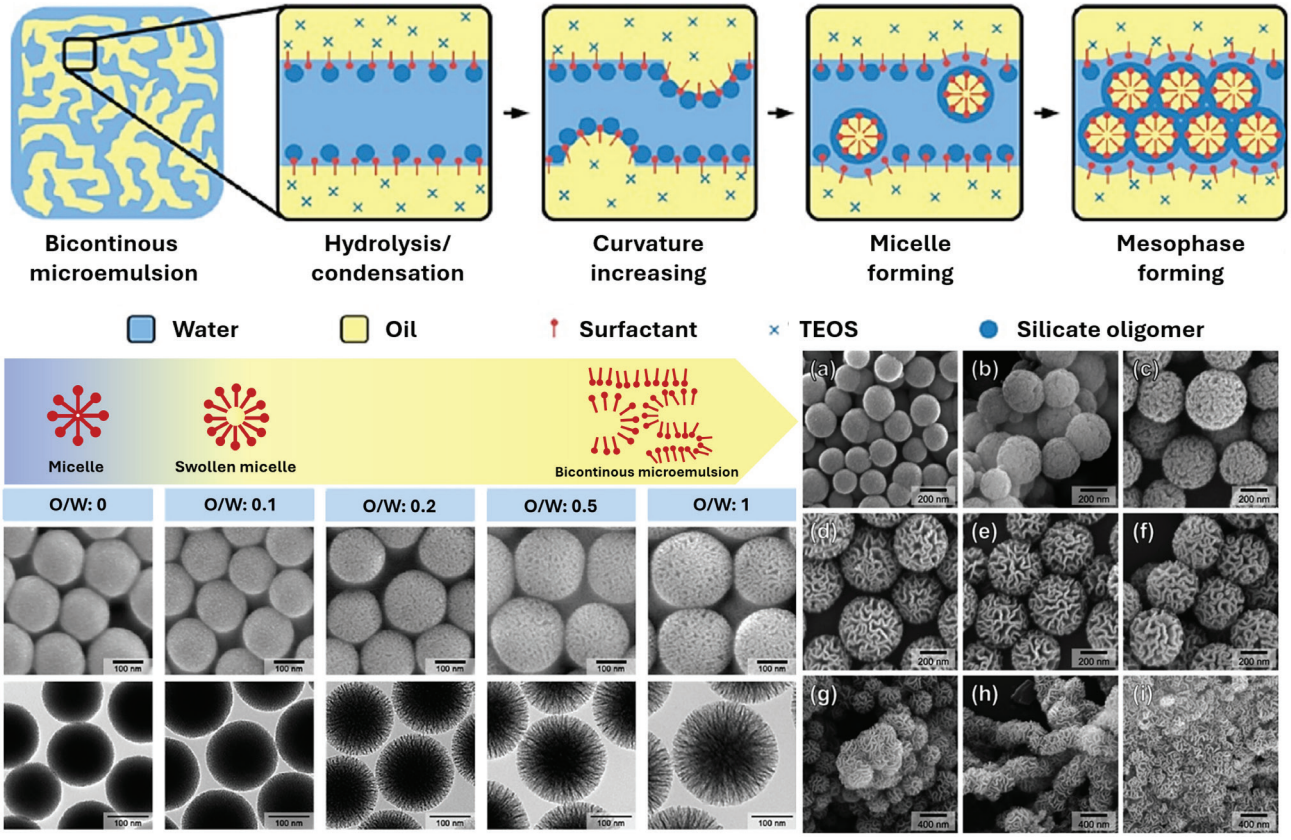


***Figure 2.*** *Formation and morphology of MSN with radial wrinkle structure. Schematic illustration of the mesophase-forming mechanism. Upper panel: the schematic from very tight mesoporous to expanded mesoporous, mixed (or broken) mesoporous, and the wrinkled structure, Lower panel: SEM/TEM images of silica nanoparticles synthesized at different volume ratios of cyclohexane to 15 mL of aqueous solution of urea (0.3 gm) and CPB (0.5 gm) and isopropanol (0.46 mL). (Adapted with permission from Moon and Lee[56] Copyright 2012 American Chemical Society). A-F: SEM images of the silica materials synthesized from the emulsion system (Adapted with permission from Moon and Lee[57] Copyright 2014 American Chemical Society).*

***Nanoflower***

The term nanoflower arises due to the morphology of a hierarchical flower composed of a collection of petals oriented outward in three dimensions.[61] FESEM images of silica nanoflower nanomaterials[62] (Figure 3A) show a hierarchical flower morphology composed of a collection of thin petals intersecting each other. TEM images (Figure 3B) of the edges of the nanoflowers clearly show that the flowers are composed of elongated spines oriented outward in three dimensions. Based on the analysis, it is shown that the nano-flower petals develop radially from the core and assemble divergently, leading to the formation of nano-flowers with a dandelion-like morphology that makes it possible to obtain a large and easily accessible specific surface area along with fine-tuning of their chemical-physical properties. However, research on the synthesis of silica with well-defined morphology and controllable size still has a long way to go. Nanoflower silica is rarely reported.

Figure 3 shows the formation scheme of silica materials with nanoflower morphology. First, a water-dispersed-in-oil (W/O) emulsion is generated by stirring a mixture of water and cyclohexane in the presence of a surfactant, water droplets are dispersed in the emulsion and stabilized by an orderly array at the interface of water and oil, to form spherically radiating micelles. Secondly, negatively charged silicon oxide is generated through the hydrolysis of TEOS with urea and then arranged on the surface of emulsion droplets to form porous nanoflowers. Finally, spherical mesoporous nanoflowers can be obtained by removing the pattern using calcination. In the use of drug delivery systems, silica nanoflower materials show excellent properties for the controlled release of pyrene due to their unique structure, and can serve as ideal candidates for more potential biomedical applications, such as cellular imaging, biosensors, and targeted drug delivery.[64]

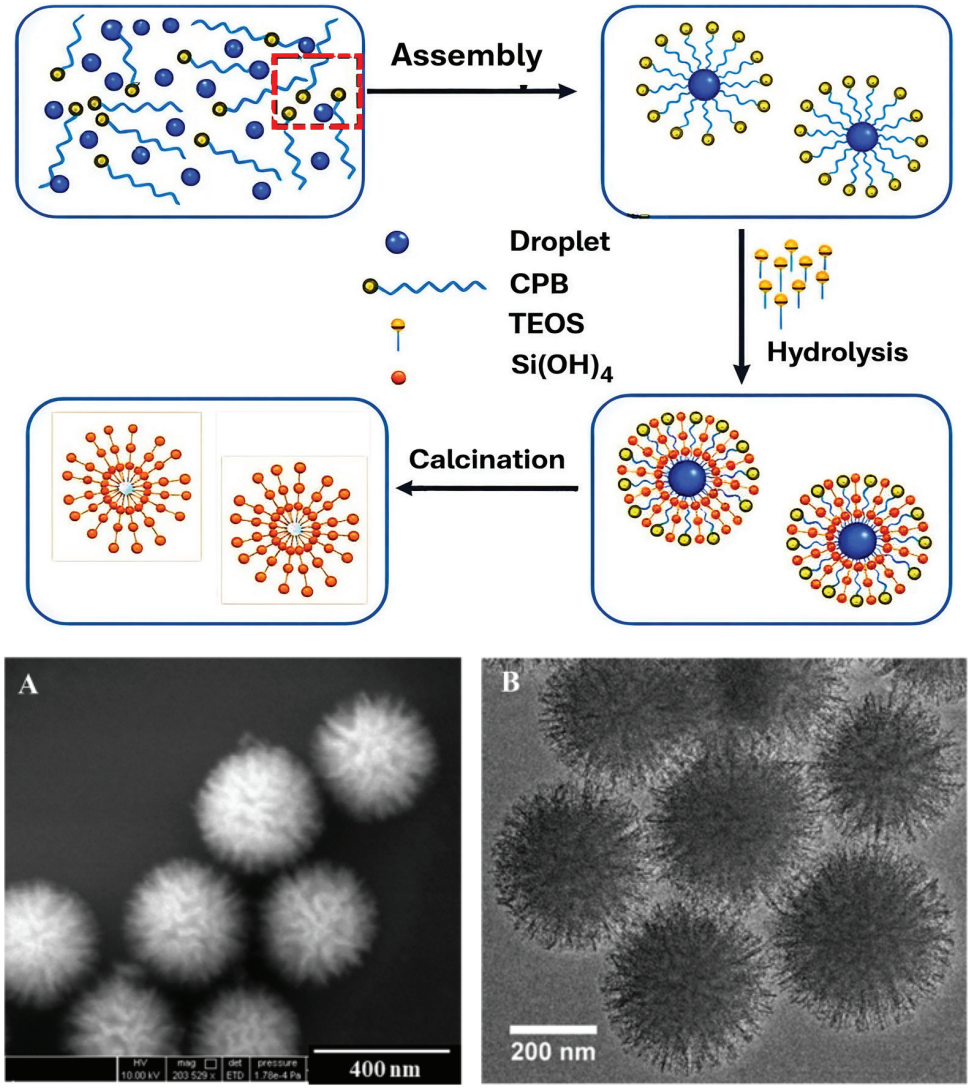


***Figure 3.*** *Formation and morphology of nanoflower silica. Upper: schematic illustration of the possible formation mechanism of porous nanoflowers, Lower: micrograph image of silica-based chromogenic NCs, representing their flowerlike morphology (A: SEM, B: TEM). (Adapted with permission from Yang H, et al.[63] Copyright 2014 Elsevier and Kole K, et al.[37] Copyright 2020 American Chemical Society).*

***Biconcentric lamellar silica***

Lastly, a thorough study to revisit the morphological nomenclature of KCC-1 and its rational formation mechanism was reported.[18] The morphology of KCC-1 was interpreted after observing and analyzing SEM and TEM images, and shows a unique morphology called bicontinuous-concentric-lamellar (bcl) morphology, which is different from other silica materials (Figure 4). This morphology can be described as bicontinuous lamellar walls arranged vertically and concentrically to form spherical particles.[32] The wrinkles in bcl silica are lamellas, which are concentric and interconnected. This structure provides easily accessible active sites compared to conventional structures, and the internal particles of bcl silica consist of lamellas that are concentrically structured and evenly distributed in all directions.[65]

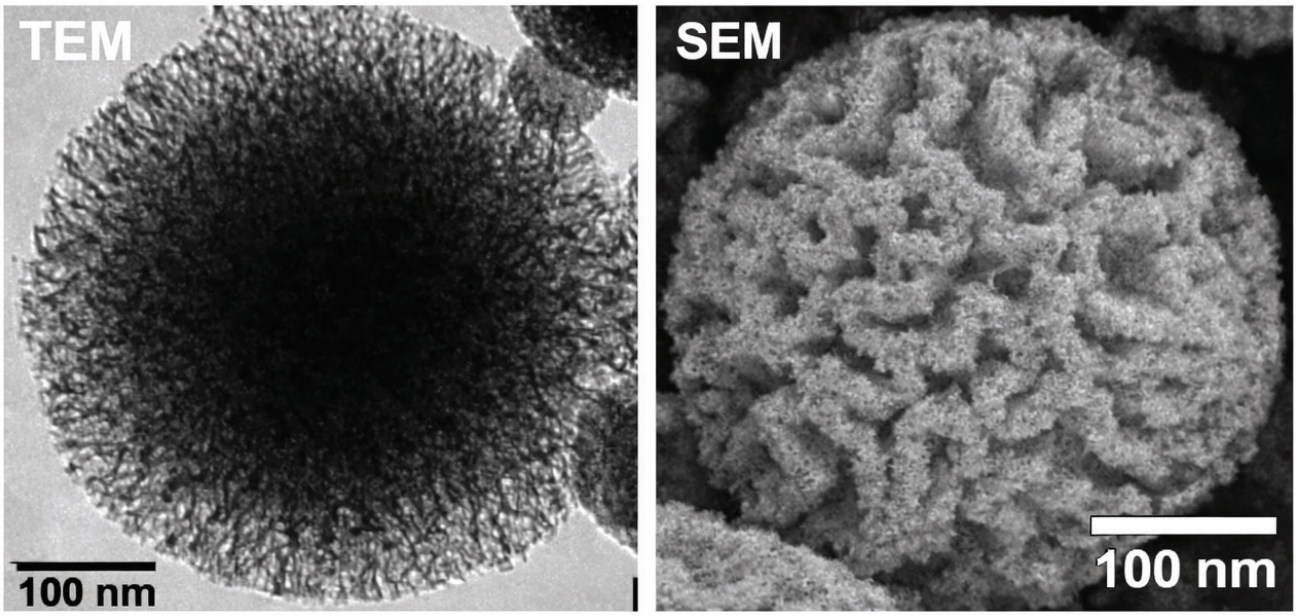


***Figure 4.*** *SEM and TEM of KCC-1 showing bicontinuous concentric. (Adapted with permission from Febriyanti E, et al.[18] Copyright 2016 American Chemical Society).*

The reverse micelle plays an important role in the formation of bcl silica. The stages of bcl silica formation, which start from the hydrolysis process, are followed by the diffusion of hydrolysis products into the reverse micelle, before ending with the condensation and phase segregation process. The formation mechanism is proposed as a hydrolysis reaction occurring outside the inverted micelles in the vicinity of the interface. In contrast, the condensation reaction begins just after the diffusion of hydrolysis products into the inverted micelles, followed by a phase separation process. Particle growth during synthesis was observed, and showed that during the first 30 minutes of synthesis, bicontinuous lamellar features (bl) of bcl silica were formed. The particles then progressed to larger sizes with similar bl morphology and spherical shape. After the synthesis runs 1 to 2 hours, concentric features of bcl silica appear as a solid material. The change of lamellar orientation in bcl silica (i.e., parallel or perpendicular orientation) is a function of the density of the 232 lamellar phases.[18,65,66]

A schematic representation of the formation of the two morphologies (bl and bcl) is presented in Figure 5a and b. The bl morphology results from thin slabs of lamellar polysiloxane stacks evolving into perpendicular lamellar structures (Figure 5, part II, routes 4-a-bc-5). These structures are considered to have the bl morphology when we apply the topological transformation to the sphere. On the other hand, the bcl morphology is a product of thick slabs of lamellar polysiloxane stacks with complex orientations (Figure 5, part III, route 4-a-b'-c'-d'-6). Thin slabs of lamellar polysiloxane stacks will form perpendicular lamellar orientation and turn into bl morphology (reversible route 4-a-b-c-5), while thick slabs of lamellar polysiloxane stacks will turn into complex lamellar orientation and turn into bcl morphology (reversible route 4-a-b'-c'-d'-6). Based on the explanation of the advantages of the morphological shape formed, this material has the potential to be developed and utilized in drug delivery system applications. However, as far as this article is written, there has not been any utilization of this bcl morphology term in drug delivery system applications.

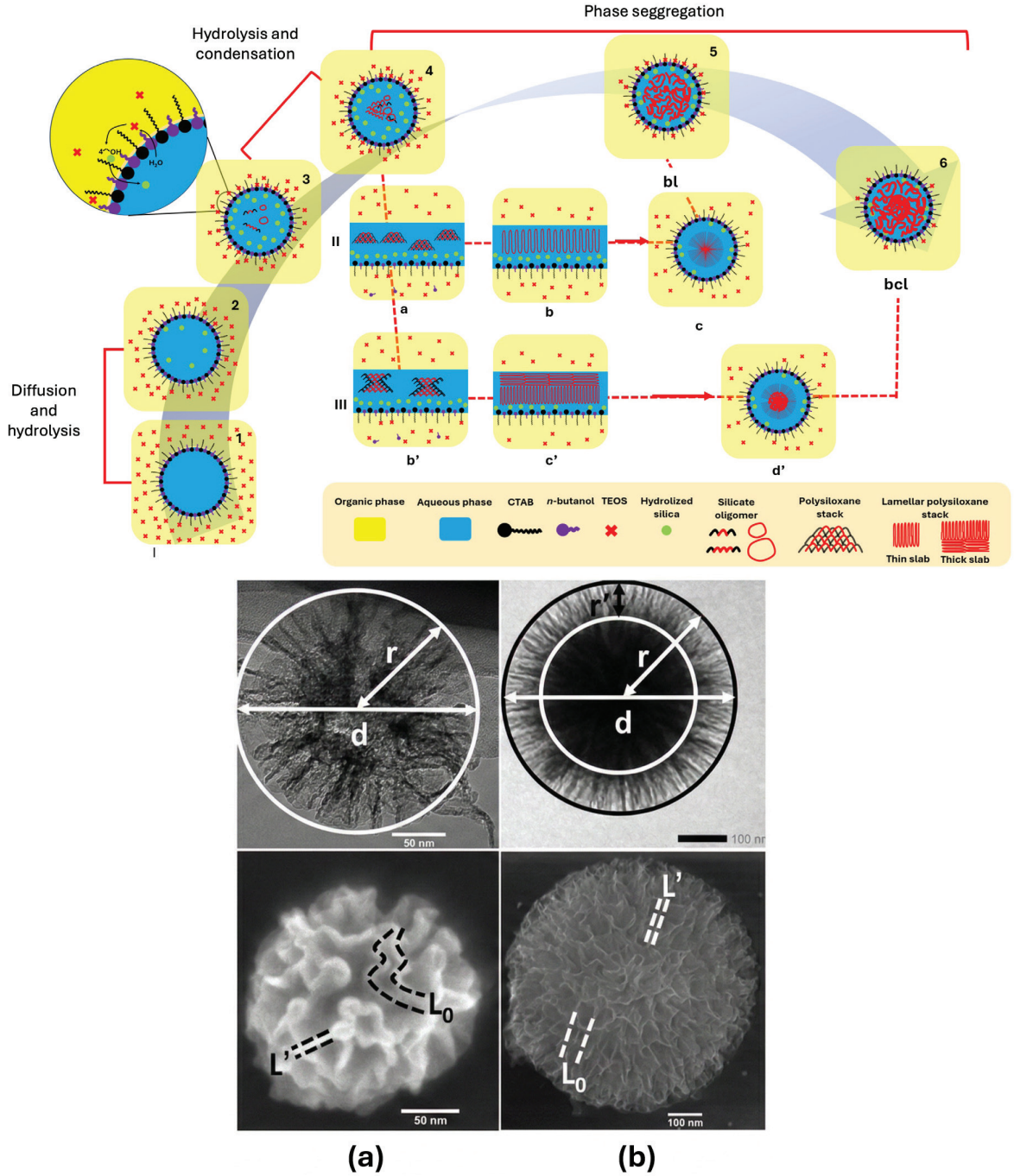


***Figure 5.*** *Growth pathways of bcl silica and schematic description of the assigned morphological parameters of the lamella model on real bcl silica particles. Upper: growth pathway with I: irreversible, II-III: reversible (dashed red line) routes, representing the thermodynamic, Lower: schematic description of the assigned morphological parameters of the lamella model on real bcl silica particles (a: bicontinuous lamellar, bl, b: bicontinuous concentric lamellar, bcl) morphologies with perpendicular and complex orientations of lamellae. (Adapted with permission from Febriyanti E, et al.*[66] *Copyright 2022 American Chemical Society).*

***Particle size***

Hydrolysis and condensation of TEOS are two important reactions in the synthesis of silica-based materials. In the research conducted that controlled the particle size by Taguchi method-based optimization, the reaction was carried out concerning three factors: 1) the amount of TEOS, 2) the pH value, and 3) the reaction time, to control the size of the silica material.[67] The results show that the pH value greatly affects the mesostructural order and particle size. Longer reaction times under alkaline conditions have little effect on the structural order but lead to a decrease in the silica framework, resulting in smaller particle sizes. The more TEOS slightly increases the particle size of the synthesized silica. The basic nature of the catalyst is also considered when forming silica materials by varying the concentration of aqueous urea in the range of 0.08-2.0 M, and a certain amount of sodium

hydroxide or hydrochloric acid is added or used only to determine the effect of the catalyst component.[56] In the synthesis by the hydrothermal method,[31] the average particle size increased with increasing reaction time from 201 nm (for 2 hours) to 260 nm (for 6 hours) and then to 311 nm (for 9 hours), but did not increase with a further increase in reaction time (297 nm for 12 hours). The use of precursors also affects the size of the particles formed. When the amount of TEOS was 50 mL, DFNSs with a large particle size (715±106 nm) having very dense fibers were obtained. Increasing the amount of TEOS to 100 and 150 mL, there was a systematic decrease in the particle size to 260±11 nm and 118±16 nm, respectively. In drug delivery applications, in tests conducted,[24] smaller particles showed much deeper penetration. So far, there have been no further studies on the effect of particle size on lamellar silica in drug delivery applications.

### *Zeta potential*

The zeta potential value indicates the surface charge value of a material. The higher the zeta potential value (negative or positive charge), the more stable material. In drug delivery applications, nanoparticles with a zeta potential greater than ±30 mV are considered strong cationic and strong anionic. In general, nanoparticles with higher zeta potential have stronger electrostatic repulsion, which can help stabilize them and prevent them from aggregating.[68] Surface modification can also affect the zeta potential value and its performance in drug loading.[42] Silica material has a negative zeta potential, and its nature will attract DOX molecules containing amino groups, which facilitates DOX loading. However, when the surface is modified with amino groups, the attractive effect will be weakened, resulting in a decrease in DOX loading. In addition, the functional groups modified on the surface have certain spatial site resistance, which will cause blockage of the pore channels, and this is also the reason for the decrease in DOX loading capacity.

Drug loading has also been reported[48] to affect the value of zeta potential, which can be inferred from the variation of particle zeta potential after hydrophobic PTX loading. Bare dendritic silica has a negatively charged surface, with a zeta potential of -24.8 mV in deionized water. The zeta potential of particles after 10 wt% and 50 wt% PTX loading increased to -20.2 mV and -3.77 mV, respectively. This is due to the shielding of negatively charged silicon hydroxyl groups by uncharged PTX molecules loaded on the particle surface. In contrast, the zeta potential of PTX-loaded dendritic silica through conventional impregnation loading only slightly increased to -23.5 mV, indicating that most of the silicon hydroxyl groups on DMSN were still exposed.

## Conclusion

Lamellar silica-based materials with various unique properties of their texture properties show great potential in drug delivery applications and are expected to be used in the future.

## Ethical approval

During the preparation of this work, the author used AI-assisted methods in order to increase the quality of some of the images in the manuscript without losing the originality of the data.

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## Conflict of interest

The authors declare no conflict of interest.

## CRediT authorship contribution statement

**Dyah Ellyawati Kusumaningtyas Maharani:** conceptualization, literature review, investigation, project administration, writing: original draft, review and edit; **Fajar Rakhman Wibowo**: review and edit, supervisor; **Rino Rakhmata Mukti**: supervisor, correspondence.

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