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(Review)

Mesoporous Silica Nanoparticles as a Potential Drug Delivery System in Dentistry: Review

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ABSTRACT

Mesoporous silica nanoparticles (MSNs) have gained substantial interest in dental applications due to their unique structural features and versatile functionalization potential. Characterized by their high surface area, tunable pore sizes, and biocompatibility, MSNs are ideal for drug delivery systems, allowing the controlled release of therapeutic agents such as antimicrobials, fluoride, and anti-inflammatory drugs directly at the sites of dental interest. Their porous nature allows for the encapsulation of larger molecules, facilitating prolonged action and enhancing local therapeutic efficacy. Additionally, MSNs can serve as carriers for bioactive agents that promote dental tissue regeneration and repair, contributing to advancements in restorative and preventive dentistry. As research advances, incorporated mesoporous silica shows great promise in developing innovative dental treatments that enhance oral health and patient care, with the potential to revolutionize both preventive and therapeutic dental management.

Keywords: Mesoporous silica nanoparticles, Encapsulation technique, Drug delivery

1. Introduction

This century has seen the emergence of modern nanotechnology as a crucial element of science, with notable advancements in biomedicine and dental applications, demonstrating progress in diagnosis and treatment [1].

In medicine, the understanding of how nanoscale materials could interact with biological systems paved the way for the development of nanocarriers. Early efforts primarily utilized simple lipid-based systems, such as liposomes, which encapsulated drugs and improved their solubility and stability [1].

The advantages of nanocarriers, including the capacity to engineer particles of varying shapes, sizes, and chemical features, as well as a high surface area to volume ratio, have been a significant benefit and have revolutionized the fields of tissue engineering and therapy. Biocompatibility biodegradability, and inertness are the main features that characterize nanocarriers as potential drug delivery systems [1].

2. Drug delivery systems

Drug delivery systems (DDS) are innovative technologies designed to transport pharmaceutical compounds to their intended sites of action within the body, thereby optimizing therapeutic efficacy while minimizing side effects. The primary objectives of drug delivery systems include improving the solubility and stability of drugs, enabling targeted delivery to specific tissues or cells, and facilitating sustained release. In contrast to systemic medication administration, local delivery of therapeutic agents offers numerous evident benefits, including the ability to target specific areas with minimal adverse reactions [1].

Transporters and correlated therapeutics are the components of drug delivery systems, which typically transport and release specific therapeutic compounds or bioactive agents to a specific location at specific rates in vivo. In contrast to systemic administration of medications, local delivery of therapeutic agents offers numerous evident benefits, including the ability to target specific areas with minimal adverse reactions. Among various drug delivery systems, encapsulation technique involves enclosing drug particles within a specific shell, forming a capsule. It is often used for oral drug delivery to mask taste or control the release rate, making it suitable for various applications [1].

3. Encapsulation procedure:

Encapsulation has been significantly used in a variety of industrial fields, such as the pharmaceutical, agricultural, and food industries. It is the process of enclosing liquid or gas molecules and solid core particles that are micron in size in an inert shell or capsule. A capsule is the term used to describe the outcome of the encapsulation process [2].

The core and the shell are the two discrete components of a capsule. The core is composed of the material that necessitates microencapsulation and may include supplementary constituents to aid in processing and discharge, if required [2].

On the other hand, the shell controls the rate at which the core contents are discharged in response to environmental factors. The dimension of these capsules comprises nanometers (nano-capsules), micrometers (micro-capsules), and millimeters (milli-capsules or macro-capsules) [2].

Microencapsulation was implemented as drug delivery systems in the industry of pharmaceutics for regulating or modifying the release of drugs' active substances. It was developed to enhance the drug's bioavailability, regulate drug release kinetics, mitigate drug side effects (such as gastric irritation induced by non-steroidal anti-inflammatory drugs, and conceal the unpleasant flavor of drug substances [3].

The physical and chemical properties of the core and exterior materials, as well as the microencapsulation techniques employed during its synthesis, can be used to acquire a variety of morphologies according to each specific application [4].

Encapsulation techniques have been extensively used in dentistry to deliver medications through microparticles and nanoparticles. These multi-particle drug delivery systems offer several advantages, including a uniform structure, enhanced safety, and reproducibility of techniques. Additionally, these structures can be incorporated into traditional oral products, such as toothpastes and suspensions, or utilized in innovative drug delivery systems like sensitive hydrogels and dental adhesives. They can also be injected directly into periodontal defects to achieve effective control over drug release. Microparticles have proven to be an effective strategy in various areas of dental research [5].

Nanosized capsules are emerging as a superior alternative to traditional microencapsulation techniques in the biomedical field. While typical microcapsules have a diameter ranging from 20 to 500 micrometers, nanosized capsules, which have diameters between 1 and 100 nanometers, are gaining attention for their potential benefits. Nanoencapsulation, the process of encapsulating nanoscale particles, offers several advantages over conventional microencapsulation methods [6].

Nanoparticles can be easily dispersed and are suitable for incorporation into the macrostructure of other materials through aqueous suspension. They are commonly used to encapsulate and release drugs and various chemicals in a controlled and predictable manner. Additionally, nanoparticles can be effectively infiltrated into the dentinal tubules for efficient drug delivery [7].

In the pharmaceutical industry, various capsule materials have been approved for use in encapsulation. These materials can be classified as either polymeric – comprising natural or synthetic polymers, or as inorganic substances such as silica. Natural polymers are known for their high biocompatibility and biodegradability. In contrast, synthetic polymers offer adjustable physical and mechanical properties; however, their degradation products may trigger inflammatory reactions [1].

4. Mesoporous Silica materials for encapsulation

Based on the principal pore sizes, the International Union of Pure and Applied Chemistry (IUPAC) categorizes porous solid materials into three categories: micro-porous materials (pore diameters up to 2.0 nm), meso-porous materials (pore sizes intermediate between 2.0 and 50.0 nm), and macro-porous materials (where its pore sizes exceed 50.0 nm). Furthermore, the mesoporous structures are distinguished by a broad spectrum of porosity (30-99%) and a high surface area (100-1200 m^2/g) [8].

Microporous materials are typically characterized by very small pore sizes and high surface areas, making them suitable for applications such as gas separation and storage, catalysis, and adsorption processes. While Meso-porous materials are often used in applications that require a balance of accessibility for larger molecules and high surface area which can be found in materials such as silica gels and mesoporous carbons. Finally, Macro-porous materials are usually involved in applications where bulk flow of fluids or gases is desired, such as in filtration, scaffolding in tissue engineering, and certain types of catalysts such as polymer foams and certain types of ceramics [8].

Mesoporous silica materials (MSMs) are a class of well-defined porous materials characterized by their pore sizes, which typically range from 2 to 50 nanometers. They are primarily composed of silicon dioxide (SiO_2) and have gained significant attention in various fields, including pharmaceutics and drug delivery [8].

Kuroda et al. first reported mesoporous silica materials (MSMs) in Japan back in the 1990s [8]. The process of generating bulk mesoporous materials involves the use of surfactant molecules that self-assemble themselves as condensation templates for the silica precursors that surround them. A material that contains network cavities is subsequently generated by the removal of the template. An ordered distribution of pores with uniform sizes between 2 and 50 nm, a high pore volume (about 1 $cm^3\ g^{-1}$), a large surface area, and a high density of silanol groups at their surface are the distinguishing characteristics of this new family of materials.

These characteristics may facilitate subsequent functionalization processes. Thus, in 2001, these attributes rendered MSMs the optimal choice for applications that necessitated the adsorption of molecules, including drug delivery systems [9].

In addition, MSMs are a form of mesostructured inorganic materials that exhibit bioactive properties due to the presence of silanol groups on their surface and a chemical composition similar to that of bioactive glasses [10]. As a result, MSMs have been utilized as raw materials in the production of 3D scaffolds for bone tissue engineering. The excellent textural properties and prospective biomedical applications of bulk MSMs inspired their translation to the nanoscale. Thus, a few years later, since 2006-2007, numerous research groups around the world devised and investigated mesoporous silica nanoparticles (MSNs) as drug delivery systems [11].

5. Synthesis of mesoporous silica nanoparticles

A silica precursor (tetraethylorthosilicate: TEOS, tetramethyl orthosilicate-TMOS, tetramethoxyvinylsilane-TMVS, sodium meta-silicate (2-hydroxyethyl) orthosilicate-THEOS), a surfactant (non-ionic or cationic surfactant) as a structure directing agent (SDA), and a catalyst are the three primary components that comprise the heart of MSN. Other additives, such as cosolvents and compounds that prevent aggregation, may also be included in accordance with specifications [12].

There are numerous methods for synthesizing mesoporous silica nanoparticles, including the surfactant templating method and the sol-gel method. The surfactant templating method is a technique that is frequently employed for the synthesis of MSNs. The desirable porous architecture within the nanoparticles is achieved by depositing the silica precursor around a sacrificial template or surfactant, which is subsequently removed. The template establishes a framework that regulates the size, shape, and arrangement of the mesopores, thereby enabling the customization of drug loading and release properties. The template framework can be eliminated through a variety of methods, including calcination, extraction, or microwave-assisted treatment, following the formation of MSNs. Calcination is the simplest method [13–15].

The self-assembly of the templates (surfactants) is the fundamental strategy of all syntheses, despite the fact that the conditions of preparation procedures and structural properties of porous silica can vary to some extent. Organic surfactant molecules undergo cooperative self-assembly in the solution phase when their concentrations surpass the critical

micellar concentration (CMC). Hydrolyzed inorganic silica precursors (e.g., tetraethyl orthosilicate or TEOS) organize themselves around these template micelles in alkaline or acidic conditions to form organic–inorganic silica-template composites. The composite materials endure additional condensation of metal and template through appropriate aging for a specific duration, resulting in an ordered arrangement such as cubic or hexagonal. After the organic surfactant molecules are eliminated from the composite materials through solvent extraction or calcination, silica with mesopores of a specific diameter is produced. Figure 1 represents a schematic illustration of the synthesis of MSN by surfactant templating method.

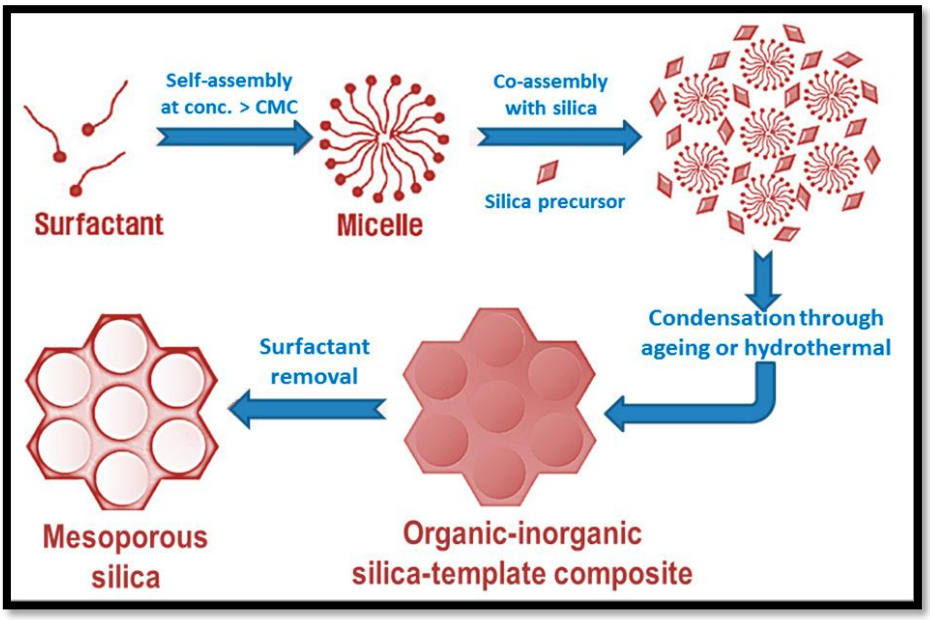

Figure 1. Synthesis of MSN by surfactant template method.

After its synthesis, MSNs are subjected to a characterization protocol using various methods for confirmation of its structure, particles size and shape, and its pore size and volume. The most used characterization methods utilize X-ray diffraction pattern for the analysis of crystallographic features of MSNs and confirm its purity after synthesis [16]. While the particles size and shape could be evaluated by transmission electron microscope (TEM) or by dynamic light scattering method. However, TEM provides a comprehensive analysis of the particles shape with the average particles size [17]. On the other hand, the surface area, pore volume and pore size could be analyzed by Brunauer-Emmett and Teller (BET) method through Nitrogen adsorption-desorption curve. The BET method is frequently utilized for determination of surface area, pore volume and pore size of the highly porous materials [16],[18].

6. Drug loading into mesoporous silica nanoparticles

MSNs must have a uniform particle size and a large pore volume to optimize their loading capacity in order to serve as an optimal drug delivery vehicle. The pH of the reaction mixture, temperature, surfactant concentration, and silica source can be adjusted to modulate these parameters during the synthesis process. The liquid crystal template mechanism aids in the synthesis of MSNs by facilitating the hydrolysis and condensation of silica on the surface of surfactant micelles. The pore size also influences the discharge of the encapsulated extract from MSNs. As the pore size decreases, the quantity of extracts deposited, and the release rate will decrease due to the increasingly tightly packed molecules in the mesopores [19].

The material loading into MSNs is dependent upon the adsorptive properties of MSNs. The apertures of MSNs can accommodate both hydrophilic and hydrophobic cargos. In comparison to other carriers, MSNs have an inherent higher loading capacity due to their substantial pore volume. Conversely, drug release is primarily contingent upon its diffusion from the pores, which can be optimized by adjusting the surface of the MSNs to accommodate biological requirements [20].

7. Drug release from mesoporous silica nanoparticles

The release profile of pharmaceuticals from MSNs is mainly driven by diffusion from the pores, which can be tailored by modifying the surface to meet the biological needs. The interaction between the drug and surface groups regulates the release. Surface functionalization with amine groups before drug loading leads to sustained release, while functionalizing after loading may cause rapid release due to drug accumulation and capping with amine groups, which obstructs release. This may occur because of drug accumulation within the pores and capping with amine groups obstructs release. If the surface is functionalized before loading, the drug could adsorb to the surface, leading to rapid release [12].

8. Applications of mesoporous silica nanoparticles in dentistry

The potential of mesoporous silica nanoparticles (MSNs) to discharge a diverse array of drugs at the desired location in response to external stimuli has gained significant interest as novel therapeutic nanocarriers. These nanostructures are being explored for various applications, such as targeted drug delivery systems for caries management, dentin hypersensitivity and oral cancer therapies. Additionally, MSNs serve as effective carriers for bioactive agents, including antimicrobial agents, growth factors, and tooth remineralization

agents, enhancing their therapeutic efficacy and prolonging their release. Their biocompatibility and ability to improve the solubility of poorly soluble drugs further contribute to their potential in advancing dental treatments and improving patient outcomes [21].

8.1. Dental caries

The primary etiological pathogen that firmly adheres to tooth surfaces and is essential for the production of an acidic environment is *Streptococcus mutans*. This environment ensures the initiation of dental caries, demineralization of the teeth, and the development of biofilms. The chlorhexidine (CHX) encapsulated into mesoporous silica nanoparticles (MSNs) that were synthesized by integrating CHX into functionalized MSNs demonstrated a stimuli-responsive and long-term release of agents [22]. Results shown by Yan et al, indicated that the release of CHX from MSNs effectively inhibited the growth of *S. mutans* up to six months, ensuring the sustained antibacterial efficacy of this delivery system in reducing bacterial load [22].

8.2. Dentin hypersensitivity

Dentin hypersensitivity is characterized by rapid pain from thermal, chemical, and physical stimuli, often caused by acid erosion, abrasion, or gingival recession. The hydrodynamic theory suggests that the best treatment involves blocking exposed dentinal tubules with biomaterials to reduce fluid [23].

Yu et al, in 2017 showed that encapsulation of nanohydroxyapatite into mesoporous silica nanoparticles has shown to be advantageous in many ways. By occluding dentinal tubules, reducing biofilm formation, and maintaining favorable acid-resistant stability, this combination provided a multifunctional biomaterial for dentin hypersensitivity and cavities [24].

8.3. Endodontics

Enterococcus faecalis is the most prevalent isolate from endodontic infections and is significantly associated with unsuccessful endodontic treatments due to its ability to persist in exceedingly difficult conditions [23]. Seneviratne et al. investigated the antibacterial effect of MSNs-encapsulated chlorhexidine against multiple oral biofilms including *E. faecalis*. The novel intervention showed a potent antimicrobial effect against *Enterococcus faecalis*, which implied the significance of MSNs as a drug delivery system in treatment of persistent endodontic infections [25].

9. Conclusion:

In conclusion, mesoporous silica nanoparticles (MSNs) present a promising and innovative approach in dentistry, owing to their unique structural properties and capability for tailored drug delivery. Their biocompatibility, high surface area, and tunable pore sizes allow for the encapsulation of a variety of therapeutic agents, including antimicrobials and anti-inflammatory drugs, which can be released in a controlled manner. This targeted delivery system has the potential to enhance treatment outcomes for treatment of dental caries, dentin hypersensitivity, endodontic infections, and other oral health issues by ensuring sustained therapeutic concentrations at the site of action while minimizing systemic side effects. Overall, MSNs represent a significant advancement in biomaterials, offering exciting opportunities for enhancing oral health care practices.

- **Conflict of Interest**

The authors declare no conflicts of interest.

10. References

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