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Mesoporous Silica Nanoparticles: Advances in Design, Drug Delivery, and Biomedical Applications

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ABSTRACT
Mesoporous silica nanoparticles (MSNs) have gained popularity as one of the most beneficial nanomaterials in biosciences and especially in drug delivery systems. They have unique inherent structural properties with high surface area, the pore size that can be adjusted, very good compatibility with other biological tissue and surfaces with diverse surfaces functionalization capability that makes them a great candidate to be used in therapy. As a comprehensive review, this paper discusses the up-to-date development of MSN research in terms of their structural properties, their synthesizing approaches, their ways of functionalization, and their application in different fields of biomedicine. We speak about the drug delivery benefits of MSNs where stimuli-responsive release strategies and targeting strategies can be implemented. Another important consideration in the review includes essential considerations of toxicology, regulatory attitudes, and future outputs of MSN technology. Clinical testing is currently in progress, and emerging manufacturing processes evolve the MSNs as a major cutting-edge innovation within nanomedicine and capable of changing the way that therapies are delivered.
Keywords: Mesoporous silica nanoparticles, drug delivery, nanomedicine, biocompatibility, stimuli-responsive systems, cancer therapy

I. INTRODUCTION

Nanomedicine has experienced incredible advances of the last 20 years, and many types of nanocarrier systems have been designed to overcome the shortcomings of the traditional drug-delivery approaches. Of these, mesoporous silica nanoparticles (MSNs) have particularly attracted a lot of interest since they possess unique characteristics and properties that enable them to be used across a wide range of potential biomedical applications [1]. Ordered mesoporous silica materials have their origin in the early 1990s when they were first identified as mere molecular sieves but have since developed into advanced drug carriers that can exhibit ordered and targeted drug delivery. MSNs belong to a novel type of inorganic nanoparticle, which has an ordered porous structure, large surface area, and adjustable physicochemical features [2]. Improved and affordable mechanisms of drug delivery that are capable of surmounting biological obstacles, minimal systemic toxicity and enhanced therapeutic effects have necessitated the development of MSNs. In contrast with traditional nanocarriers, liposomes or polymeric nanoparticles, MSNs possess better chemical stability, high control structure, and can be multiple-functionalized. Modern medicine is already too concerned with the fact that MSNs are more than drug encapsulation [3]. These complex nanocarriers may be designed to recognize certain biological cues and can hence be used to selectively and precisely release a drug to sites of disease. Their static structure of silica not only secures encapsulated therapeutics but also possesses good biocompatibility and biodegradability in physiological agent [4].

This review gives an overview analysis of MSN technology in terms of their structural characteristic, their synthesis technique, their strategies in functionalizing as well as their various biomedical applications. We discuss the existing knowledge of their toxicological profiles, regulatory and perspectives in personalized medicine. The increasing number of studies on MSNs prove that they have a prospect of tackling major issues in drug delivery, especially in cancer treatment, infections, and regenerative medicines. This review is motivated by the recent pace of discovery in MSN research and the growing number of clinical trials into MSN-based therapeutics. As these nanomaterials approach clinically based practice there is a need to bring together the current state of knowledge as it applies to this area as well as make some determination on any future research directions that would enable the development of these nanomaterials to be successfully tested and used in the clinic.

II. STRUCTURAL FEATURES AND SYNTHESIS OF MESOPOROUS SILICA NANOPARTICLES

2.1. Physicochemical Characteristics of MSNs

Silica nanoparticles are mesoporous arranged nanostructures that have some novel structural particularities which differentiate the system among the other nanocarriers. The highly distinctive feature about their structure is that it is mesoporous in nature and usually containing pore sizes between 2 to 50 nanometers as per IUPAC standards. This mesoporous scaffolding leads to very high surface areas which tend to be more than 1000 m 2 /g, which allows enormous drug loading and surface functionalisation sites. The MSN silica skeleton forms an intertwined three-dimensional structure of silicon and oxygen interactions, which is chemical stable and strong mechanically. The pore walls normally consist of amorphous silica and the pore structure may have a high order with different structural motifs that include hexagonal, cubic, or lamellar arrays. Such structural flexibility enables construction of specific control over drug loading capability, release kinetics, and cellular uptake processes [5].

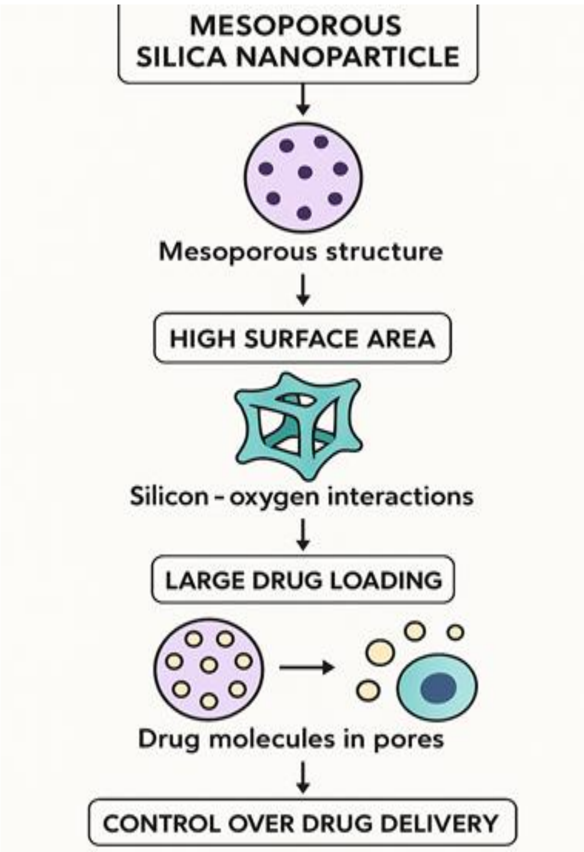

Fig 1: Mesoporous nature of MSN particles

Silanol (Si-OH) and siloxane (Si-O-Si) groups are the most characteristic elements of the surface chemistry of MSNs. Such silanol groups present on the surface can be used as a handle to undergo any type of functionalization reaction such as the addition of organic molecules, polymers, and targeting ligands. Loadings of surface silanol groups themselves are normally between 2 and 5 groups per square nanometer giving plenty of surface modification possibilities without jeopardizing structure [6]. Another important parameter affecting the MSN behavior in bio systems is particle size. MSNs may be prepared in a controlled range of particle sizes between 50 nanometers and several micrometers with drug delivery using 100-300 nanometers-particles being the most common. This is optimal size range in that, it balances two competing needs: the ease of cellular uptake and time that it spends in the systemic circulation and, secondly, to avoid being rapidly cleared by the reticuloendothelial system. MSNs morphological diversity does not limit itself to plain spherical particles only. Recent developments in synthesis techniques have provided the capability to produce a range of morphologies (Rod-like, hollow, core-shell, hierarchically structured particles) and forms. These morphological differences access more chances of perfecting the loading capacity of drugs, release rates and biological interaction [7].

2.2. Synthesis Methods

2.2.1. Sol-Gel Method

Sol-gel procedure is one of the most basic methods used in producing mesoporous silica materials. This works by hydrolysis and condensation of silicon alkoxide precursors (usually tetraethyl orthosilicate (TEOS) or tetramethyl orthosilicate (TMOS)) that occurs in the presence of structure-directing agents. The sol-gel is the process which is distinguished with the succession of chemical reactions which convert the liquid pre customers into solid silica network. The process occurs as the alkoxy substituents are displaced by hydroxyl groups via reaction with water in what has been termed the hydrolysis reaction and then via condensation reactions producing siloxane linkages and the three dimensional silica structure [8]. Different parameters like pH, temperature, water-to-precursor ratio as well as catalysts can be used to control the kinetics of such reactions. Low temperature of synthesis which usually ranges between 60-100o Celsius is one of the major strengths of the sol-gel technique of synthesizing MSNs. This mild condition of synthesis maintains the integrity of the organic structure-directing agents and also lets compounds with thermally sensitive be used in the synthesis. The sol-gel process also allows custom particle size and morphology by the considered manipulation of the synthesis parameters [9].

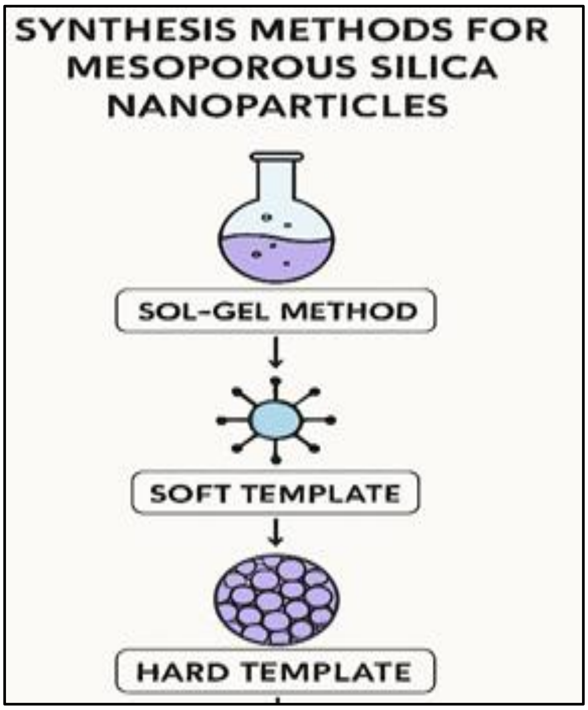

Fig:2 Synthesis of mesoporous silica nanoparticles

2.2.2. Stober Process

MSN are most often synthesized in the Stober process, derived originally for the synthesis of monodisperse silica spheres, but highly modified since. The approach entails the use of base-catalyzed hydrolysis and condensation of silicon alkoxides in alcohol solutions where a base catalyst is usually employed in aqueous environment (in this case, ammonia). This is because the resultant product is of high size uniformity spherical silica particles [10]. In the chemical preparation of materials containing mesoporous phases, the classical Stober method, has been modified to allow the use of surfactant templates in the controlling mesopore growth. Various advantages associated with the modified Stober process include good particle size distribution control, scalability of the synthetic procedures and association with different surfactant systems. The process of the Stober is a mechanical process which consists of two phases where primary silica nuclei are formed by initial reactions of hydrolysis and condensation, and a second phase of growth by addition of silica species onto the pre-existing nuclei. Surfactant templates present in this process help direct the synthesis of organized mesoporous structures but it preserves the mesoporous morphology of the Stober method: the spherical shape of the particles [11].

2.2.3. Microemulsion Method

This microemulsion approach exploits water-oil or oil-water microemulsions in order to provide a microscopically confined reaction space to synthesize MSN. This strategy entails the establishment of the thermodynamically stable and isotropic water, oil, and surfactants blends to produce nanoscale layers of aqueous or organic phase nanoparticle construction. The microemulsion of the water-in-oil system uses aqueous droplets of silicon precursors and catalysts that are immersed in an uninterrupted water phase that is stabilized with surfactants [12]. These droplets have a confined geometry that gives a great control over the size and the morphology of the particle and, in many cases, highly monodisperse MSNs with narrow size distribution are produced. Microemulsion technique provides distinct MSN synthesis advantages not available in other methods such as the capability to synthesize very small nanoparticles (usually between 20-100 nanometers), good control of the size during synthesis and the possibility of inserting multiple functional components into the reaction. Nonetheless, such technique usually involves higher concentrations of organic solvents and surfactants, which can make the purification processes problematic [13].

2.2.4. Hard and Soft Templating

The most critical step in the production of mesoporous silica is the use of templating techniques where hard and soft templates have been commonly used. Soft templating (cooperative self-assembly) is a template-based process where organic surfactants self-assemble into micelles or liquid crystalline phases, which govern the ordering of the mesoporous structures by formation of electrostatically or hydrogen bonded complexes with silica precursors. Typical examples of commonly used soft templates are cationic surfactants, e.g., cetyltrimethylammonium bromide (CTAB), non-ionic surfactants e.g., triblock copolymer) [14]. The pore structure which subsequently forms is highly dependent on the type of surfactant used, where cationic surfactants tend to produce a hexagonal shaped pore structure (MCM-41 type) and triblock copolymers larger pores (SBA-15 type). In hard templating, pre-formed solid templates are used, in the form of carbon nanoparticles, polymer spheres or other nanostructures, around which silica is deposited. Following the formation of silica the hard template is then dispersed by either calcining or chemical removal, leaving a match porous structure in its place. This technique has the advantage of good predictability of pore size and connectivity, but is more complicated and time-consuming than the soft template technique in general [15].

2.3. Surface Functionalization Strategies

2.3.1. Organic Group Modification

Organic group modification of MSNs by functionalization of the surfaces is one of the most significant steps towards the invention of functional drug delivery systems. The high silanol density on the surfaces of MSNs gives motivated functionalities of reactive positions upon which different organic molecules may be covalently linked in the process of silane chemistry. Typical functionalization methods are grafting reactions of organosilanes; these preferentially react with silanols on the surface to give stable siloxane bonds [16]. Introduction of an amino group which can be an active site of further functionalization or confer positive charge to impart electrostatic interactions with negatively charged drugs are often introduced through Aminosilanes like 3-aminopropyltriethoxysilane (APTES). Silanes with thiol functional groups facilitate the linking of molecules using disulfide bonds that are cleaved under reducing conditions and which can be broken to achieve localized release of the drug. One of the two methods used to carry out the grafting procedure is the post-synthesis modification and co-condensation of the synthesis. Post-synthesis grafting is more controllable in terms of functionalization level, and leaves the mesopore structure intact, whereas co-condensation is capable of giving a more homogenous distribution of the functional groups but potentially interferes with pore ordering [17].

2.3.2. PEGylation and Ligand Conjugation

PEGylation, i.e., polyethylene glycol (PEG) modification, is one of the most significant functionalization approaches of the MSNs that enhances the biocompatibility and circulation-time of the MSNs. The action of PEG coating produces a hydrophilic surface list, which would decrease protein adsorption, decrease immune cell recognition, and prolong the half-life of the biological system. PEGylation may proceed using many techniques, such as direct grafting of PEG-silanes, linking reactions of amino-modified MSNs and PEG products, or physically adsorption of PEG-containing polymers [18]. The degree of grafting and molecular weight of the PEG greatly affect the biological performance of MSNs because the higher the molecular weight and the density, the greater the stealth. Ligand conjugation is a process that entails the binding of special targeting ligand to MSNs, e.g., antibodies, peptides, aptamers, or small molecule ligands to MSN surfaces. Such targeting ligands facilitate proactive targeting of specific cell types or tissue, which increases the efficacy of therapy in addition to reducing off-target effects. Conjugation involves usually impacting the bifunctional linkers which couple and bind the ligand of targeting with the functionalized surfaces of MSN [19].

2.3.3. Polymer Coating for Controlled Release

The concept of polymer coating strategies engulfs the laying of layers of polymers on the surfaces of MSNs to regulate drugs release kinetics as well as enhance the biocompatibility of the drug. Such coatings may be deposited in numerous ways: by physical adsorption, by electrostatic assembly, by covalent grafting or in-situ polymerization. PH-sensitive polymers like poly(acrylic acid) or poly(methacrylic acid) may be used as coating to swell or dissolve in certain pH, which allows drug liberation at the desired pH profile (e.g. in tumor tissues, inside cells). In analogous fashion, the thermo-triggered release mechanism is also available in temperature-sensitive polymers such as poly(N-isopropylacrylamide). The use of biodegradable polymer coating, such as chitosan, alginate, or synthetic polyester, provides controlled degradation pattern, which facilitates prolonged release of the drugs. The rate of degradation could be modified in terms of the composition of the polymers, their molecular weight, and the crosslinking density in order to suit the particular therapeutic demand [20].

III. CLASSIFICATION OF MSNS BASED ON STRUCTURE AND MORPHOLOGY

3.1. Structural Variants (MCM-41, SBA-15, KIT-6, etc.)

Mesoporous silica materials have a classification which is mainly dependent on the pore structure and symmetry whilst various families have been established during the years. MCM-41 is among the first and presently best analyzed mesoporous silica materials of unidirectional cylindrical pores arranged in a hexagonal lattice. It has a pore diameter of 2 to 10 nanometers and the material has high thermal and hydrothermal stability. The larger pores (5-30 nanometers), as well as increased pore wall thickness, allow SBA-15 materials to have greater mechanical stability and flexibility in drug deliveries than MCM-41. The SBA-15 most likely utilizes the synthesis of triblock copolymer template in acidic environments, with the materials having hexagonal symmetry in their pore and non-interconnected walls, microporous [21]. KIT-6 is a three dimensional cubic mesoporous architecture having an interconnected pore structure resulting in added merits in mass transport and accessible pore architecture in contrast to one-way pore system. Due to its bicontinuous cubic structure, KIT-6 offers numerous diffusion routes and can, therefore, be selected in cases involving applications requiring swift drug expulsion or the delivery of drug with a large molecular weight. Other interesting structural variations are MCM-48 (cubic), MCM-50 (lamellar), and other lots of hierarchical materials with the combination of meso and macroporous properties. All the different structural types provide different benefits according to the specific application needs and the factors you need to consider when selecting the right material include pore size, connectivity, accessibility among others [22].

Table 1: Classification of Mesoporous silica nanoparticles

Name	Pore structure	Crystal structure	Pore size	Surfactant	Silicone source	Synthetic environment
MCM-42	Two-dimensional straight channel	Hexagonal	2-10	CTAB	TEOS	Alkaline
MCM-48	Three dimensional (Cross hole)	Cubic	2-4	PF-127	TEOS	Alkaline
MCM-50	Two-dimensional straight channel	Lamellar	10-20	C_nH_{2n+1} N(CH3)$_3$	TEOS	Alkaline
SBA-1	Three dimensional (Cage hole)	Cubic	2-3	PAA, CPC	TEOS	Acidic
SBA-15	Two-dimensional straight channel	Hexagonal	5-30	$EO_{20}PO_{70}EO_{20}$	TEOS	Acidic
SBA-16	Three dimensional (Cross hole)	Cubic	5-30	$EO_{106}PO_{70}EO_{106}$	TEOS	Acidic
HMS	Short range ordered channels	Hexagonal	2-10	CnH2n+1NH2	TEOS	Neutral
MSU-X	wormhole	Hexagonal	2-15	CnH2n+1 (EO)m	TEOS	Neutral

3.2. Pore Size and Morphological Adaptability

The pore size in MSNs is a fundamental parameter which determines directly drug loading capacity, drug releasing kinetics and interactions with cells. Pore sizes of small molecules drugs (2-5 nanometers) are loaded and allow more control over the release rates because of the stronger interaction between hosts and guests of single molecules [23]. The medium pore range (5-15 nanometers) has the capacity to adjust to larger therapeutic molecules such as peptides and small proteins; and the drug-matrix interaction is reasonable. Macromolecular therapeutics can also be entrapped into large pore MSNs (15-50 nanometers) allowing protein, nucleic acid, and even small nanoparticle encapsulation. Greater pores can however lead to quicker rates of drug release with the possibility of decreased selectivity, necessitating more controlled release methods. MSNs are morphologically adaptable well beyond the control of pore size to a wide range of different shapes and architectures of particles. The most notably prevalent morphology is spherical MSNs because it is easy to synthesize and has desirable biology properties. Nonetheless, other shapes that include rod-shaped, disk-shaped, and irregular shaped particles are produced as specialized applications. Hollow MSNs bear huge inner chasms enveloped with mesoporous walls that allows a great drug packaging capacity yet retains desired advantageous surface characteristics of traditional MSNs. MSNs have the potential to be core-shell materials with different materials or properties in different areas thereby allowing multifunctional behavior: that is, combine drug delivery with imaging capabilities simultaneously [24].

IV. MSNS FOR DRUG DELIVERY APPLICATIONS

4.1. Advantages of MSNs in Drug Delivery

The mesoporous silica nanoparticles have many benefits compared to the traditional drug delivery systems and therefore possess a lot of attraction to pharmaceutical purposes. Their great drug loading capacity is the main benefit, which is due to the large surface area and adjustable pore volume. Compared to polymer-based nanocarriers with drug loading throughput of as little as 1-10%, MSNs were able to handle drug loadings at the higher levels of 20-40% or higher depending on drug and pore characteristics. The stability of the chemical silica framework offers good protection of encapsulated drugs against degradation, which is important, especially with sensitive drug types, e.g., proteins, nucleic acid, and some chemotherapeutic drugs [25]. This is followed by stability across different environmental conditions such as through pH change, temperature and ionic strength which are typical of biological systems. MSNs exhibit better biocompatibility than a number of organic nanocarriers, and the silica scaffold is considered a generally worthwhile design (by regulatory bodies). The possibility of controlling the properties of the surface of the materials through functionalization also contributes to the biocompatibility profile as it allows to optimize cellular interactions and minimize possible toxicity. The size, morphology and surface properties of MSNs are versatile, such that they can be tailored specifically to a particular therapeutic application. This ability to customize can be used to develop personal drug delivery system to meet specific needs of individual patients and the features of a specific disease [26].

4.2. Stimuli-Responsive Drug Release Systems

4.2.1. pH-Responsive MSNs

One of the most well-researched methods of controlled drugs release in case of MSNs is the pH-responsive drug delivery system. The pH differences in the various physiological environments such as tumor microenvironment (pH 6.570), intracellular compartments (pH 5.06.0), and site of inflammation are used in these systems by two mechanisms namely pH-responsive surface modification, acid-cleavable linkers, and pH-responsive gatekeepers can be designed into pH-responsive MSNs [27]. The amino functionalized MSNs are known to be pH-responsive in nature where amino groups undergo protonation at low pH resulting in electrostatic repulsion and hence increasing the drug release. In the same manner, the carboxyl functionalized MSNs indicate pH estimated swelling and drug liberation as a result of changes in ionic state. To obtain the pH triggered drug release, acid-cleavable linkages can be added to MSN systems, e.g., hydrazones, acetals, ortho esters. These binding processes remain intact in physiological conditions but quickly transform in acidic settings, thus targeted drug liberation can be produced at diseased tissue. pH-sensitive gatekeepers, like polymer coatings, molecular caps, and nanoparticles can be made to block the MSN porousness under normal conditions and liberate medications when reacting to alterations in pH. Such systems provide accurately timed and controlled release and in some cases they can reduce the leakage of drugs during their circulation [28].

4.2.2. Redox-Sensitive Systems

Redox-based drug delivery systems make use of the discrepancy between reducing environments of the extracellular and intracellular environs in an attempt to realize controlled substance delivery. Such reducing agents as glutathione (GSH), cysteine and NADH are much higher in intracellular environment compared to extracellular spaces. The disulfide bonds are the commonly used redox-sensitive bonds in MSN systems. These bonds will not be cleaved under the protein reducing conditions of the extracellular oxidizing environment but will be readily cleaved by intracellular reducing agents allowing drug release into the cytoplasm [29]. All of the redox-responsive systems (disulfide-bridged gatekeepers, drug-MSN conjugates, and crosslinked polymer coatings) have been succesfullyutilised. Complex redox-responsive systems use more than one disulfide bond or integrate other stimulus-responsive units with disulfide linkages to give more complex release behavior. Such systems with multi-responsiveness are able to offer increased specificity and decrease off-target effects in comparison to single-stimulation systems. Precise balance between stability and responsiveness must be ensured in the design of the redox-responsive MSNs since the bonds used to determine the responsiveness (i.e. the disulfide bonds) should remain stable enough in the circulation system so as not to release the drugs prematurely but labile enough so as to respond quickly in the intracellular environment [30].

4.2.3. Enzyme and Temperature-Triggered Release

Enzyme responsive drug delivery systems exploit the high concentration of particular enzymes found in diseased locations or in target cells so as to provide regulated drug delivery. Such systems normally utilize enzyme-cleavable peptide motifs or other recognizable and cleavable substrates that can be specifically digested by the intended enzymes. The most popular targets of enzyme-responsive systems are matrix metalloproteinases (MMPs), the overexpression of which is associated with the pathology of many diseases such as cancer or inflammation. MMP cleavable peptide sequences may be included as drug-MSN linking agents or part of the gatekeeper constructs so that they may release drugs at sites of significant MMP expression. Esters and phosphates are other enzymes used in MSN-based drug delivery together with glycosidases and a variety of cancer enzymes [31]. Enzyme-substrate binding is highly specific and therefore has great application in causing targeted drug release, which would help decrease side-related effects to the system. Temperature-actuated release devices may take advantage of raising temperatures in the inflamed or cancerous tissues or they may use external sources of heating, e.g. focused ultrasound or magnetic hyperthermia. The use of temperature-responsive polymers with lower-critical solution temperature (LCST) in the physiological range as thermoresponsive gatekeepers or conjugate molecules that contain drugs is possible. The additive effect of temperature stimulations with other stimulations make up a multi responsive system that would provide a greater degree of control regarding the release span and location of drugs. In combination with external heaters that could be used to precisely time and space control the release of drugs, these systems are especially useful [32].

4.3. Active and Passive Targeting Approaches

Passive targeting is based on enhanced permeability and retention (EPR) effect, whereby, the leaky vasculature and the lack of lymphatic drainage in solid tumors, cause the EPR effect. Passively targeted MSNs are usually involved with stealth coatings like PEG so that they are not recognized by the immune system and they are circulated longer thereby, increasing the likelihood that the tumor is being accumulated. MSNs are technically sized to efficiently target passively, with the general rule that they be 100-200 nanometer in size. The renal filtration may offer a quick disposal of the particles below 100 nanometers whereas the particles more than 200 nanometers are subject to the augmented uptake with the liver and spleen macrophages [33]. Active targeting In active targeting, the targeted ligands are conjugated with MSN surfaces in order to bind to the target cells or tissues selectively. Such ligands may consist of antibodies, antibody fragments, peptides, aptamers, carbohydrates and small molecule ligands specific to targets or biomarkers. Targeting of folate receptors is one of the most actively investigated active targeting methods because the folate receptors are overexpressed in most types of cancer with low expression in healthy tissues. In contrast, increased cellular internalization and efficacy of the folate conjugated MSNs against targeted formulations are observed. Additional effective targeting approaches are targeting transferrin receptors to specifically deliver agents to the brain, integrins to target angiogenic vessels, and lectins to target a particular cell type. Specificity and efficacy should also be improved by developing multi-targeted systems involving a combination of targeting ligands. The active targeting systems optimization must be well thought, especially with regard to the ligand density, linker-chemistry as well as possible steric hindrance issues. Excessive ligand densities can interfere with the cellular uptake because of the membrane gets rigid with low densities, whereas the ligand density may be insufficient to achieve high levels of targeting [34].

V. BIOMEDICAL AND THERAPEUTIC APPLICATIONS

5.1. Cancer Therapy

Cancer therapy is, by far, the broadest area of MSN utilization that has been already put to the test both in preclinical, and clinical trials that have shown their effectiveness as tools in enhancing chemotherapies. The discrete features of the MSNs solve some major roadblocks in cancer therapy such as low drug solubility, non-specific distribution, drug resistance, and the high externalities. Applications of MSN-based chemotherapy delivery systems have been established on very diverse anticancer drugs such as docrubicin, paclitaxel, camptothecin, cisplatin and 5-fluorouracil. Such systems have been known to realize substantial increases in drug loading capacity, stability and therapeutic potency as compared to non-modulated systems. Drug resistance to combination therapy regimes has also been overcome using MSNs and this approach has also been promising in achieving higher levels of treatment and success [35]. Synergistic combinations of drugs with controlled release characteristics can be provided by multi-drug loaded MSNs but with the added benefit of not having the multiple dosing schedules morass. Recently, the response of tumor microenvironment in MSNs has been developed to allow targeting cancer cells with a more specific dose to healthy tissues. To effectively reach selective release of drug, these are capable of responding to the specific conditions presented by tumors that may include acidic pH, presence of high enzyme inventory, hypoxia, or high temperatures. Photodynamic therapy (PDT) MSNs In photodynamic therapy (PDT) applications, MSNs have a wide range of capabilities. These MSNs allow the encapsulation or conjugation of photosensitizers to produce reactive oxygen species under the activation of light. Unlike the free photosensitizers, there is better cellular uptake, better stability of the photosensitizers and lower dark toxicity of the MSN-based PDT systems. The latest advancements in MSN-associated cancer immunotherapy incorporate the conveyance of immune-checkpoint inhibitors, cancer injections, and immunomodulators. These are applications that utilize immunostimulatory effects of the silica nanoparticles with the advantageous feature of controlled deliveries of the therapeutic agents [36].

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5.2. Diagnostic and Imaging Applications

The distinctive merit of MSNs is that they can integrate into all types of contrast agents, fluorescent markers, and targeting ligands, which provide good platforms in diagnostic and imaging application. The mesoporous assembly offers sufficient loading volume of imaging agents and they are stable and biocompatible. MSNs loaded with gadolinium complexes, iron oxide nanoparticles or manganese-based contrast agents are used in the applications of magnetic resonance imaging (MRI). The use of these systems provides greater relaxivity, a lower toxicity and better targeting potential than conventional contrast agents. The use of fluorescence imaging involved embedding different systems of fluorescent dyes, quantum dots, or lanthanide complexes into structures of MSNs. The silica matrix helps shield fluorescent operators against photobleaching and environmental loss as well as releasing purpose under controlled circumstances in terms of dynamic imaging investigation [37]. Computed tomography (CT) scanning involves MSNs functionalized with iodine, bismuth, or gold nanoparticle-based contrast absorbing scanners. The systems offer more contrast with less toxicity relative to the typical iodinated contrast agents. Multimodal imaging systems consist of multimodal devices where different imaging modalities are embedded in one MSN platform so that complementary information could be obtained and better diagnostic accuracy could be obtained. Such systems have the capacity to offer anatomical, functional and molecular information in parallel. Theranostic tools merge therapeutic effects with diagnostic capabilities in one MSN framework to allow real-time tracking of medicines distribution and treatment outcomes. These platforms symbolically contemplate the serious step forward to the personified manifestations of medicine [38].

5.3. Antibacterial and Antimicrobial Uses

Growing resistance to antibiotics has fueled the development of great enthusiasm in MSN-factor antimicrobial systems. Such platforms have a number of advantages compared to conventional antibiotics namely, enhanced drug stability, low resistance development and sustained release patterns. One of the most studied antimicrobial systems due to the combination of the widespread antibacterial properties of silver and the controlled release capacity of MSNs are silver nanoparticle-loaded MSNs [39]. The systems have showed very good activity against gram positive and gram negative bacteria and have a low cytotoxicity against mammalian cells. Several examples of antibiotic delivery systems using MSN have been established against different antimicrobial agents incorporating the following agents, namely, vancomycin, gentamicin, rifampin, and ciprofloxacin. Such systems are found to generate prolonged release of drugs over a long duration, and so, they may not require frequent administration, which makes drug compliance better in cases of the patient. Antimicrobial peptide delivery is a new area of application given that these natural occurring defense molecules can provide broad spectrum activity with less propensity to resistance. MSNs ensure full protection of peptides to prevent enzyme-mediated degradation, and induce the release of the latter in specific locations at controlled periods. Photodynamic antimicrobial therapy is a therapy that involves the use of photosensitizers, smeared onto MSN, which produces reactive oxygen species to kill bacteria when illuminated by a light source. This mode of action is especially useful in localized infection and biofilm-related infections. With the creation of infection-responsive systems of MSN, it is possible to release theoretical drugs only at the site of infections, which may limit systemic exposition and adverse effects. The systems react to an infection-related condition like pH levels, the level of enzymes or bacterial metabolites [40].

5.4. Gene and Vaccine Delivery

In gene delivery, applications of MSNs aim at the protection and release of nucleic acids such as DNA, RNA, siRNA, and microRNA. The electrostatic interaction between negatively charged nucleic acids and positively charged surface modifications on the MSNs is the major reason why MSN based applications are efficient in siRNA delivery processes. These nano-carriers avoid siRNA degradation in the body by nuclease action and facilitate the targeted and transport of the molecule inside the cell in addition to being able to provide better gene silencing than traditional delivery strategies. Another potential use of DNA vaccines involves the delivery of DNA vaccines, where MSNs have been used as delivery vehicles that also work as adjuvants to stimulate greater immune responses [41]. The silica scaffold and the particulate structure of MSNs lead to uptake by antigen-presenting cells and the presentation of immunostimulatory signals, respectively. The use of MSNs in protein vaccine delivery systems enables delivery of multiple antigens in a single system because of a high loading capacity of MSNs, with a high level of control released profiles. The systems have the potential to enhance immunity, stability of vaccines and eliminate the requirement of cold chain storage. The mRNA delivery technology has gained much interest since the success of the COVID-19 vaccines, and the MSNs provide an opportunity with advantages of stability and control release over lipid nanoparticle delivery forms. This evolution of the targeted gene delivery schemes involves the use of specific ligands in delivering gene to specific types of cells that may assist in the reduction of off-target effects and enhancing the efficacy of the therapy [42].

5.5. Regenerative Medicine and Bone Tissue Engineering

In regenerative medicine, of interest are MSNs to deliver growth factors, stem cell therapy, and tissue engineering scaffolds in a controlled manner. Silica has both biocompatibility and osteoconductivity, which qualifies MSNs to be used in bone and cartilage regeneration. Bone morphogenetic protein (BMP) releasing systems based on MSN have proven to have great bone regeneration potential. These systems also produce a prolonged delivery of growth factors that are maintained in their biological activity resulting in increased bone formation than when using conventional delivery systems [43]. MSNs are used in stem cell delivery applications in which mesenchymal stem cells can be loaded and delivered at the conclusion of burns or other injuries to a targeted site of delivery in conjunction with controlled release of supportive factors. Such systems are capable of enhancing the survival, engraftment as well as differentiation of stem cells. Our injectable hydrogel systems containing MSNs can supply minimally invasive methods of tissue regeneration. Such composite systems integrate the mechanical materials with the controlled release performance of MSNs. The process of vascularization is an important part of tissue engineering and vasculogenesis using MSN-based angiogenic factors stimulates the growth of blood vessels in regenerating tissue. Such systems are able to circumvent the weakness of growth factor instability and half-life shortages. Advances in the creation of biodegradable MSN systems make possible temporary scaffolding, which dissolves over time as new tissue develops without having to surgically remove that scaffolding, which can reduce long-term complications [44].

VI. TOXICOLOGICAL AND BIOCOMPATIBILITY CONSIDERATIONS

6.1. In Vitro Toxicity Studies

The systematic investigation of the in vitro toxicity is a vital procedure in establishing the MSN-based therapeutic systems. Such studies normally analyze more than one endpoints of toxicity with a variety of cell lines and experimental conditions in order to offer comprehensive insights of the possible side effects. Cell viability assays, such as an MTT, MTS, and LDH release assay are routinely performed to determine cytotoxicity in response to MSN exposure. Such studies typically show that synthesized well, the MSNs are not cytotoxic (at therapeutically relevant doses) with IC50 values usually above 100 g/mL in most cells. The genotoxicity determination depends on the analysis of DNA damage and chromosome alterations and mutagenesis capabilities after exposition to MSN [45]. Nearly all reports indicate little genotoxic potential in pure MSNs, but functionalization of the surfaces and their impurities may affect the genotoxic profile. Oxidative stress parameters can be used to determine the production of reactive oxygen species and antioxidant concentrations deficiency after being exposed to MSNs. There are conflicting reports regarding low level oxidative stress at high doses, but in general these are reversible and have not been shown to cause a great deal of cell damage. The capacity of the MSNs to destroy cell membranes by direct contact or osmotic stress is examined by a membrane integrity testing procedure. MSNs synthesized correctly are normally not grossly disruptive to the membrane but in some instances, membrane contacts have been shown to depend on particle size and charge. Evaluation of inflammatory response evaluates the possibility of MSNs to initiate the inflammatory cascades with a cytokines release or their facilitation of inflammatory cascades. Overall, the results of these studies demonstrate small amounts of inflammatory response to well-understood and in part neutral or negatively charged surfaces MSNs [46].

6.2. In Vivo Biocompatibility and Biodistribution

In vivo biocompatibility studies can give important details regarding biocompatibility and destiny of MSNs in a living system. Those studies are normally performed with several species, with different administration routes and with longer-term observation, on a large population, to analyze the safety profile in detail. Biodistribution analysis was used to monitor where MSNs would go after being administered to the binary system and it was discovered that the nanoparticles biodeposit in majorly liver, spleen and lungs with little presence of biodeposits seen in other organs. The bi-distribution pattern could be altered by means of surface functionalizing, particle size, and conjugation to target ligands [47]. MSNs clearance involves renal and hepatic clearance mechanisms, whose clearance is dominated by renal processes in small MSNs (< 10 nm) and in large particle (>10 nm) by mononuclear phagocyte system. MSNs can also be slowly absorbed in biological environments through dissolution of silica crystal structure, with the half-life of clearance usually between days and weeks. After MSN administration, the organs are usually examined histopathologically without significant tissue damage or inflammations especially when the surface of particles is properly modified. Other impacts noticed are always transitory and clear up on their own. Extensive long-term toxicity studies undertaken over several months prove the exquisite safety profile of MSNs where no hint of chronic toxicity, alteration in organ functions, or tumor development is found at any doses up to the therapeutically relevant doses. Albeit limitedly, reproductive and developmental toxicity studies indicate that MSNs induce few to no reproductive or developmental adverse effects which indicates, more detailed studies are required to establish safety comprehensively in that aspect as well [48].

6.3. Influence of Physicochemical Properties on Toxicity

Physicochemical properties of MSNs, such as particle size and surface area, surface charge, morphology and chemical composition, largely contribute to their toxicity profile. These relationships are very important in developing safer and more effective MSN-based therapeutics. Particle size is perhaps one of the most important parameters that affect the MSN as they tend to cause more toxicity when they are small in size due to their increased cellular uptake levels. Yet, size-toxicity relationships are nonlinear and very instance specific as a result of biological system being exposed to. Porosity and surface area affect the interaction surface available to biological molecules and a larger surface area would result in increased protein adsorption and cellular interactions [49]. The mesoporous MSNs structure, nevertheless, often yields reduced apparent surface areas of biological interactions when compared to their respective BET surface areas. Surface charge plays an important role in cellular uptake, protein adsorption and inflammatory response. Since positively charged MSN usually have better cellular uptake, however, they can elicit stronger membrane perturbation and inflammation than neutral or negatively charged nanoparticles. Cellular interactions and uptake mechanisms are affected by morphological factors such as the shape of the particle and their surface roughness. Cylindrical structures tend to be more biocompatible than the high aspect ratio spherical structures which can be damaging to membranes or inflammatory. Toxicity profiles can vary deeply according to chemical constitution, such as the existence of surplusive surfactants, catalysts or impurities. The biocompatibility level should be constant and quality control and thorough purification should be offered [50].

6.4. Approaches to Enhance Biosafety

Some approaches have been established to make MSN-based systems safer in terms of their biosafety without compromising their efficacy as therapeutic agents. These methods are aimed at maximising the physicochemical properties, better biocompatibility and safer synthesis. One of the most promising methods of enhancing the biosafety of MSN is surface modification with biocompatible polymers, especially PEG. PEGylation lowers the adsorption of proteins, lessens inflammatory reactions, changes the persistence of the circulation and decreases its accumulation in purifying organs. Optimizing the size of a particle or range of their sizes falls under the aspect of selecting sizes that meet both therapeutic and safety goals [51]. Conventionally, the best biodistribution profiles are obtained using particles that correspond to the 100-200 nm range that shows low chances of rapid clearance and over-accumulation in the filter organs. Biodegradable MSN systems: Bioerodible MSN systems are used in order to break down quickly into biodegradable and easily dissolved species, and can be achieved through implementing labile bonds or biosynthesis of compositions. This will be able to decrease accumulation long-term and still have therapeutic efficacy. Synthetic reaction residues such as unreacted precursors, surfactants and catalysts can be highly hazardous to health and their absence is demonstrated through quality assurance and purification methods. Consistent biocompatibility profiles require standard remove purification processes. The therapeutic index can be improved by seeking means of improving the therapeutic site and decreasing delivery to healthy tissues, to minimize possible side effects. There is generally an improved safety profile of the active targeting methods in contrast to the passive accumulation of the targets. Therapeutic drugs co-delivered with cytoprotective agents are expected to decrease the treatment-related toxicity by keeping the therapeutic efficacy equal or even increasing it. The strategies are especially of worth to highly toxic treatment drugs like chemotherapeutics agents [52].

VII. REGULATORY AND TRANSLATIONAL PERSPECTIVES

7.1. Regulatory Guidelines and Standards

Regulatory affairs relating to MSN-based therapeutics is a highly complex process that includes a variety of jurisdictional and agency scaling; as the technology develops, guidelines are also being refined. Regulatory authorities (such as the Food and Drug Administration (FDA), European Medicines Agency (EMA), and others) have worked out procedures to assess products involving nanomedicine, but definitive guidance on MSNs are continuing to work out. Existing regulatory strategies normally mandate extensive description of MSN products with respect to particle size distribution, surface area, pore dimension, surface chemistry and impurity profile. Such characterization needs are more than is the case with conventional pharmaceuticals, given the special nature and possible risks of nanoparticles [53]. The manufacturing control standards of MSNs should cover consistency through the batches, stability over time, and testing procedures of quality control. Because of the complexity of MSN synthesis and functionalization, highly analytical techniques and product control systems are needed to ascertain product consistency. The preclinical testing requirements pertaining to MSN-based products usually comprise prolonged toxicology, biodistribution profiles/ tests, biocompatibility reports, and are above and beyond the traditional pharmaceutical testing requirements. These experiments need to deal with the peculiarities of behavior of nanoparticles in the biological environment. MSN-based therapeutics Clinical trial design Considerations must be paid to dose rationale, safety monitoring plans, and effective outcomes that are not necessarily similar to the typical approach to a drug development program. The pharmacokinetics and biodistribution of MSNs is complicated, which requires special study designs and analytical approaches. Regulatory bodies also consider the analysis of risk and benefit of nanomedicine products more significant and there should be thorough assessment of possible risk against therapeutic advantage. This has to be analyzed under both short-term and long-term impacts and the existence of alternative forms of treatment [54].

7.2. Clinical Trials and Status of MSNs

The advanced stages of clinical development of MSN-based therapies are on course with a number of products having gone to different levels of humanization. Such trials reveal much about the safety, efficacy, practicality of MSN-based treatment. Clinical trials at an early stage have in general verified the safety profiles identified in preclinical studies and it is found that MSN-based therapies have an acceptable tolerability at the therapeutic doses. Such studies have also brought valuable pharmacokinetics information that are used in deciding on dosing schemes and administration schedules. Clinical efficacy of therapeutics based on MSN has achieved promising results especially in the cancer treatment use [55]. These findings point toward MSN-based formulations being capable of being as or more effective than currently existing treatment methods at a reduced side effect risk. The methods of patient selection in terms of MSN-based-therapeutics are also changing with regard to clinical experience and the designing of biomarkers. Tailored medicine methods of aligning MSN properties with patient parameters can lead to a better outcome of treatment. Scale-up challenges to manufacture have been identified as MSN-based products develop to enter clinical trials. Such challenges are to ensure the consistency of the product on commercial scales, establish low cost production processes and achieve reliable supply chain. Clinical trial regulatory feedback has informed development strategies and the major regulatory factors that will be considered with MSN based products in the future. This has been used to make corrections in the manufacturing procedures, the methods of controlling the quality and overall design of clinical studies [56].

7.3. Scalability and Manufacturing Challenges

Scaling-up MSN-based therapeutics to commercial-sized batches poses many challenges during the manufacturing process which need to be resolved in order to commercialize the product. These problems cut across chemistry, engineering, quality control and regulatory compliances. The scalability of synthesis is one of the main obstacles since most of the laboratory methods of synthesis do not scale up to the industrial manufacturing levels [57]. Multi-step functionalization procedures commonly used in the production of functionalized MSNs are demanding, hence warranting a keen approach to optimization to warrant quality and ensure economic feasibility. At commercial scales, the process control is sophisticated to meet the requirement of batch-to-batch consistency by monitoring and control systems. Sensitivity of MSN to the synthesis conditions will require exacting temperature, pH, mixing and reaction time control during the manufacturing process. Analysis Commercially viable quality control studies should be fast, accurate, and economical yet concurrent in nature to meet the thorough characterization needed to satisfy regulatory proscriptions [58]. In quality control, artificial testing systems and high-level analysis techniques are required. The nature of the raw materials used and their standardization remain a challenge, however, because the quality of the silicon precursors, surfactants and other components of the synthesis can have a big influence on the final product characteristics. The supply chain management should work to sustain steady quality of raw materials at an economic cost. Some of the environmental and safety facts on commercial manufacturing of MSN entail management of wastes, safety in the workplace arrangements, and environmental effects analysis. All these factors also play a crucial role when taken into consideration since MSN products are formulated in nanoparticles. The approaches to cost optimization should find the balance between production efficiency and the quality of products and regulatory compliance. The costly synthesis and purification procedures of the MSNs remain a persistent problem that is to be solved by implementing and advancing the innovation and optimization of the processes [59].

7.4. Comparison with Other Nanocarriers

There are numerous alternative nanocarrier systems, the competitive environment of which shows the distinct advantages and limitations of each system in competition with MSN-based therapeutics. This study about comparisons is imperative when it comes to positioning MSN products in therapeutic markets, as well as defining ideal application areas. One of the most mature nanocarrier technologies is the delivery of drugs using liposomal carriers; a small number of products have been approved and a substantial volume of clinical experience has been gained. MSNs have a high loading capacity and good stability than liposomes but they might be more associated with the complexity of regulation compared to liposomes due to being inorganic. The polymeric nanoparticles have a fantastic customization potential and relatively desirable regulatory background [60]. Nevertheless, most polymers do not provide an as high drug loading capability and control of release kinetics as MSNs do. Nanocarriers made of protein (such as albumin nanoparticles) have ideal biocompatibility and regulatory routes in place. MSNs have benefits with regards to stability, versatility, and possibly needing greater safety testing. Lipid nanoparticle system has emerged to be so vast after the success of the COVID-19 vaccine vaccines because it proves the economic potential of the nanocarriers. Other benefits that are provided by MSNs such as better stability, and controlled release may prove useful in other types of therapies. Nanocarriers based on carbon, e.g., carbon nanotubes and graphene derivatives, have properties that are not found in other nanocarriers, and they also have considerable regulatory and safety issues. Having good biocompatibility profiles and competitive performance features, MSNs are usually preferred. The best nanocarrier systems to use are subject to the determination of particular therapies, regulation, production, and market aspects. MSNs will most be successful in applications that make the most of their unique strengths by imparting substantial therapeutic or commercial value [61].

VIII. EMERGING TRENDS AND FUTURE PROSPECTS

8.1. Smart and Multi-Stimuli Responsive MSNs

The emergence of intelligent MSN systems that react to a variety of stimuli is the new step forward in the targeted drug delivery technology. Such advanced systems are able to incorporate several responsive units to effect novel levels of control in terms of timing, location and drug dosing. The complex responsive ones normally have two or more stimulus response triggers, e.g. pH and redox sensitivity, temperature / enzyme programmed, or light / magnetic field

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activated. These combinations can give greater specific management of therapeutic delivery over the traditional activation processes where redundant processes of activation is possible. Cascade responsive systems make use of a time based stimulus response which must be triggered in a particular sequence to allow the drug release to occur [62]. The threshold of these systems is more selective and all the off-targets effects are minimized because multiple biological conditions are obligatory to be satisfied. The programmable release systems have feedback systems that have the ability to change the release profiles according to the local biological situation or responses to therapy. These systems are precursors of autonomous therapies altering the requirements of the evolving patients. External energy sources such as radiofrequency, magnetic field, ultrasound, and light are applied to activate wireless activation systems on demand by releasing a drug. Such systems allow accurate time management of the delivery of therapeutics and are compatible with monitoring systems to maximize treatment strategies. Biomimetic responsive systems involve as components of biomimetic activation called biological recognition elements, including an enzyme substrate, or receptor ligand that can result in highly specific activation when disease-linked biomarkers are present. These systems are able to offer outstanding selectivity of the diseased tissues with as low dose exposure to normal tissues as possible [63].

8.2. Biomimetic and Hybrid MSNs

Incorporating biological material or structure into biomimetic MSN systems provides specificity and improved biocompatibility, targeting specificity, and therapeutic effectiveness. Such hybrid systems are a functional combination of the positive attributes of MSNs with the complex behaviour of biological systems. Cell membrane (CM)-coated MSNs employ natural cell membranes or synthetic derived cell membranes as a stealthed layer, immune escape and active targeted delivery. The surface properties of certain cell types can be introduces to these systems without losing the benefits of delivery of drugs through the MSNs. Enzymes, antibodies, or other proteins sometimes are used to decorate protein-decorated MSNs and confer nanomaterial-specific functionality (e.g., catalytic activity, specificity of targeting or release on demand). Such hybrids have the potential to attain complex biological performance steady with the stability and loading limit of MSNs [64]. Nucleic acid elements are incorporated into DNA-functionalized MSNs to offer either recognition, structural organization or therapeutic functionality. The specificity of DNA hybridization can be used in these systems to target or they could be developed into responsive systems that respond to a specific genetic sequence. Living cell-MSN hybrids combine MSNs and living cells and synthesize complex biological functions by forming complex therapeutic systems. These systems are able to give prolonged therapeutic production, responsive behavior, and increased tissue incorporation. Organelle-mimetic MSNs reproduce the structure and functionality of cellular organelles so as to offer specialist therapeutic functions. These systems are able to combine the advanced chemical processing functions of natural organelles and give additional stability and control. Biological membrane integration Building in the context of MSNs The MSNs can also be built into natural biological membranes through the method of biological membrane integration, making hybrid systems with increased biocompatibility and functionality. These strategies are able to generate better tissue integration as the controlled drug release ability keeps a balance [65].

8.3. MSNs in 3D Bioprinting and Tissue Scaffolds

3D bioprinting and tissue engineering platforms with MSNs integration are a new frontier where high technology advanced manufacturing technologies meet highly sophisticated drug delivery capabilities. With these applications, the special characteristics of MSNs are utilised to make functional tissue structures that incorporate supply delivery systems.Bioink containing MSNs has the potential to deliver growth-factors, nutrients and other bioactive molecules required to build and maintain tissues in good condition in a controlled manner [66]. Such formulations allow production of tissue constructs with integrated and active processing capabilities that can sustain tissue over a long period of time. Improvement of vascularization using angiogenic agents provided by MSNs is one of the essential methods of effective tissue engineering. Such systems offering a sustained delivery of various angiogenic factors in order to induce blood vessel growth across tissue constructs can be made available [67]. Controlling differentiation of stem cells with locally delivered MSN-encoded signaling molecules allows the possibility to exert precise control over fates of cells during tissue development. Such systems have the abilities to administer differentiation cues both in space and time to form complicated tissue architectures. By regulating mechanical properties via incorporation of MSN, it is possible to improve a structure property and offer therapeutic capability to the bioprinted structure. Meanwhile, MSNs have the silica fixed skeleton which can form a mechanical strength and the mesopore dimension can be used as the drug loading site. Multimaterial printers have the potential to combine MSNs with other materials to build complex tissue constructs whose properties and functions vary regionally. Such systems allow developing the models of tissues that closely mimic both tissue architecture and physiology. Cost-effective analytics methods and manufacturing practices that involve the use of sophisticated standards are needed to control quality and standardization of MSN-containing bioprinting materials. Such considerations are critical to consistent performance and regulatory compliance of the bioprinted tissue products [68].

IX. CONCLUSION

There is great promise and versatility in the use of mesoporous silica nanoparticles as advanced drug delivery and biomedical platforms, in particular. The extensive overview included in this review shows how much the MSN technology has advanced in the last 20 years since the first discovery of their role in material science to the more advanced therapeutic systems nearing clinical reality. Their distinctive structural properties, such as the large surface area and the controllable pore size, coupled with outstanding biocompatibility and wide flexibility in functionalization, offer great opportunities that make MSNs outclass the traditional drug delivery platforms. These characteristics have made possible high drug loading, fine control over the release rate and carry the capability in having more than one therapeutic and diagnostic purpose under one nanoparticle platform. Synthetic flexibility of MSNs can be used to enable particle properties to fit exact therapeutic needs and more-complex functionalization protocols can lead to the creation of more-complex stimulus-responsive and targeted drug delivery systems. The fact that it is possible to develop smart MSN systems that react on various biological cues is an important move in the direction of personal care to patients in terms of personal joint medicine that may accommodate personal patient demands and natures of diseases. It is increasingly understood through the preclinical evidence that MSNs have therapeutic applications, in many areas of medicine, including cancer treatment and infection treatment, regenerative medicine, and vaccines. The overall good safety profile demonstrated both in in vitro and in vivo settings justifies the further progress of MSN-based therapeutics whereas the current focus on clinical trials can also help to gain more insight into its clinical potential. Problematic regulatory and translation issues related to MSN based therapeutics are being actively dealt with as a result of collaboration between researchers, industry and regulatory bodies. The process of establishing proper guidelines on how to deal with MSN based products, manufacturing standards and quality control measures will be critical towards successful commercialization of such products. The future of MSN technology in therapeutic applications appears equation-ed even further with emergent technological advances in smart multi-stimuli responsive systems, bio-mimetic design, integration with advanced manufacturing technologies and use of artificial intelligence optimization technologies. This progress brings out the possibility of increased use of MSNs to progressively increase nanomedicine and personalized medicine. MSN-based therapeutics have an upside potential and the indwelling factor that will positively impact the future success of the therapeutics is further innovations in the material design, scalability to manufacture this treatment, regulatory clearance, and clinical validation. The MSN technology coupled with the progress of other technology, such as artificial intelligence, 3D bioprinting, and personalized medicine, are rife with possibilities of disruptive applications in healthcare. The functionality of MSN technology is still being optimized and one should remain focused on dealing with the challenges still remaining, also taking advantage of the distinct advantages offered by such materials. As seen in the level of investment done on the research and development of MSN by academic institutions, pharmaceutical companies, and government agencies, they are filled with confidence about their potentials to solve critical healthcare needs. The all-encompassing aspect of current MSN research, which covers material science basics all the way through to advanced engineering, biological research and clinical development offers a firm platform on which it can build. Executing MSN research with the demanding potential of such remarkable materials will depend on the interdisciplinary cooperation, which has been the trademark of MSN development.

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