Journal of Pharmacy

Fabrication, Applications and Future Prospects of Mesoporous Silica Nanoparticles

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Abstract

In past decades, nanomedicine has become a prominent area of focus within the discipline of nanotechnology, eliciting significant anticipation within the field of biomedical research. Scientists are creating unique nanoparticles for diagnosis, utilising techniques for imaging as well as therapy applications using medication delivery techniques. Mesoporous silica nanoparticles (MSNs), a recent addition to this area, serve as a sterling example of innovative nanostructures that offer distinctive and exceptional features. These features make them valuable for developing drug delivery systems with consistent and positive advancements in preclinical. MSNs efficiently encapsulate, control, and sometimes deliver biologic agents intracellularly for clinical use due to their distinct physicochemical characteristics, such as high porosity, large surface area, adjustable pore size and dimensions, good biocompatibility, and significant loading capacity. In this article, we discuss the latest advancements in fabrication, their presumed usefulness in delivering medications, and their application as diagnostic tools. It has been demonstrated that silica can store and release therapeutics, such as antibiotics, in a sustained and controlled manner. The desirable properties of MSNs have been further enhanced by modifying the surface of the siliceous frameworks through incorporating supramolecular assemblies and various metal species and their conjugates. These substantial advancements in innovative colloidal inorganic nanocontainers have driven researchers to explore their use in novel applications, such as stimuli (light/ultrasound/ magnetic)-responsive delivery-associated therapies with exceptional in vivo performance. This article provides a brief overview of the fabrication of siliceous frameworks and discusses significant advances in the engineering of MSNs. The precise control of the shape, dimension, homogeneity, and dispersity of MSNs is crucial, as these characteristics are critical quality attributes necessary for regulatory approval. Currently, explicit FDA guidelines for developing nanomaterial-based formulations intended for diagnostic or therapeutic purposes are lacking. Therefore, establishing standardised protocols and techniques for the synthesis and characterisation of nanoparticles, particularly for their use as theranostics, is essential for future commercial potential.

Article history:

Received: 9 October 2023
Accepted: 2 January 2024
Published: 31 July 2024

Keywords:

Nanomedicine
Nanotechnology
Biocompatibility
Characterisation
Biocatalysis
Homogeneity
Theranostics

doi: 10.31436/jop.v4i2.264

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Introduction

The emergence of nanotechnology has yielded robust methodologies for fabricating nanostructured substances with significant potential for various biomedical applications, including drug delivery, illness diagnosis, medical imaging, and tissue regeneration. Nanomaterials have been utilised as carriers for active pharmaceutical ingredients to enhance distribution and targeting in biological and medical imaging applications (Fadeel & Garcia-Bennett, 2010). Experts have shown considerable interest in developing nanocarriers for the controlled and targeted delivery and release of drugs at specific disease sites (Scicluna & Vella-Zarb, 2020).

The molecules under consideration are classified as organic or inorganic nanocarriers, which demonstrated significant success in treating several infections. These organic nanometric molecules are encompassed within various polymeric agents (Begines et al., 2020), lipid-based transporters (Plaza-Oliver et al., 2021), dendrimers (Mandal, 2021) and micelles (Atanase, 2021). In contrast, inorganic nanocarriers have garnered significant interest compared to their organic counterparts due to their superior physicochemical and thermochemical stability. The primary molecules utilised in this context predominantly encompass tiny carbon, metal, or silica carriers. Inorganic nanoparticles such as quantum dots, mesoporous silica, carbon nanotubes, and gold, silver, or iron nanoparticles have the advantages of being hydrophilic, non-toxic, and biocompatible with living systems. Furthermore, the stability of inorganic nanoparticles is superior to that of organic nanoparticles. Mesoporous Silica Nanoparticles (MSNs), compared to organic carriers, such as micelle, gel, and liposome, have higher loading capacity (Yu et al. 2018). Due to their high drug encapsulation efficiency, they significantly affect nanobiotechnology research. MSNs have been successfully used as a carrier for the oral delivery of hydrophobic drugs, such as praziquantel in murine Schistosomiasis mansoni, significantly increasing the dissolution rate and bioavailability compared to standard drugs (Tawfeek et al. 2019). Recent advancements have led to the development of MSN-based drug delivery systems for the treatment of periodontitis, cancer, dentin hypersensitivity, and dental cavities.

MSNs are inorganic molecules characterised by their nano-sized pores, typically ranging from 1 to 100 nm (Manzano & Vallet-Regí, 2020; Wu et al., 2013; Zhang et al., 2018). They have strong biocompatibility yet have a mild degradation trend. Regarding dimensions, apertures size, and shape, the aforementioned mediums shared major characteristics such as excellent loading and encapsulating performance, quick and simple manufacturing technique, biocompatibility, no early discharge, and enhanced customisation (Alyassin et al., 2020).

The most advantageous characteristics of MSNs as a medication delivery method is their capacity for "zero premature controlled release", as elucidated by Slowing et al. in 2008. This property ensures the delivery of drugs without undesired leakage. Achieving this attribute involves designing MSNs as intelligent drug delivery carriers, allowing for targeted drug release in specific areas of interest while avoiding premature release at off-target sites. However, there remains a lack of information concerning the challenges encountered in their fabrication, application, and clinical translations. Therefore, this review aims to explore these issues, with particular emphasis on the regulatory aspects associated with theirs theranostic applications.

Types of MSN

The synthetic production of MSNs can be traced back to before the 1970s (Danks et al., 2016; Stober et al., 1968). In 1992, Mobil Research and Development Corporation successfully synthesised MSNs using alumino-silicate gels (Danks et al., 2016; Mohamed et al., 2022). The researchers employed a liquid crystal framework and designated these substances as Mobil

Composition of Matter or Mobil Crystalline Materials (MCM) (Grun et al., 1997; Lin & Mou, 1996). MSNs are typically classified into several categories, including Santa Barbara (SBA-1, 2, 3, 6, 12, 15, & 16), MCM (MCM-41, 48, and 50), Michigan State University (MSU), Fudan University (FDU), and Hexagonal Mesoporous Silica (HMS) (Alothman, 2012; Oo & Chatterjee, 2019; Vivero-Escoto et al., 2010). These classifications arise from the use of specific surfactants under optimal reaction conditions, which determine pore diameters (Beck et al., 1992; Danks et al., 2016). Physically, MSNs appear as fine white powder, and their porous structure can only be observed under an electron microscope (Figure 1).

Fig. 1: Circular-shaped MSN: (a) Physical appearance and (b) Enlarged 3D structure. Reproduced from Lundquist et al. (2014).

Various reaction conditions have led to the development of different members within the MCM family. MCM-41, distinguished by its use of cationic surfactants as templating agents, has become a widely utilized carrier. It features pores ranging from 2.5 to 6 nm in diameter and a 2-dimensional hexagonal shape(Munoz et al., 2003; Y. Wang et al., 2014). Another significant member, MCM-48, has a 3-dimensional cubic structure and is employed in drug carrier formulations due to its bi-continuous channels that facilitate faster ingredient transfer compared to MCM-41(Grun et al., 1997; Wang et al., 2014). MCM-50, on the other hand, adopts a lamellar configuration (Oye et al., 2001).

The symmetry of silica layered materials is influenced by the initial templating agent used during synthesis. For instance, SBA is a very structured mesoporous framework synthesised at the University of California. It features thick silica layers and larger apertures ranging from 4.6 to 30 nm) (Jarmolińska et al., 2020; Zhao et al., 1998). One templating agent, neutral copolymer alkyl poly (ethylene oxide), induces the production of cube-shaped mesopores known as SBA-11. In contrast, oligomeric surfactants result in the formation of 3-dimensional hexagon-shaped mesoporous structures called SBA-12 (Zhao et al., 1998). Moreover, this process may produce a conventional hexagon-shaped mesostructured transporter called SBA-15 and a cube-shaped cage-type configuration called SBA-16 (Feliczak-Guzik et al., 2016; Wang et al., 2009).

MSNs, including MCM-41, 48, SBA-15, and SBA-16, are extensively used in pharmaceuticals and genetics. Building on these discoveries, two trends have been identified for the four primary types of MSN, which are MCM, SBA, TUD, and KIT. Firstly, the geometrical shape of these MSN is affected by the initial templating agent employed during synthesis. Previous research suggests that a spherical shape can aid in achieving uniform dose distribution, a regulatory requirement that is challenging to meet (Mohamed et al. 2022). Therefore, it is imperative to compile a catalogue of surface templating agents, typically surfactant-based, capable of generating spherical MSNs. This can simplify regulatory compliance while optimizing the drug release profile, as the spherical shape facilitates the study of factors influencing release, drug loading percentage, and interactions with biological receptors.

Secondly, all currently produced MSNs are in powder form, indicating the need for formulators to understand the desirable characteristics of powders. This knowledge is essential for synthesizing fine, free-flowing powders suitable for industrial and bulk powder handling using high-speed machinery.

Advancement in Msn Production Technique

Considering the easily tailorable nature of mesoporous frameworks, there has been significant interest in altering the overall morphology of MSNs

to enhance their properties for diverse applications (Meng et al. 2011). Among various morphological attributes, particle diameter and shape modification play crucial roles in influencing the behaviour of the delivery system. These factors, along with surface chemistry, affect blood circulation, immune responses and delivery efficiency through specific cellular uptake pathways (Lin et al. 2010). These critical aspects and the potential for further advancements have made MSNs one of the predominant inorganic constructs for versatile delivery systems and catalysis supports.

MSN can be created using various processes, including hard or soft templates, quick self-assembling, the Stober approach, customised aerogel techniques, the hydrothermal approach, and dissolving restoration strategies. Stober pioneered a way to synthesise circular micro-sized silica nanoparticles through precise chemical procedures, later known as Stober synthesis (Stober et al., 1968). Most MSNs are made using Stober's sol-gel method, which forms colloidal fragments through hydrolysis and condensation under basic or acidic pH conditions. These colloids condense to form a three-dimensional gel state linked by cross-linked siloxane bonds (Medina et al., 2012). The common synthesis steps of MSNs can be simplified and illustrated, as shown in Figure 2.

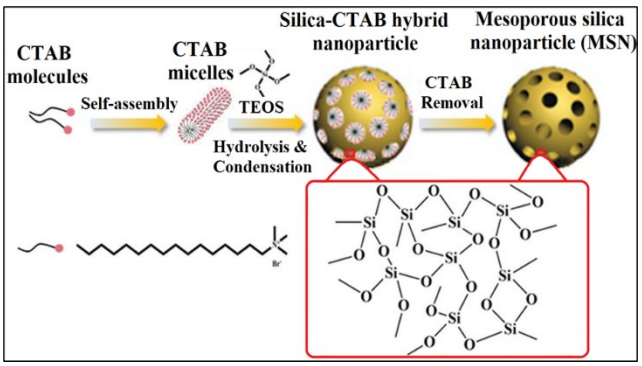

Fig. 2: Schematic illustration of the mesoporous silica synthesis from cetyltrimethylammonium bromide (CTAB) template using tetraethyl orthosilicate (TEOS) as silica precursor. Reproduced from He et al. (2020).

Apart from Stober method, diverse alterations may be applied to produce nanoparticles via distinct geometries that are exceptionally ordered and called as modified Stober method (Wang et al., 2016). This process can be improved by using a cationic surfactant precursor to generate a circular MSN framework instead of a hexagonal version yet retaining equivalent characteristics with robust and monodisperse MSN (Grun et al., 1997). The technique has a homogeneous design and controllable characteristics, making it simpler and cheaper than others. It also uses fewer excipients and is quicker (Bharti et al., 2015).

An alternative method for synthesising MSNs involves the use of hard and soft templating techniques. Biological-based templating agents are used in the soft template strategy to create porosity in MSNs, followed by heating to remove the pure mesoporous transporters (Wu et al., 2013). In hard-templating or nano-casting, capillary pressures fill templating mesopores with silica precursors. After the templating agent is removed chemically or thermally, a reverse assembly of the mesoporous silica structure is formed (Egger et al., 2015).

The main advantages for sol-gel method or Stober method are increased purity and ease of synthesis under moderate reaction conditions. In contrast, the hydrothermal technique is beneficial for obtaining MSNs with greater hydrothermal stability (Bharti et al., 2015; Shahbazi et al., 2012).

A recent modification to the synthesis of MSNs involves encapsulating drugs in hollow mesoporous silica nanoparticles (HMSNs). The large hollow cavity inside each MSN has garnered tremendous attention due to its ability to hold a high amount of drug compared to non-hollow counterparts. This unique property makes HMSNs particularly useful in cancer therapy and imaging (Chen et al. 2014).

The microwave-assisted technique is a low-cost approach for synthesizing MSNs. Various reports indicate that the method can rapidly produce MSNs with ordered pore size and arrangement (Bian et al. 2013). Another rapid, cost-effective method for the fabrication of MSNs is sonochemical synthesis. The use of photoacoustic cavitations in this process generates ordered MSNs, allowing for fine-tuning in a shorter time (Snoussi et al. 2018).

A key finding from Kankala and his team (2020) highlights advancement in three main areas:

a) Surface modification: Enhancing the MSN surface through surface engineering using various components such as polymers, liposomes, biomembranes, proteins, and metal shielding through direct immobilization or functionalization of the mesostructured surfaces.

b) Framework alteration: Modifying siliceous frameworks with various organic moieties (periodic mesoporous organosilicas) and metal species, resulting in metal-encapsulated MSNs and heterostructures.

c) Porosity changes: Adjusting the porosity of MSNs, including the development of cage-like and hollow structures. This includes hollow, yolk–shell, and core–shell architectures, resulting in different mesophases with enriched biomedical applications.

British Geologist Roderick Murchison invented a hydrothermal process for MSN synthesis to produce minerals from hot water solutions of cooling magmas. This reaction occurs in a sealed container under high pressure and temperature (Feng & Guanghua, 2011). This approach is similar to the sol-gel procedure, but the mixture is shifted into a Teflon-lined autoclave at a specific temperature, followed by template removal. The hydrothermal approach produces MSNs with higher uniformity and consistency (Jarmolińska et al., 2020; Oo et al., 2022). However, it remains uncertain at this stage whether acquiring magmas at pharmaceutical-grade quality would be feasible for biomedical or pharmaceutical applications, given the regulatory requirements for raw material quality control.

Factors Affecting Cellular Uptake and Drug Loading in MSN

Various factors affect the cellular absorption of MSNs, including particle size, pore size, shape, charge, and surface modifications. To create MSNs suitable for drug delivery, the particles must have a consistent shape and a larger pore volume, allowing for a higher drug-loading capacity. The key characteristics of MSNs are influenced by these criteria.

Particle Size

Particle size is a critical quality attribute for any product, including nanoparticles, regardless of the dosage form. It plays a significant role in delivering the encapsulated molecule to the desired target site. Smaller nanoparticles are generally more desirable for efficient drug administration due to their superior cellular absorption properties. Numerous studies on MSNs have extensively discussed factors influencing particle size, including functional organo-silanes, pH, temperature, and synthesis timing. For clinical applications of MSNs, particularly for chronic use, ultrasmall particulates (those smaller than 400 nm) are crucial to minimise toxicity. These particles must be easily transported through the circulatory system and excreted properly to avoid potential organ toxicity due to accumulation over time (Yang et al., 2018). In oncological applications, the enhanced permeability and retention (EPR) effect is a noteworthy biophysical characteristic of tumours

(Bertrand et al., 2014), where the diminutive size of nanoparticles facilitates their absorption and retention within tumour cells (Maeda, 2015). Therefore, controlling the MSN dimensions is essential to maximise therapeutic effectiveness (improving drug delivery to tumour cells) and minimise adverse reactions (favouring intravascular transport and breakdown). Researchers must ensure that particle size is well-defined for dried, reconstituted and post-reconstitution stability with a polydispersity index of less than 0.3 as targeted specification before administration.

Pore Size

The abundant mesopore channels within the MSN structure provide exceptionally spacious interior cavities, facilitating the permeation and transport of large particles such as medicines, protein molecules and nucleic acids. The types, loading quantities, and release dynamics of medicinal payloads depend on the MSN pore diameter. Smaller MSNs can only carry small drugs due to steric interference, while larger ones can transport organic substances, nanomaterials, and larger drugs. Vallet-Regí et al. observed that the bovine serum albumin uploading efficacy increased from 15% to 27% as the SBA-15 pore diameter expanded from 8.2 to 11.4 nm (Vallet-Regí et al., 2008). Reducing steric barriers by increasing pore diameter can enhance the delivery of medicinal payload through mesopores. Horcajada et al. discovered that reducing MCM-41's pore diameter from 3.6 to 2.5 nm lowered ibuprofen release in simulated body fluid (Horcajada et al., 2004). In summary, it is imperative to align the molecular weight of the therapeutic molecules with the targeted pore size of the MSNs cargo and adjust the processing parameters accordingly to achieve the desired outcome.

Hollow Structure

By adjusting the synthesis variables, MSNs may transform into homogenous or porous spheres, tubular structures, fibres, gyroids and complex networks Sun et al., 2017). Circular nanomaterials, especially hollowed ones, are being extensively developed in medical theranostics (Chen et al., 2014; Li & Shi, 2014).

Hollow structures have minimal density, huge voids, and large surfaces, making them ideal drug carriers. Incorporating pliable liquid components like an emulsion particle, vesicles, or bubbles of gas within a water-based fluid substrate creates multimodal soft-templating cores for hollow nanostructures (Li & Shi, 2014). Extraction or calcination removes the disparate central framework surfactant, forms a pattern, and produces the hollow composite. A self-generated soft-templating approach uses precursor molecule droplets as the core template, consuming the inner molecules to form outer mesostructured shells without a core template removing step.

Solid nanomaterials such as polymer latex, silica and carbon rings form cavities in the hard-templating method (Li & Shi, 2014). Depending on the solid base templates used, this method might be disparate or uniform. The approach of "structural difference-based selective etching" was first developed for constructing HMSNs by utilising the variation in structure among the silica core and the mesoporous silica layer to generate vacuous regions (Chen et al., 2010).

Chemical Composition

Mechanically stable biosystems are enabled by the inorganic Si-O-Si structure of MSNs, which facilitates effective drug delivery (Stober et al., 1968). Nevertheless, the utilisation of its chemical structure in vivo can give rise to specific limitations, such as restricted degradation as well as a singular utility (Bindini et al., 2021). Such methods for regulating structure are usually categorised by two primary approaches. The initial method entails the integration of organic and inorganic elements within the Si-O-Si structure of MSN, with the goal of achieving degradation in response to stimuli and better performance. By adding organic R subunits within a silica structure (Si-R-Si), MSN's robustness is combined with liposome and micelles' suitability. This integration results in broader application potential (Chen & Shi, 2016). The second methodology entails constructing core/shell structures to regulate the composition and structure of MSNs (Ishii et al., 2015). Hard-templating techniques promote mesoporous silica shells to

appear around bioactive inorganic nanomaterial bases (Xie et al., 2016).

Exterior/Surface Transformation

The surface properties of MSNs significantly impact their physiological behaviour. Nanomaterials with a neutral charge have a longer circulatory lifespan, whereas positively charged particles may trigger stronger immunological reactions (Nel et al., 2009). Within the last 20 years, numerous investigations into surface modification methods have greatly improved the use of MSNs in biomedicine.

To improve the in vivo biocompatibility of MSNs, they are often mixed with biodegradable polymers like polyethylene glycol (PEG). PEG reduces protein absorption and degradation due to its low interfacial energy, non-adhesive characteristics, and robust dynamics (Banche-Niclot et al., 2021; Perera et al., 2021). PEGylation is known to protect nanomaterials from accumulation, opsonisation, coagulation or in vivo scavenging, thereby extending their circulation time and enhancing their biomedical applications (Perera et al., 2021; Suk et al., 2016). Similar to other PEG-decorated nanoparticles, the scalability of these stealth MSNs is less of a concern because PEG is a well characterised Generally Recognised as Safe (GRAS) material commonly used as an excipient in large- scale pharmaceutical manufacturing.

Therapeutic Applications of MSN

Stimuli-Responsive Drug Release

Traditional cancer treatments often suffer from limited absorption and tumour resistance to chemotherapeutic agents (Park et al., 2013). MSNs are increasingly tailored with functional moieties to enable stimuli-responsive cancer therapies (He & Shi, 2014). Decorative multifunctional features around mesopore apertures can act as "sensors" (such as noble metal decorated MSNs or sugar decorated MSNs), regulating the release of therapeutic agents in response to external influences (Hosseini et al., 2023).

These mesoporous nanosystems are categorised based on the nature and triggers they respond to:

a) endogenous-triggered nanosystems respond to biological stimuli within the tumour microenvironment, such as pH, redox conditions, and proteins (Mi, 2020; Yang et al., 2018);

b) exogenous-influenced nanosystems respond to external triggers like radiation or ultrasound (Tharkar et al., 2019; B. Yang et al., 2018).

Tailored Drug Distribution

Indirect nanomaterial aggregation within tumour cells is feasible due to tumour biophysics, however, it is often insufficient for significant intratumoral deposition and effective treatment. Since cancerous tissues overstate certain biomolecules within their membrane and organelles, active targeting drug transport is widely studied (Rosenblum et al., 2018). Many agents are modified using nanotechnologies, such as MSN-based systems to accurately target malignant cells.

An additional advantage of MSNs over other inorganic nanoparticles is their relatively superior safety profile. For instance, the FDA has approved colloidal silica for use as a glidant in tablet production (Janjua et al., 2021). In addition, the widely used food additive E511 consists of amorphous silica NPs with a diameter of 100 nm. Importantly, numerous clinical trials and studies confirm the safety and efficacy of silica nanoparticles in applications such as oral drug delivery, bioimaging and photothermal therapy. Many silica-based nanoformulations have been developed, and their systematic safety evaluation is ongoing. Nonetheless, MSNs are considered more promising in the biomedical field than other inorganic nanoparticles (Bolong et al., 2023).

Gene Delivery

Substantial advancements have been achieved in enhancing the delivery of nucleic acid cargo over the past decade, leading to the creation of numerous nanocarriers with diverse structural and compositional characteristics tailored for gene transportation (Lostale-Seijo & Montenegro, 2018).

Unlike conventional chemotherapeutic drugs, gene segments are relatively large and challenging to load into typical MSNs having narrow pore sizes (< 3 nm). To overcome such constraints, two main approaches are being developed: attaching genomes to the exterior of smaller pore-sized MSNs or enclosing genes within the larger pores of MSNs by conjugation (Sun et al., 2017). Similar approaches have been previously adopted by other nanoparticles, including lipids, exosomes, polymers, polypeptides, graphene-family nanomaterials, inorganic materials, such as gold nanoparticles or their combinations (Caccamo et al. 2020). However, since genetic materials are exposed to the biological environment and liable to degradation, an excess of therapeutic molecules may be applied when designing the theoretical loading efficiency. This approach helps maintain the thermodynamic of drug release and achieve an appropriate dosage.

Additional Treatment Approaches

In addition to directly delivering the chemotherapeutic drugs or nucleic acids, MSNs are dynamically coupled with biological and chemical functionality to improve treatment efficacy. As a result, MSNs are employed in various therapeutics and diagnostics areas of biomedicine (Figure 3). Many inorganic or organic nanoparticles exhibit strong photothermal transformation, making them suitable for photothermal therapy (Wang et al., 2020). Various catalytic nanoparticles react with intratumoral H_2O_2, promoting •OH generation for chemodynamic therapy (Yang et al., 2018). Mechanically superior 3-dimensional hydrogels may facilitate osteogenesis for bone tissue engineering. Other applications include phototherapy, ultrasound therapy, radiotherapy, chemodynamic therapy, immunotherapy, tissue engineering, animal cell culture, and scaffold-based nanomaterials.

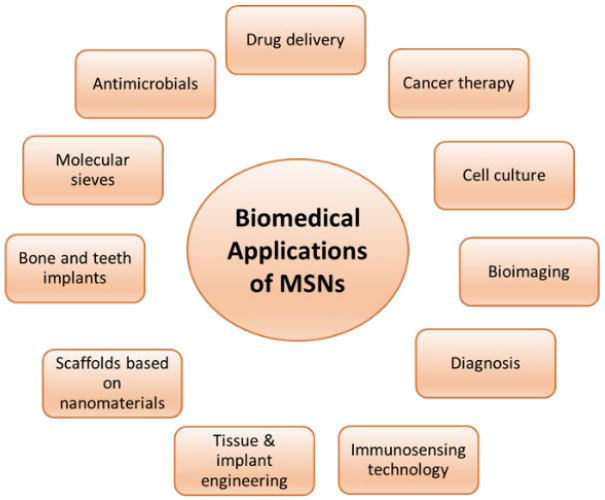

Fig. 3: Biomedical applications of mesoporous nanoparticles. Reproduced from Ahmed et al. (2022), Mi (2020), and Tharkar et al. (2019).

Biomedical Applications of MSN

Delivery of Bioactive Molecules

MSNs are considered to have great potential as nanocarriers for drug delivery due to their unique characteristics (Vivero-Escoto et al., 2010; Wang & Kohane, 2017). Their features encompass a permeable framework for better utilisation of material, resistance to chemical changes, surface properties that promote equilibrium, compliance with biological systems, and a capacity to dissipate substances in a regulated manner regardless of external triggers, including the ability to mark certain cells specifically (Hosseini et al., 2023; Mi, 2020). MSNs showed the potential for encapsulating and controlling the flow of diverse bioactive compounds, including chemotherapy agents, genetic material, growth stimulants and catalysts (Ahmed et al., 2022). MSNs can inhibit biological substances from diffusing prematurely into the channels by functionalising multiple receptors.

Regulate Chemotherapy Release of Medication

MSN-based carriers are being utilised for dispensing chemotherapy medications like DOX, camptothecin, 5-F- Erlotinib, methotrexate, irinotecan, cisplatin and banoxantrone along with RNA particles (Liu et al., 2018; Wu et al., 2018). Despite MSNs having great medication transporting ability because of product dispersion, MSNs could fail to maintain or regulate cytotoxic medication distribution and thus may cause general impairment of natural tissues. Thus, different methods have emerged to mitigate encapsulated medication burst discharge. MSN can be functionalised with agents that respond to stimuli such as light, temperature, electromagnetic fields, pH, catalysts, reactive oxygen species or specific ligands. These functionalised MSNs can selectively release cytotoxic drugs and target specific types of tissues.

Disease Treatment

MSN-based nanocarriers have demonstrated promise in addressing conditions such as Alzheimer's disease and heart failure. The onset of Alzheimer's disease, linked to metallic ions that accelerate Aβ accumulation and ROS development, can be mitigated by metal chelators (Leyane et al., 2022). For instance, phenylboronic acid-functionalised MSNs carrying β-D-glucose-AuNPs with clioquinol (CQ) showed H2O2-regulated distribution within the dementia surroundings. By inhibiting Aβ accumulation, CQ reduced phagocytosis within dementia-related PC12 cells (Yang et al., 2016). In zebrafish studies on acute killer red (SqKR15)-based ROS-triggered heart failure. MSN-based nanoparticles delivered curcumin or captopril locally, improving pulse and heart rate. Additionally, glucose-responsive customised MSNs have shown potential in regulating blood sugar levels in diabetic animal models (Hou et al., 2018).

Lesion Restoration and Tissue Regrowth

MSN-based carriers have shown promise in healing lesions and promoting tissue regrowth. Increased ROS levels in damaged regions can trigger cell death, fibrosis and inflammation. ROS-responsive MSN-based carriers have facilitated improved wound repair (Wang et al., 2016). For instance, a flexible ROS-scavenging composite was created by doping amino-functionalised MSN with ultra-small ceria nanocrystals. This composite enhanced epidermal outgrowth and decreased scarring by strengthening tissue adhesion and accelerating the recovery process. In addition, hepatocyte nuclear factor 3β plasmid DNA (pHNF3β) delivered via a positive-charged MSN-based nanosystem significantly promoted the differentiation of induced pluripotent stem cells into functional hepatocyte-like cells within just two weeks of in vitro study. Enhancing the delivery rate of pHNF3β further improved the cell differentiating process (Wu et al., 2018).

Medical Imaging and Diagnostic Applications

To minimise overall cytotoxicity, localised and customised anticancer administration strategies are essential. Using nanocarriers such as FITC, Hoechst, carbon dots, 64Cu, fluorescein, multicolour up-conversion nanoparticles, chlorin e6, and N,N-phenylenebis (salicylideneimine) dicarboxylic acid (Salphdc) facilitates targeted delivery and distribution monitoring of cancer treatments (Lai et al., 2015; Mi, 2020). In particular, nanoparticles incorporating DOX-loaded 64Cu-labeled MSNs, controlled by AuNPs, provide near-infrared (NIR) triggered DOX release and a combined photothermal therapeutic response against cancer. Additionally, these nanocarriers also serve as bio-tools for PET imaging, capable of detecting clinically significant lung tumours spontaneously in mice with urethane-induced lung cancer (Cheng et al., 2016).

Biocatalysis

MSNs are excellent biocatalysts due to their large surface area, durability, uniform porosity, and good functionalisation. They shield catalysts against proteolysis and reduce immune response, enabling intracellular bioanalysis. For instance, a self-catalysed luminescence nanosystem has been developed with luciferin placed inside MSN pores, AuNPs providing capping components through disulfide bonds and PEGlyated luciferase, designed for assessing tumour progression (Sun et al., 2011).

Another approach involves the in-situ creation of AuNPs on amino-functionalised MSNs to produce an efficient nanoreactor exhibiting enzyme-mimetic catalytic characteristics, allowing a chain reaction via a self-activated process. This method can develop

synthetic catalysts with varied functions and reactivities for biocatalysis, bioassays, nano-biomedicine, and nanotechnology (Lin et al., 2013).

Other Applications

Biosensors, bioassays, and antimicrobial activities utilise modified MSNs to be nanocarriers which show extremely precise affinity for attached catalysts via His-tag_Ni ion coupling. Identifying histidine-tagged catalysts is easy and has a high throughput with such substances, which can separate and immobilise a variety of polyhistidine-tagged proteins (Raducanu et al., 2020). MSNs modified using phenyltrimethyl moieties may trap thymophthalein, a pH marker for preferential monitoring of prostate-specific agents, offering a cheap, fast way of screening biomarkers within intricate specimens. AuNPs-modified MSNs containing antibiotic-loaded nano-vehicles had combinatorial activities, suggesting drug-resistant illness therapy (Wang et al., 2016).

Safety, Biodistribution and Fate of MSN

MSNs represent exciting biological vehicles that prevent premature release of medicines and enhance their stability (Hosseinpour et al., 2021). Current research focuses on the surface remodelling of MSNs by customising functional domains externally or internally to improve drug uptake and release at targeted regions (Li & Shi, 2014; Mohamed et al., 2022). MSNs can be paired with polymeric molecules, chemical compounds, or nucleic acids to produce hybrids with various biological functions, primarily for tailored medication delivery and controlled release profiles (Lostale-Seijo & Montenegro, 2018; Sun et al., 2017).

Although MSNs have several biomedical applications, the US FDA has yet to authorise their use until their fate, biodistribution, and clearances are well understood (Lérida-Viso et al., 2023). MSNs tend to accumulate in the reticuloendothelial system, particularly in the organs associated with liver function, because of protein adsorption on their surface, usually from serum(Zhang et al., 2021). These issues can be resolved by coating the MSN surface with a hydrophilic polymer like PEG (Banche-Niclot et al., 2021; Perera et al., 2021; Suk et al., 2016). Protein absorption affects hepatobiliary evacuation and bile discharge, whereas finer particles tend to aggregate or accumulate in faeces. Studies have also demonstrated enhanced renal clearance of these nanoparticles.

Conclusion

In modern medicine, MSNs have revolutionised both diagnosis and therapy by enhancing drug stability and addressing issues related to low drug solubility. However, their clinical application is complicated by immunogenicity and toxicity due to the accumulation of inorganic substances. A major barrier to the use of MSNs for biomedical delivery is the lack of understanding of their long-term safety. In addition, the inconsistency in characterisation procedures and toxicity assessment tools hinders their commercialisation and clinical use. Nevertheless, with growing knowledge of MSNs' behaviour in the body and advancement in their formulation, MSNs are expected to reach therapeutic applications soon.

Authors contributions

The authors contributed to this review article in the following ways:

Fatema Tuz Zohera (First author): Articles collection, content analysis, and main content writer of the manuscript.

MD. Abul Kalam Azad: Manuscript editing, providing valuable insights, and interpretation of relevant articles for the manuscript.

May Kyaw Oo: Manuscript editing, referencing, and formatting for submission.

Farahidah Mohamed (Corresponding author): Conceptualisation and critical revision of the manuscript for intellectual content, providing valuable insights, and ensuring accuracy in the presentation of information.

All authors have reviewed and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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