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Engineering silica nanoparticles for precision nanomedicine: synthesis & functionalization – a review

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Silica nanoparticles are extensively utilized in the biomedical field due to their large surface area, biocompatibility, chemical stability, and tunable surface properties. Their surface can be conveniently modified to support a wide array of applications such as targeted drug delivery, biosensing, and cellular imaging. The silica surface offers abundant reactive sites, enabling straightforward functionalization with a variety of chemical groups to impart specific properties or enhance performance for desired applications. This review presents a detailed account of different synthesis approaches for silica nanoparticles along with methods for introducing various functional groups onto their surfaces. Special emphasis is placed on functionalization techniques tailored for applications in drug delivery, cancer treatment, bioimaging, and biosensing. Furthermore, the review provides a critical evaluation of nanosilica toxicity to ensure their safe deployment in nanomedicine. By critically evaluating current progress and limitations, this review aims to support the development of next-generation silica-based nanocarriers for efficient and safe drug delivery systems.

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Sustainability spotlight

Engineering silica nanoparticles for precision nanomedicine represents a sustainable convergence of materials science and healthcare innovation. By enabling the synthesis and functionalization of biocompatible, abundant, and cost-effective silica, this approach reduces dependence on scarce or toxic nanomaterials while minimizing environmental footprints. Harnessing green synthesis routes and waste-derived silica sources, such as agricultural residues, further advances circular economy principles, transforming low-value byproducts into high-value medical nanomaterials. In doing so, silica nanomedicine not only offers precise, targeted drug delivery and diagnostic solutions but also exemplifies how sustainable material engineering can align advanced healthcare with ecological responsibility.

1 Introduction

Nanotechnology is the interdisciplinary field dedicated to understanding the design, synthesis, and manipulation of matter at the nanoscale. Various nanodevices, such as carbon nanotubes, quantum dots, and polymeric micelles, have been extensively explored in the realm of nanotechnology. They have recently emerged as highly promising materials for drug delivery in nanomedicine, offering advantages such as improved encapsulation, enhanced bioavailability, controlled release, and reduced toxicity.[1] Nanoparticles, including liposomes, polymeric nanoparticles, and metallic nanoparticles, provide multiple benefits compared to conventional drug delivery approaches.[2] Their higher encapsulation efficiency towards both hydrophilic and hydrophobic drugs protects them from degradation and enhances their stability. Encapsulation enhances the bioavailability of drugs with poor solubility and enables targeted transport to specific cells or tissues, minimizing off-target effects while improving therapeutic effectiveness.[3,4] Controlled release is another significant advantage of nanoparticle-based drug delivery. These systems can be engineered to release drugs at a controlled rate over an extended period, maintaining therapeutic drug levels within the desired range. Furthermore, nanoparticle-based drug delivery systems can be designed to respond to specific biological cues, such as pH or redox conditions, to release drugs at the desired site of action.[5]

Precision nanomedicine refers to the tailoring of therapeutic and diagnostic interventions to the individual characteristics of each patient – such as molecular, cellular or microenvironmental heterogeneity – using nanoscale delivery systems. Traditionally, nanoparticle-based therapies have often applied a "one-size-fits-all" approach. However, in the precision era, the goal is to engineer nanoparticles that can navigate the specific

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biological barriers, target the relevant cell types, and adapt to the patient's unique disease biology. For instance, the review by Mitchell *et al.* describes how nanoparticles are being designed to overcome heterogeneous systemic, microenvironmental and cellular-barriers to delivery, thereby enabling a more personalized approach.[6] Thus, precision nanomedicine merges the fields of nanotechnology, drug delivery and personalized medicine to refine efficacy, reduce off-target effects, and account for patient-to-patient variability. Recent advances in nanoparticle technology that support precision nanomedicine include polymeric nanocarriers and functionalized materials, inorganic nanoparticles, "smart" nanoparticle systems, *etc.* For example, recent work on functional polyaspartamide-based polymers has shown their promise as biocompatible, tunable nanocarriers for biomedical applications (drug delivery and imaging) thanks to their degradability and functionalization potential.[7] A recent review focusing on silica-based nanoparticles highlights how detailed investigation into nano-bio interactions is critical for the successful translation of nanoparticle systems.[8] Nanoparticles are increasingly being built to respond to specific cues (*e.g.*, tumor microenvironment pH, enzyme overexpression, and redox state) enabling triggered release and improved specificity – a clear advantage in precision therapy.[6] Thus, precision nanomedicine leverages the ability of nanoparticles to deliver therapeutic and diagnostic cargoes in a targeted and patient-specific manner.

Silica and silicon-based nanomaterials are utilized across a wide range of fields, including drug and gene delivery, regenerative medicine, tissue engineering, lightweight aggregates, cancer diagnosis and treatment, catalytic processes, and energy storage.[9] Among them, silica nanoparticles, especially mesoporous silica nanoparticles (MSNs) first reported in 1992 by the Mobil Oil Corporation, have attracted considerable interest because of their distinctive chemical and structural features.[10] MSNs exhibit a large surface area, adjustable pore sizes, low toxicity, and excellent drug-loading potential, all of which support effective encapsulation and controlled release of therapeutic agents.[11] Structurally, the MSNs possess a honeycomb-like framework with an active surface that can be easily functionalized, allowing the modification of surface properties and the attachment of drugs or biomolecules. Different pore geometries of the MSNs are illustrated in Fig. 1.

Their mesoporous structure provides the encapsulation of a variety of therapeutic agents like small molecules, proteins, and nucleic acids, enhancing their stability and bioavailability.[12] In 2012, Caruso and team developed a novel method by utilizing mesoporous silica particles as templates to fabricate submicrometer-sized polymer capsules intended for anticancer drug delivery.[13] A list of various drug delivery methods for silica nanoparticles and their specific applications is summarized in Table 1.

The synthesis of MSNs typically involves sol–gel processes and surfactant-templated approaches, which allow fine control over particle morphology, pore structure, and surface chemistry. These nanoparticles can be easily functionalized with targeting ligands, responsive moieties, or polymeric coatings to achieve site-specific and stimuli-triggered drug release, making them highly suitable for treating complex diseases such as cancer, infections, and inflammatory disorders.

Furthermore, MSNs demonstrate good biocompatibility and biodegradability, and their surfaces can be tailored to enhance cellular uptake and reduce immunogenicity. The versatility of mesoporous silica in encapsulating hydrophilic, hydrophobic and even bio macromolecules positions them at the forefront of nano-medicine research. This review explores the significance of mesoporous silica nanoparticles in precision nanomedicine applications (*i.e.* drug delivery), detailing their synthesis, surface engineering, advantages and disadvantages over conventional drug carriers.

2 Feedstocks for silica nanoparticle synthesis

Silica nanoparticles are commonly synthesized using both conventional chemical precursors and natural or waste-derived materials. The choice of feedstock plays a critical role in determining the properties, cost and environmental impact of the nanoparticles produced. Tetraethyl orthosilicate (TEOS) and tetramethyl orthosilicate (TMOS) are widely used silica precursors in the sol–gel and Stöber methods. These are silicon alkoxides that undergo hydrolysis and condensation reactions in the presence of a catalyst (acid or base) to form colloidal silica nanoparticles with controlled growth of monodisperse silica spheres in the micron size range.[20] To promote sustainability as well as to reduce costs, researchers have recycled agricultural waste as a renewable resource of silica due to their high silica content.[21–23] Table 2 summarizes the synthesis of various silica particles by using different feedstocks and methods.

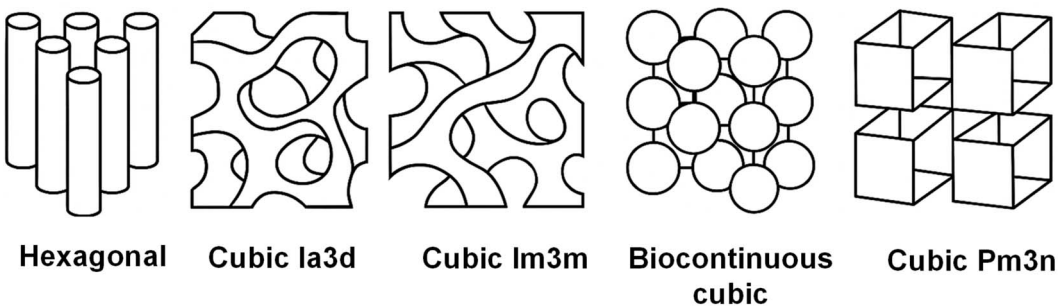

Fig. 1 Various pore geometries of mesoporous structures of silica nanoparticles.

Table 1 Drug delivery methods for silica nanoparticles and their applications

Type of silica nanoparticle system	Drug delivery method	Applications	References
Bare MSNs	Physical encapsulation and adsorption	Anticancer drug delivery	14
Surface-functionalized MSNs	Stimuli-responsive release (pH, redox, and enzyme)	Targeted cancer therapy and intracellular release	15
Polymer-coated MSNs	Controlled/sustained drug release	Oral delivery, improved stability in the GI tract	16
Targeted MSNs (*e.g.*, folate and antibody)	Ligand-mediated receptor targeting	Tumor-specific delivery, *e.g.*, breast or liver cancer	17
Biodegradable MSNs	Gradual release and breakdown	Safer delivery in chronic treatments	18
Hollow silica nanoparticles (HSNs)	Drug encapsulation in hollow core	Large molecule/protein delivery, chemo drugs	19

Table 2 Some examples of synthesized silica particles from different feedstocks

Feedstocks	Synthesis methods	Products	Size	References
Rice husk	Acid treatment	Amorphous silica	0.50–0.70 μm	24
Coconut husk	Acid treatment	Crystalline silica	200–750 nm	25
Fly ash	Acid leaching followed by NaOH treatment	Amorphous silica	2.8 nm	26
Rice husk	Open burning followed with acid treatment	Amorphous silica	NA	27
Coconut husk	NaOH treatment	Amorphous silica	NA	28
Rice husk	NaOH treatment	Amorphous silica	<200 nm	29
Palm kernel cell	Sol–gel method	Amorphous silica	50–98 nm	30
Wheat straw	Acid treatment and calcination	Silica particles	100–120 nm	31
Banana leaves	Precipitation method	Silica powder	1–2 μm	32
Sugarcane bagasse	Surfactant mediated synthesis	Amorphous silica	20 nm	33
Olive stones	Alkali leaching treatment	Amorphous silica	15–68 nm	34
Corncob husk	Biogenic synthesis using *Fusarium culmorum*	Silica nanoparticles	40–70 nm	35

3 Synthesis methods of silica nanoparticles

The synthesis method plays a very important role in controlling nanoparticle properties like structure, size and morphology.[8,9] As shown in Fig. 2, the various techniques for synthesizing silica particles are classified into two main groups: top-down and bottom-up approaches. The methods for preparing silica nanoparticles can be further categorized into physical methods, chemical methods, and green synthesis techniques.

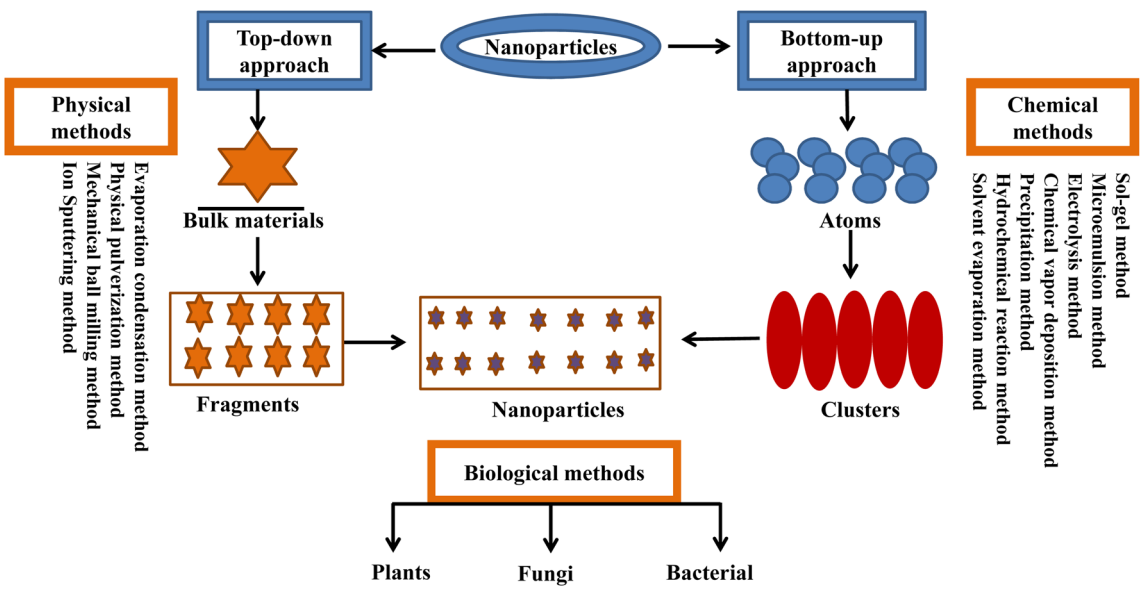

Fig. 2 Classification of synthesis methods for silica nanoparticles.

3.1. Physical methods

The synthesis of silica nanoparticles using physical methods involves the application of external forces like heat or mechanical energy to promote particle formation. Examples of these methods include evaporation condensation method, physical pulverization, mechanical ball milling, and ion sputtering method.

3.1.1 Evaporation condensation method. This method has wide applications, involves heating a silica source until it evaporates, and followed by cooling the vapor to condense it back into fine silica particles. This process allows the formation of nanoparticles through the transition between the gaseous and solid phases. The method is relatively straightforward; however, it suffers from low yield and requires sophisticated equipment. Additionally, the collection of silica nanoparticles during the operational process is complex and presents significant challenges.[36,37]

3.1.2 Physical pulverization. This involves the mechanical breakdown of bulk silica particles into nanoparticles through processes like grinding and milling. This technique relies on applying outside tension to reduce the particle size but often requires prolonged processing times and can result in a broad particle size distribution.[38]

3.1.3 Mechanical ball milling. This process involves grinding samples using high energy collision with balls in a rotating mill. This method requires a lot of time and can result in uneven particle sizes and potential contamination from balling media.[39]

3.1.4 Ion sputtering. In this technique, an inert gas typically argon is introduced in a vacuum chamber. The energetic ion collisions cause atoms or clusters to be ejected from the target surface, which then condense to form nanoparticles.[40] This technique allows for precise control over particle composition and size. However, it requires complex and expensive equipment, and the overall yield of nanoparticles is relatively low, making it more suitable for specialized applications rather than large scale production.

3.2. Chemical methods

3.2.1 Sol–gel method. To synthesize mesoporous silica nanoparticles (MSNs) with controlled size and enhanced properties using the sol–gel method, a carefully modified procedure is employed, often based on the Stöber process. Stöber was the pioneer in developing a system of chemical reactions for the synthesis of spherical monodisperse micro size silica particles. This is a well-established sol–gel method used to produce uniform and monodisperse silica nanoparticles.[41,42] The synthesis begins with the preparation of a surfactant solution, typically using cetyltrimethylammonium bromide (CTAB), which serves as a structure-directing agent to form the mesoporous framework.[43] This solution is stirred and mildly heated to ensure complete dissolution. The pH of the solution is then adjusted using a catalyst commonly ammonia for basic conditions or hydrochloric acid for acidic ones which significantly affects the rates of hydrolysis and condensation of the silica precursor. TEOS is introduced slowly into the surfactant solution under vigorous stirring, initiating hydrolysis and subsequent condensation to form silica networks around the CTAB micelles.[44] The reaction mixture is allowed to age for several hours, during which particle growth and pore formation occur. The resulting MSNs are then collected by centrifugation, thoroughly washed with ethanol and water, and dried. To remove the surfactant template and create accessible pores, the particles undergo either calcination at high temperatures or solvent extraction using acidic ethanol.[45] Key synthesis parameters such as CTAB and TEOS concentrations, pH level, reaction temperature, stirring rate, and the use of co-solvents or swelling agents are systematically adjusted to control particle size, pore structure, and surface characteristics. The size of the particles can be finely tuned by adjusting the concentration of TEOS, ammonia, water, and ethanol, with higher concentrations of TEOS and ammonia generally leading to larger particles.[41,46] This tailored sol–gel approach allows for the fabrication of MSNs with desirable properties for a wide range of applications, including drug delivery, catalysis, and sensing.[47]

3.2.2 Evaporation-induced self-assembly (EISA). The EISA method is an effective technique for synthesizing MSNs, prized for its ability to produce highly ordered microstructures with precise control over pore organization and particle morphology. In this method, a precursor solution is first prepared by mixing a silica precursor like TEOS, surfactants, and a solvent.[46] The surfactant molecules spontaneously self-assemble into micelles, which act as templates for the formation of mesoporous silica. As the solvent gradually evaporates, the concentration of the precursor and surfactant increases, driving the self-assembly of the silica and surfactant into a mesoporous network. This process leads to the creation of a highly ordered silica framework around the surfactant micelles. Once the evaporation is complete, the surfactant template is removed through calcination or solvent extraction, leaving behind a mesoporous silica structure with well-defined pore channels.[48] The advantages of EISA include the ability to control pore size, pore distribution, and the overall structure of the nanoparticles, as well as its scalability, making it suitable for producing large quantities of MSNs. Furthermore, the method allows for the creation of nanoparticles with various shapes, such as spherical or cylindrical, and enables easy functionalization for targeted drug delivery applications. The high surface area and tunable pore sizes of MSNs synthesized *via* EISA make them ideal for drug loading and controlled release, enhancing their potential for clinical use in drug delivery and other biomedical applications.[49]

3.2.3 Micro emulsion method. The micro emulsion method is a versatile technique used for the synthesis of nanosilica, including MSNs, offering fine control over particle size and uniformity.[50] This method utilizes a thermodynamically stable mixture of water, oil, and surfactants, forming nanoscale droplets that serve as reaction vessels for the synthesis of silica nanoparticles.[51] In the micro emulsion process, a silica precursor, such as TEOS, is dissolved in the oil phase, while the water phase contains a small amount of water and surfactants, which stabilize the formation of tiny water droplets within the oil.[52] These water droplets act as nano reactors, where the hydrolysis and

condensation of TEOS occur, leading to the formation of silica. The size of the resulting silica nanoparticles is primarily controlled by the size of the water droplets in the micro emulsion, which can be fine-tuned by adjusting the surfactant concentration, the water-to-oil ratio, and the type of surfactant used.[53] One of the key benefits of the micro emulsion method is its ability to produce uniform, monodisperse silica nanoparticles with a narrow size distribution, typically ranging from 10 to 100 nm. This precise control over particle size is especially beneficial for drug delivery applications, where uniformity in size and surface properties can significantly impact the loading capacity, release profile, and biodistribution of the nanoparticles.[5] Additionally, the micro emulsion method can be used to synthesize nanoparticles with a variety of surface modifications, such as functional groups that enhance drug loading or enable targeted delivery.

The main advantages of the micro emulsion method include its simplicity, the ability to produce small and uniform nanoparticles, and its scalability for producing large quantities of nano silica particles.[52] However, challenges such as controlling the exact pore structure and achieving high drug loading capacities may require further modifications and post-synthesis treatments. Despite these challenges, the micro emulsion method remains a promising approach for the synthesis of nanosilica and MSNs for various biomedical applications, particularly in the field of drug delivery, due to its versatility and control over particle characteristics.

3.2.4 Soft and hard templating. Soft and hard templating are two methods used to synthesize MSNs, each offering control over their structure and properties. Soft templating uses surfactants or block copolymers, which self-assemble into micelles that direct the formation of mesoporous silica when combined with a silica precursor like TEOS.[54] After synthesis, the surfactants are removed, leaving behind a well-ordered mesoporous structure. This method provides excellent control over pore size and surface area, making it ideal for drug delivery applications. Hard templating, or nano casting, involves using preformed solid templates, such as polymer beads or carbon particles, around which silica is deposited. After the silica condenses, the template is removed, leaving a mesoporous silica structure with a similar shape to the original template.[55] This method allows for more complex shapes but is typically more complicated and less scalable than soft templating. Both methods offer advantages depending on the desired particle shape, pore structure, and application, with soft templating excelling in uniformity and hard templating providing flexibility for creating intricate structures.

3.2.5 Electrolysis method. The electrolysis method typically involves two approaches: aqueous solution electrolysis and molten salt electrolysis. It uses direct current to drive non-spontaneous chemical reactions, enabling the separation of elements from natural materials like ores. This technique is capable of producing high-purity ultrafine metal particles, including those that are difficult or impossible to obtain using conventional preparation methods.[56]

3.2.6 Chemical vapor deposition method. This method involves producing silica nanoparticles through chemical reactions occurring on a substrate under heated conditions. It is commonly used for silica nanoparticle synthesis due to its theoretically straightforward operation, ease of product recovery, and the ability to achieve a narrow particle size distribution.[57]

3.2.7 Precipitation method. In aqueous solutions, precipitation involves transforming dissolved raw materials from a supersaturated solution into insoluble solids, known as precipitates. Silica nanoparticles are then obtained through subsequent post-treatment steps. This method can be categorized into direct precipitation, co-precipitation, and uniform precipitation techniques.[58]

3.2.8 Solvent evaporation method. The solvent evaporation method is a technique used to produce silica nanoparticles by dissolving silica precursors in an organic solvent, which is then emulsified in an aqueous phase containing a surfactant. As the organic solvent gradually evaporates under controlled conditions, silica nanoparticles form through hydrolysis and condensation reactions.[59] This method is valued for its ability to produce uniform nanoparticles with controllable size and morphology, making it suitable for applications in drug delivery and coatings and as nanocomposites.

3.3. Biological methods (green approaches)

The green synthesis of silica nanoparticles involves eco-friendly and sustainable methods that avoid the use of toxic chemicals and excessive energy. These approaches make use of natural materials like plant extracts, agricultural residues, and microorganisms to produce nanoparticles in an environmentally responsible manner.[9,22,30,60,61] Additionally, green synthesis provides a cost-efficient alternative to conventional methods by eliminating the need for sophisticated equipment and complicated purification processes. Following are the green synthesis methods for producing silica nanoparticles:

3.3.1 Use of agriculture waste. Agricultural waste, especially rice husk and sugarcane bagasse, is a rich and renewable source of silica. Numerous studies in the literature have reported the use of agricultural materials for the synthesis of high-quality silica nanoparticles.[62–65] For example, Jansomboon *et al.* were the first to synthesize silica micro- and nanoparticles using rice husk as a precursor.[62] Similarly, Lu *et al.* utilized rice straw as a silica source to produce highly pure amorphous silica nano discs.[63]

Rajotia *et al.* reported the utilization of rice-husk-derived amorphous silica nanoparticles for the fabrication of bioglasses for antibacterial and wound healing applications.[64] The primary advantage of using agricultural waste lies in its abundant availability at the end of each harvest season. Consequently, nanoparticle synthesis methods based on agricultural waste are generally more cost-effective than conventional approaches.[65]

3.3.2 Industrial waste. Some industrial waste products have proven to be valuable resources for the synthesis of silica nanoparticles with minimal processing. A notable example is the transformation of fly ash into nanosilica. Fly ash, a by-product of coal-fired power plants, is rich in silica. Yadav *et al.* reported the successful synthesis of amorphous silica nanoparticles from this waste material.[61]

3.3.3 Plant extract-mediated synthesis. This method uses extracts from various plants which contain natural compounds such as flavonoids, polyphenols, and sugars. Numerous studies in the literature have documented the green synthesis of nanoparticles using a wide variety of plant sources. Durairaj *et al.* synthesized silica nanoparticles using the well-established sol–gel method with ash derived from *Bambusa vulgaris* leaves and applied them in environmental applications.[65] Jabeen *et al.* demonstrated the synthesis of silica nanoparticles utilizing *Azadirachta indica* (Neem) leaf extract, which functioned as an efficient chelating agent in the process.[66]

3.3.4 Microbial synthesis. Certain bacteria, fungi, and diatoms naturally interact with silica compounds and can be used to synthesize silica nanoparticles biologically. Microorganisms are cultured in the presence of silica precursors. Through metabolic processes, they help in the formation of silica particles either within or outside their cells. This method is highly specific, biodegradable, and suitable for biomedical applications due to its biocompatibility. A comparative study summarizing the benefits and limitations of both chemical and biochemical synthesis routes, including aspects such as eco-friendliness, scalability, cost, particle uniformity, reaction control, and biological compatibility is given in Table 3.

3.4. Surface functionalization of MSNs

Surface functionalization of silica nanoparticles enables precise control over their surface chemistry, facilitating targeted delivery and improved drug loading. These features make them a promising choice for biomedical applications.[73–75] Through the incorporation of dopants, chemical alteration of surface

Table 3 Advantages and disadvantages of different methods used for silica nanoparticle synthesis[67–72]

Methods	Advantages	Challenges	Typical Applications
Sol–gel method	• Simple and widely studied • Enables controlled composition & size • High-purity amorphous silica • Allows mesoporous control *via* surfactants	• Long processing time • Requires organic solvents	• Anticancer drug delivery, catalysis, sensors, and coatings
Evaporation-induced self-assembly	• Highly ordered pore arrangement • Tunable pore size and morphology • Scalable synthesis	• Sensitive to humidity & solvent rate • Requires template removal	• Drug delivery, catalysis, adsorption, and optical coatings
Microemulsion method	• Excellent control over particle size • Uniform and monodisperse nanoparticles • Mild synthesis conditions	• High surfactant cost • Difficult purification • Limited control over pore ordering	• Drug delivery, imaging, and biosensors
Soft templating	• High surface area & pore uniformity • Easy control of pore size • Suitable for MSN	• Template removal required • Sensitive to pH & temperature	• Drug delivery, adsorption, and catalysis
Hard templating (nanocasting)	• Complex and tunable shapes possible • High pore regularity and uniformity	• Multi-step, costly • Difficult to scale-up • Template removal may damage structure	• Catalysis, photonics, and advanced composite materials
Electrolysis method	• Produces high-purity ultrafine particles • Suitable for special material synthesis	• Requires specific equipment • Energy intensive • Limited uniformity control	• Metal-silica composites and specialized coatings
CVD	• Produces uniform coatings and nanoparticles • Scalable and clean process • Narrow particle size distribution	• High temperature needed • Expensive precursors & setup	• Coatings, optical films, and microelectronics
Hydrothermal method	• Uniform & well-dispersed nanoparticles • High crystallinity & purity • Controlled morphology	• Expensive equipment • Long reaction time • Limited scalability	• Catalysts, sensors, and bioactive materials
Solvent evaporation method	• Produces uniform nanoparticles • Tunable morphology • Simple operation	• Requires surfactant stabilization • Control of solvent rate critical	• Drug delivery, coatings, and nanocomposites
Green synthesis with waste	• Renewable, cost-effective & eco-friendly • Utilizes waste materials • High silica yield	• Impurities (metal oxides, carbon, *etc*) • Irregular particle size	• Adsorbents, bioactive glass, composites, construction, and adsorbents

Table 4 Surface functionalization of silica nanoparticles for different applications

Methods	Substrate materials	Applications	References
Co-condensation and post-grafting	Amino groups	Cancer drug delivery	73 and 79
Polymer coating	poly(2-(diethylamino)ethyl methacrylate)	Drug delivery	75 and 80
Hydrophobic silanization	Alkyltrichlorosilanes	Adsorbent, catalyst, microfluidic	81
Plasma polymer coating	SUS 304 stainless steel, petroleum hydrocarbon removal	Biomedical implant	82 and 83
Doping	Metal and metal oxides (ag, Ni)	Catalyst	84
Surface coating	CdSe@ZnS QDs, γ-Fe_2O_3	Bio imaging	85
Silanization	3-Glycidoxypropyltrimethoxysilane (GPTS) and amines	Gene transfer	86
Surface coating	Gd[DO3A-hexylamine]	MRI	87 and 88
Silanization	(3-Aminopropyl) triethoxysilane	Drug delivery	89

groups, and diverse assembly strategies, it is possible to design multifunctional nanoparticles that serve both therapeutic and diagnostic roles, such as carrying imaging agents along with drugs or heat-generating elements.[74,76] Several techniques are used for the surface functionalization of silica particles to enhance their properties for specific applications. Common methods include silanization, where organosilanes are grafted onto the surface to introduce functional groups,[77] co-condensation, which involves incorporating functional groups during the synthesis process, and layer-by-layer assembly for multilayer coatings. Additionally, physical adsorption and polymer grafting are employed to attach biomolecules, drugs, or imaging agents.[78] These techniques enable precise control over surface chemistry, improving biocompatibility, targeting ability, and loading efficiency in biomedical applications. Table 4 summarizes some important studies based on the surface functionalization of silica nanoparticles.

From the table, we can observe that the choice of agents for functionalization affects its field application. To enhance the specificity of silica nanoparticles for interacting with target cells, linker molecules are also employed during the bio conjugation process. These linkers connect antibodies to the nanoparticle surface *via* interactions between functional groups on the silica and specific amino acid residues of the antibody. The primary role of the linker is to introduce spatial separation between the antibody and the nanoparticle surface, thereby reducing the risk of antibody denaturation or steric hindrance that might impair its biological activity. Two main strategies are typically used: monovalent and multivalent linkers.[90] Monovalent homofunctional linkers, such as glutaraldehyde, facilitate the formation of imine bonds between amine groups on the silica nanoparticle surface and lysine residues on immunoglobulins (IgG). However, this approach can lead to undesirable aggregation. To overcome such limitations, monovalent heterofunctional linkers like sulfosuccinimidyl 4-[*N*-maleimidomethyl] cyclohexane-1-carboxylate (sulfo-SMCC) are preferred. Sulfo-SMCC enables effective coupling between sulfhydryl groups on the nanoparticle surface and lysine residues on IgG, offering improved stability and reduced aggregation during conjugation.[91,92]

3.5. Key challenges

The key challenges in producing high-quality and reproducible silica nanoparticles for biomedical and therapeutic applications are batch-to-batch reproducibility, control over particle size and uniformity, surface modification and functionalization, scalability and process standardization, aggregation and stability, and quality control and characterization.[5,16,93,94] Maintaining consistent particle size, morphology, and surface characteristics remains difficult due to the sensitivity of sol–gel and templating synthesis methods to reaction parameters such as pH, temperature, precursor concentration, and mixing rate.[5,16] Precise control of nanoparticle size and pore structure is crucial for predictable drug loading and release, yet even small variations in synthesis can lead to polydispersity and altered functionality.[16] Achieving stable, uniform, and reproducible surface coatings or targeting ligands without altering nanoparticle stability or aggregation behavior is technically challenging.[5,16,93] Transitioning from laboratory-scale synthesis to industrial production often leads to changes in particle properties and reproducibility issues due to lack of standardized manufacturing protocols.[5,94] Silica nanoparticles are prone to aggregation during synthesis, purification, and storage, affecting their dispersibility, bioavailability, and reproducibility.[16] Reliable analytical techniques are required to ensure reproducibility in structural, chemical, and surface properties across batches – an area still limited by methodological variability.[5] Thus, reproducible synthesis of high-quality silica nanoparticles is hindered mainly by difficulties in controlling physicochemical parameters, ensuring batch consistency, and scaling up production while maintaining uniformity and stability.

4 Characterization of MSNs

The synthesis of MSNs has evolved through several advanced characterization techniques aimed at improving structural control, scalability, and drug-loading efficiency.[95,96] These methods help to determine various properties including particle size, shape, crystalline, pore size, and surface area. The EISA method allows reactants to undergo concentration changes during solvent evaporation, leading to the formation of liquid crystal-like silica structures. Fontecave *et al.* later modified this approach by incorporating amphiphilic drugs as both structure-directing agents and active cargos, eliminating the need for toxic surfactants and achieving high drug-loading efficiency with minimized burst release.[97] A spray dryer operating under adequate airflow and pressure conditions was utilized to transform the precursor droplets into solid mesoporous particles. TEM analysis confirmed that the resulting

particles exhibited pore size and structural features comparable to those obtained using cetyltrimethylammonium bromide as the surfactant template.[98] An alternative mechanism, known as the "swelling-shrinking mechanism", also has been proposed to explain the formation of MSNs, based on observations made using time-resolved synchrotron small-angle X-ray scattering (SAXS) analysis.[99] The *in situ* time-resolved small-angle neutron scattering (SANS) technique has been employed to monitor the real-time formation of MSNs.[100,101] This analysis revealed that during the initial hydrolysis of TMOS, silicate species begin to accumulate around surfactant micelles. As hydrolysis and condensation progress, the surface charge decreases, reducing intermicellar repulsion and promoting the aggregation of silica frameworks. Later, well-defined hexagonally ordered mesopores were observed, as confirmed by TEM, supporting the "current bun model" of MSN formation.[100,101]

5 Silica nanoparticles for precision nanomedicine

5.1. Drug delivery

Silica nanoparticles have emerged as versatile platforms for targeted and controlled drug delivery due to their tunable pore size, large surface area, and easy surface functionalization. They enable high drug loading efficiency, protection of therapeutic agents, and stimuli-responsive release, enhancing drug bioavailability and reducing systemic toxicity.[96,102,103] Their surface can be modified with ligands for site-specific delivery, improving therapeutic outcomes in diseases such as cancer and autoimmune disorders.[104,105] Overall, silica nanoparticles represent a promising nanocarrier system for achieving precision and efficacy in modern drug delivery applications, as depicted in Fig. 3.

5.1.1. Targeted drug delivery. Silica nanoparticles can be modified with targeting molecules such as antibodies, peptides, or vitamins.[106,107] These modifications enable the particles to specifically recognize and bind to receptors on diseased cells, such as cancer cells. This selective targeting helps concentrate the drug at the intended site, thereby reducing damage to healthy tissues and improving treatment efficiency.

5.1.2. Controlled and sustained drug release. The porous structure of MSNs makes them excellent carriers for sustained drug release. Drugs can be stored within the nanopores and released slowly over time. Additionally, the release rate can be fine-tuned using external stimuli like pH, temperature, or enzymes, making them ideal for site-specific delivery in environments like tumors or infected tissues.[107] Panja *et al.* reported the grafting of hyperbranched polyglycerol (HPG) onto silica-coated nanoparticles to enhance their colloidal stability and biocompatibility.[108] The HPG layer provided excellent aqueous dispersibility, resistance to aggregation, and low nonspecific protein adsorption, making the modified nanoparticles ideal for biomedical applications requiring stable and non-fouling nanomaterials.

5.1.3. Combination drug delivery. Silica nanoparticles can carry multiple therapeutic agents simultaneously. This allows the co-delivery of drugs that work together to enhance treatment outcomes or overcome drug resistance.[109,110] For example, in cancer therapy, combining chemotherapy drugs in single nanoparticles can produce a stronger effect than using them separately.[111] Mesoporous organosilica nanoparticles (MONs) have emerged as promising nanocarriers for the targeted chemotherapy of prostate cancer due to their tunable pore structure, high surface area, and functionalizable organic–inorganic hybrid framework. Das *et al.* reported the development of antibody-conjugated biodegradable periodic MONs for targeted chemotherapy of prostate cancer.[112] Using super-resolution microscopy, they quantified nano periodic mesoporous organosilica (PMO) nanoparticle biodegradation in response to glutathione, as well as the effects of antibody multivalency and orientation on cancer cell targeting.

5.1.4. Cancer immunotherapy. Recent advances in nanotechnology have significantly improved cancer therapy through the development of innovative nanocarrier systems. Theivendran *et al.*[113] highlighted the potential of mesoporous silica and

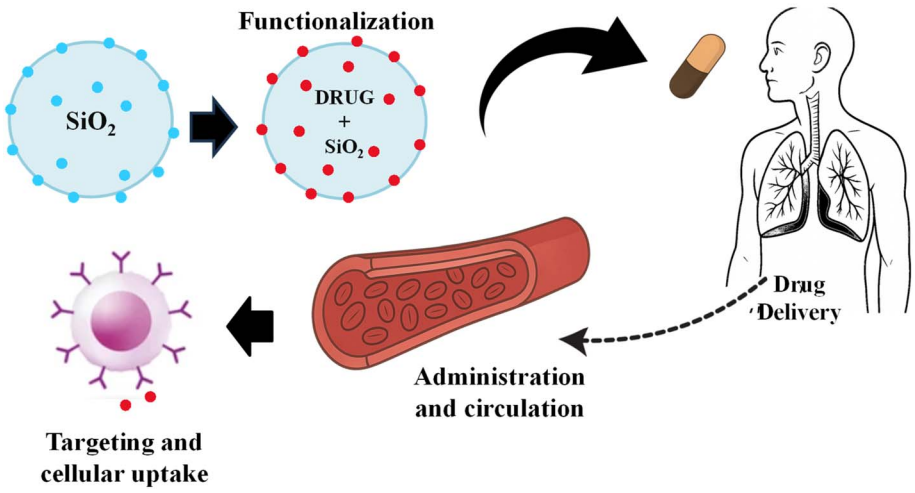

Fig. 3 Schematic representation of applications of silica nanoparticles in drug delivery.

organosilica nanoparticles as versatile platforms for cancer immunotherapy. Their tunable porosity, large surface area, and modifiable surface chemistry enable efficient antigen delivery, immune activation, and combination with checkpoint inhibitors for enhanced therapeutic efficacy. Complementarily, Cao *et al.*[114] introduced deformable nanocarriers designed to navigate physiological barriers and achieve superior tumor penetration and drug release. These flexible nanocarriers adapt to the complex tumor microenvironment, improving bioavailability and minimizing off-target effects. Together, these studies emphasize that structurally engineered and functionally adaptable nanocarriers represent a promising direction for next-generation, high-precision cancer therapy.

5.1.5. Gene and nucleic acid delivery. With the right surface coatings, silica nanoparticles can also transport genetic material such as DNA, RNA, or mRNA into cells. These particles protect the genetic material from degradation and improve its uptake by target cells, which is beneficial for gene therapy and RNA-based treatments.[115]

5.1.6. Drug delivery across blood–brain barriers. Some drugs have difficulty reaching certain parts of the body, like the brain. Silica nanoparticles can be designed to cross biological barriers such as the blood–brain barrier.[116] This enables the delivery of drugs that would otherwise be ineffective in treating brain-related diseases.

5.1.7. Antimicrobial applications. Silica nanoparticles have shown promise in delivering antibiotics directly to sites of infection. This targeted approach can help reduce bacterial resistance and enhance the effectiveness of antimicrobial treatments, especially in cases of biofilm related infections.[117,118]

5.1.8. Gene therapy. Nanoparticles are utilized to deliver genetic material in gene therapy applications, offering the potential to correct genetic disorders by transporting therapeutic genes directly to targeted cells.[119]

5.2. Impact of silica nanoparticles on hemocompatibility

Hemolysis, defined as the rupture of erythrocyte membranes leading to hemoglobin release or destruction of red blood cells (RBC), serves as a crucial indicator of the hemocompatibility of silica nanoparticles. The extent of hemolytic activity is strongly influenced by multiple physicochemical parameters such as particle size, morphology, surface chemistry, and surface roughness.[8] Experimental investigations have demonstrated a size and concentration dependent hemolytic response; wherein larger silica nanoparticles generally induce greater erythrocyte membrane disruption due to enhanced interfacial interactions between surface silanol groups and phosphatidylcholine moieties of RBC membranes. Lin *et al.* had studied the effect of different particle sizes in hemolysis and reported that hemolytic activity is directly proportional to the size of MSNs.[120] Also, some studies showed that high mass with a small size of silica nanoparticles demonstrated increasing hemolytic activity. In contrast, smaller silica nanoparticles (<50 nm) typically exhibit reduced hemolytic potential owing to their larger surface area-to-volume ratio and improved colloidal stability.[121] Furthermore, particle morphology also plays a critical role, and spherical nanoparticles tend to exhibit superior hemocompatibility compared to their rod-shaped or tubular counterparts. Surface functionalization, including amine modification, PEGylation, or lipid bilayer coating, has been shown to substantially mitigate hemolytic activity by shielding reactive silanol groups and diminishing electrostatic interactions with erythrocyte membranes.[122,123] Additionally, surface roughness modulates MSN-cell membrane interactions, where smoother surfaces such as those in HMS and MSU-type silica nanoparticles enhance hydrothermal stability and reduce membrane perturbation.[124] Collectively, these findings suggest that hemolytic behavior is governed by a complex interplay between MSN physicochemical characteristics and membrane interaction dynamics, emphasizing the necessity of precise surface engineering to ensure the biocompatibility and safety of MSN-based drug delivery systems. Rajotia *et al.* developed silica-incorporated bioactive glass composites and evaluated their potential in wound healing applications. The *in vivo* studies demonstrated that the silica-based bioglass exhibited excellent regenerative and wound healing efficacy, promoting rapid tissue repair and enhanced epithelialization. These findings highlight the crucial role of silica incorporation in improving the bioactivity, biocompatibility, and therapeutic performance of bioglass materials for advanced biomedical applications.[64]

5.3. Safety and biodegradation of silica nanoparticles

The safety and biodegradation of silica nanoparticles are critical factors that influence their suitability for clinical drug delivery applications. Among the most used administration routes for silica nanoparticles are intravenous, subcutaneous, and intratumoral injections. Intravenous administration offers the advantage of rapid systemic distribution *via* the bloodstream, enabling the nanoparticles to reach target sites throughout the body efficiently.[125] Their structural integrity ensures that the drug remains shielded from enzymatic degradation, hydrolysis, and other destabilizing factors in the blood.[102,105] Importantly, once the nanoparticles reach their target site and release their therapeutic payload, it is desirable for them to undergo biodegradation into non-toxic by-products that can be safely eliminated from the body, typically through renal or hepatic pathways.[104,106] The degradation of silica nanoparticles generally occurs *via* hydrolysis of the silica matrix into silicic acid, a biocompatible compound that is naturally excreted.[126] The degradation rate can be finely tuned by modifying the synthesis parameters, such as pore size, particle size, surface functionalization, and degree of condensation of the silica network. Fig. 4 depicts the interconnection between oxidative stress, autophagy dysfunction, and inflammasome activation leading to inflammatory outcomes. In addition, Rabolli *et al.* (2010) reported an *in vitro* study of the effect of size, porosity and surface area on the cytotoxicity of silica nanoparticles.[127] Dong *et al.* (2020) reported a detailed study on the size dependent cytotoxicity of silica nanoparticles.[128]

Despite notable advancements in silica nanoparticles over other inorganic nanomaterials, investigating their potential

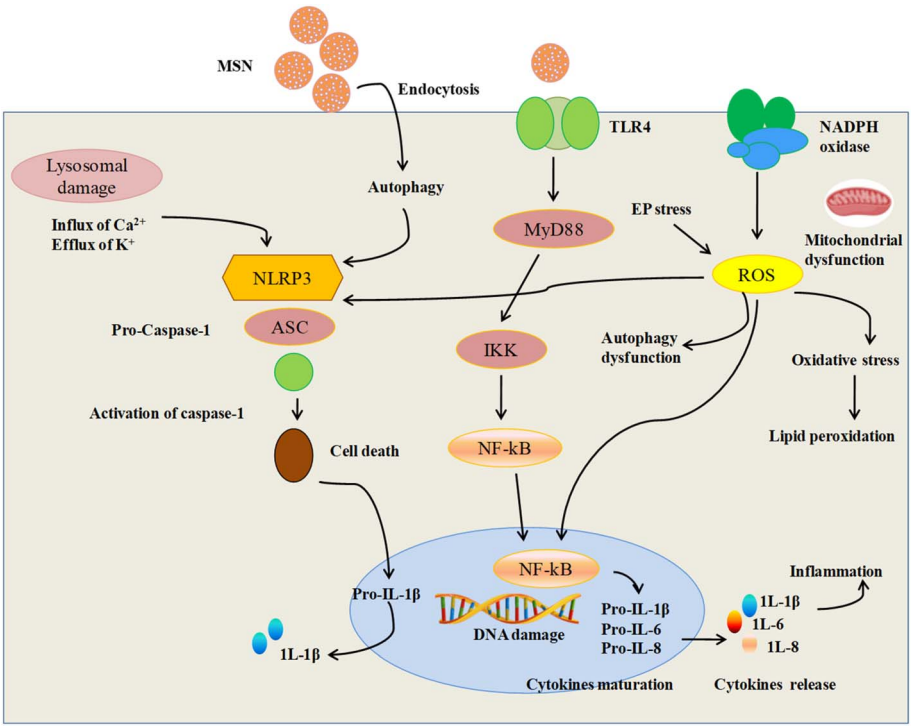

Fig. 4 The mechanism for toxicity of silica particles includes pro-inflammatory response, autophagy and oxidative stress.

toxicity is still crucial. The harmful effects of silica nanoparticles are largely influenced by characteristic size, shape, surface charge, crystalline structure, and concentration. For example, positively charged silica nanoparticles have been found to generate stronger toxic responses through reactive oxygen species (ROS) compared to their negatively or neutrally charged counterparts.[129] The cytotoxicity of silica nanoparticles toward normal cells can be explained by two main factors: (i) they increase oxidative stress within cells by promoting the generation of harmful ROS and reducing glutathione levels a key molecule involved in maintaining redox balance which in turn causes lipid peroxidation and eventually leads to cell death, and (ii) the free Si–OH groups present on the surface of silica nanoparticles can electrostatically interact with the phospholipids in the cell membrane, resulting in membrane disruption and damage. Considering all these points, we need to give attention to the surface functionalization of silica nanoparticles to decrease their toxicity.

6 Conclusions and perspectives

Silica nanoparticles, particularly mesoporous silica nanoparticles (MSNs), have established themselves as one of the most versatile and promising nanoplatforms for biomedical applications. Their unique combination of large surface area, tunable pore structure, controllable morphology, and ease of surface modification enables efficient drug loading, targeted delivery, and controlled release. The review highlights that diverse synthesis strategies, from conventional sol–gel and micro-emulsion techniques to sustainable green approaches using agricultural or industrial wastes, offer flexibility in tailoring structural and physicochemical properties for specific biomedical purposes. Surface functionalization through silanization, co-condensation, polymer coating, and bio-conjugation further extends their potential, allowing the integration of targeting ligands, responsive moieties, and imaging agents for multifunctional therapeutic systems.

However, despite significant progress, several critical challenges remain before silica nanoparticles can be fully translated into clinical practice. Controlling batch-to-batch reproducibility, ensuring colloidal stability, minimizing aggregation, and achieving scalable manufacturing remain key technical hurdles. Moreover, understanding the complex interactions between MSNs and biological systems, including protein corona formation, immune response, hemocompatibility, and long-term biodistribution, requires deeper investigation. Although silica degradation into biocompatible silicic acid is advantageous, the rate and mechanism of biodegradation must be carefully optimized to balance drug retention and clearance. Addressing toxicity concerns through the rational design of particle size, surface charge, and functionalization is essential to ensure biosafety.

Looking forward, the next generation of silica-based nanomedicines will likely evolve toward precision-engineered, stimuli-responsive, and biodegradable systems capable of delivering therapeutics with spatiotemporal control. Integration of artificial intelligence (AI) and machine learning (ML) tools into nanoparticle design can accelerate optimization by predicting nano–bio interactions and performance outcomes. Furthermore, combining silica nanoparticles with other

functional materials such as polymers, lipids, or metals could yield hybrid nanostructures with enhanced diagnostic and therapeutic functionalities. Emphasis should also be placed on developing environmentally sustainable, cost-effective synthesis routes to promote scalability and regulatory acceptance.

In conclusion, silica nanoparticles stand at the forefront of precision nanomedicine due to their structural versatility, tunable surface chemistry, and proven biocompatibility. Continued interdisciplinary research bridging materials science, biology, and clinical translation will pave the way for safe, effective, and personalized nanotherapeutics that can transform the future of disease diagnosis and targeted treatment.

Author contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript. M. R. did formal literature review, analysis of data, and prepared the original draft. A. Y. did analysis of data and initial revision of the original manuscript. V. K. S. helped in data acquisition and analysis. S. P. supervised, edited and reviewed the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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