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SYNTHESIS AND RECENT DEVELOPMENTS OF MESOPOROUS SILICA NANOPARTICLES IN TARGETED ANTI-TUMOR THERAPY

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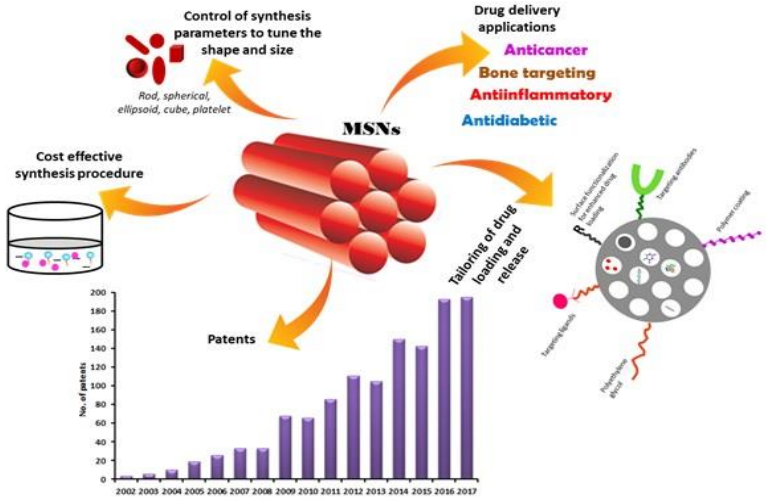
Abstract
Current approaches to diagnosis and treatment have undergone a revolutionary shift as a result of recent developments in drug delivery technologies that make use of a range of carriers. Mesoporous silica nanoparticles have been developed as a result of the need for materials with high mechanical, chemical, and thermal properties (MSNs). Because of what sets these ordered porous materials apart from the rest, they have attracted a lot of interest as drug carriers. It is affordable since they may be produced through a somewhat easy procedure. Furthermore, the morphology, pore size and volume, and particle size can all be altered appropriately by adjusting the parameters during the synthesis. The last several years have seen a sharp rise in the amount of research on MSNs as drug carriers for the management of diverse diseases. Its broad use as a carrier for loading macromolecules like proteins, siRNA, and other macromolecules as well as tiny compounds has made it an adaptable tool. Researchers have recently made several changes to the MSN architecture to investigate its potential for use in antimicrobial therapy and drug-resistant chemotherapy. We have covered the synthesis of

these multifunctional nanoparticles as well as the variables affecting the shape and size of this amazing carrier in this review. This review's second section focuses on the developments and applications of MSNs, particularly in the realm of biomedicine, to increase their potential applications. Additionally, we have discussed the gaps in our understanding of how it interacts with a biological system, which poses a significant obstacle to this carrier's advancement to the clinical stage. The last section of our examination covered a few of the most significant patents related to MSNs used for medicinal purposes.

Keywords: Mesoporous silica nanoparticles, sodium orthsilicate, Drug resistance, nanomedicine



Graphical abstract

INTRODUCTION

In the twenty-first century, modern nanotechnology has emerged as the primary scientific discipline. The use of nanotechnology in the realm of biomedicine has allowed illness detection and treatment to continuously advance throughout time (1). Thanks to the benefits of nanocarriers, which include a high surface area to volume ratio, special features of surface modification, and engineering to obtain particles of different sizes, shapes, and chemical characteristics, the field of nanomedicine and green technology for its production have flourished and changed paradigms in therapy and tissue engineering. Its benefits are increased by the fact that these are non-toxic, biocompatible, and biodegradable (2). Polymeric nanoparticles (3), dendrimers (4), and lipid-based nanocarriers (5) have transformed the treatment of a number of diseases in particular, infectious disorders and cancer. In addition to the organic nanoparticles discussed above, inorganic nanoparticles have also been thoroughly investigated for potential use in biomedicine (6). Of them, iron oxide and quantum dots nanoparticles have received approval and are marketed commercially. For a variety of therapeutic and diagnostic applications, carbon dots, silica nanoparticles, layered double hydroxide nanoparticles, gold, silver, and other metal oxide nanoparticles have all been extensively employed (7,8). Of these, Cornell dots (C dots), a type of silica nanoparticle that combines radioactive iodide with organic colors, has successfully achieved an important safety benchmark by being approved for Phase I human trials. This is a necessary step for any medication that needs to be approved as an Investigational New Drug (IND) (9). C dots are core-shell silica nanoparticles having a silica shell encircling a silica core that contains fluorescent molecules. This has an additional polyethylene glycol (PEG) coating applied. Ulrich Wiesner, the Spencer T. Olin Professor of Engineering at Cornell University's Department of Materials Science and Engineering, created C dots for the first time (10). Mesoporous silica nanoparticles (MSNs) are silica nanoparticles that have mesopores; they have become very popular in recent years. It is a unique and potential drug carrier because of its features, which include uniform and adjustable pore size, simple independent surface functionalization, internal and external pores, and a gating mechanism for the pore opening (11). Researchers have been able to load a wide range

of cargo onto these carriers, including medicines and macromolecules including proteins, DNA, and RNA (12, 13). There is a wealth of literature accessible, and studies are constantly being conducted to assess novel approaches to the delivery of drugs using MSNs. Numerous studies on MSNs' effects on drug solubility (14, 15), as a controlled/sustained drug delivery mechanism (16), and applications in in biology, with publications (17, 18). The literature reviewed in this research covers a wide range of MSN topics, from synthesis to filed patents.

THE SOURCE OF MESOPOROUS SILICA MATERIALS

While mesoscopic materials have been synthesized since the 1970s, Mobil Research and Development Corporation was the first to create mesoporous solids from aluminosilicate gels in 1992 through the use of a liquid crystal template mechanism. They dubbed it MCM-41, which stands for "Mobil Crystalline Materials or Mobil Composition of Matter." According to IUPAC, mesoporous materials are those with ordered pore arrangements that give them an ordered structure with pore sizes between 2 and 50 nm (19, 20). By using different surfactants, the pore size of these may be adjusted. With a pore diameter ranging from 2.5 to 6 nm, MCM-41 is typically hexagonal in shape and was created using cationic surfactants as templates. Among the materials that have been studied the most for medication administration is MCM-41 (21). In addition, several mesoporous materials have been created by altering the initial precursors and reaction conditions. These could differ in terms of pore size or structural configuration. MCM-50 exhibits a lamella-like configuration while MCM-48 has a cubic arrangement (22). Based on the symmetry of the mesoporous structure and the triblock polymers used, non-ionic triblock copolymers such as poly (alkylene oxide) block copolymers and alkyl poly (ethylene oxide) oligomeric surfactants have also been used as a template. These copolymers have been named SBA-11 (cubic), SBA-12 (3-d hexagonal), SBA-15 (hexagonal), and SBA-16 (cubic cage-structured) (23). The optimum symmetry of mesoporous materials was obtained by adjusting the ethylene oxide to propylene oxide ratio. SBA-15's highly structured mesoporous structure has also been applied extensively in the biological field. The Santa Barbara Amorphous type material (SBA) was initially synthesized by the University of California, Santa Barbara, and is hence known by that name. They differ from MCM in that they have stronger silica walls and bigger holes, ranging from 4.6 to 30 nm (24). Another kind of mesoporous material is FSM-16 or folded sheets of mesoporous material. These are made by layering polysilicate kanemite and utilizing quaternary ammonium surfactant as a template. FSM-16 has been shown by Tozuka et al. to have potential uses in pharmaceuticals beyond catalysis and adsorbents (25). Other MSNs with different pore symmetry and shapes have been synthesised, including Technical Delft University (TUD-1), Hiroshima Mesoporous Material-33 (HMM-33), and Centrum voor Oppervlaktechemie en Katalyse/Centre for Research Chemistry and Catalysis (COK-12) (26). A few MSNs are represented in Figure 1. MCM-41, MCM-48, SBA-15, and SBA-16 are commonly utilised for the delivery of drugs. They have also been investigated for use as biosensors, adsorbents, and catalysts. It has been reported that MCM-50, SBA-11, and SBA-12 exhibit outstanding adsorbent and catalytic properties (27).

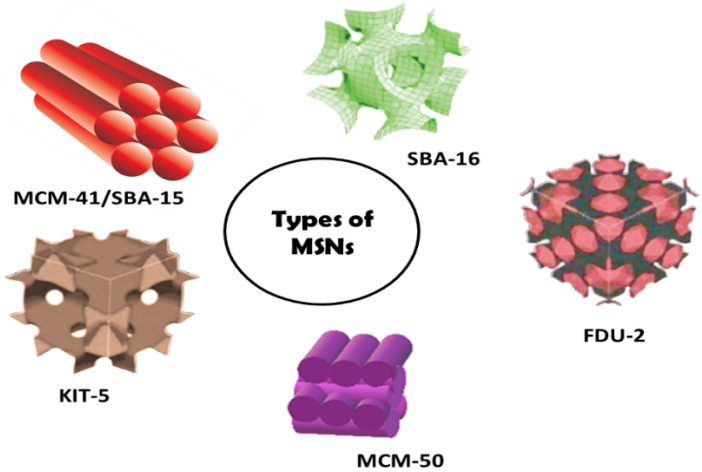


Figure 1. Representation of different types of mesoporous silica nanoparticles (MSNs).

MESOPOROUS SILICA NANOPARTICLE SYNTHESIS

In order to create spherical monodisperse micron-sized silica particles, Stober was the first to design a system of chemical reactions (28). The process is currently referred to as Stober synthesis. To produce monodisperse, organized, nanosized silica particles, Stober's synthesis has undergone numerous variations over time. It is possible to synthesize MSNs in basic, acidic, and neutral environments. Different shaped and sized particles were produced by varying the reaction conditions. Grun et al. first altered Stober's synthesis process by using a cationic surfactant as a template to produce a spherical MCM-41 structure as opposed to a hexagonal one. They were able to produce spherical MCM-41 that had characteristics comparable to those produced by alternative techniques (29). Many changes have been made to the synthesis conditions and techniques to produce stable, monodisperse MSNs as a result of ongoing research. MSNs must have uniform particle size and a large pore volume to improve loading capacity to be an optimal drug delivery vehicle. By altering the reaction mixture's pH, temperature, surfactant content, and silica supply, these factors can be managed during the synthesis process. Through the hydrolysis and condensation of silica on the surface of surfactant micelles, MSNs are synthesized using a liquid crystal template mechanism (30).

MECHANISM OF SYNTHESIS OF MESOPOROUS SILICA NANOPARTICLES

To produce particles with the right characteristics for medication delivery, a complete grasp of the mechanism underlying MSN production is necessary. According to the early reports on the mechanism, non-ionic surfactants' liquid-crystalline phases are where the silica network is constructed. This is especially true for materials made using a diluted surfactant solution, since typical mesostructured materials were not detected (31). According to published research, either the hydrolyzed silica is adsorbed around the micelles or, in the case of SBA-15, the silica and surfactant interact early on to create a structure resembling a shell (32). Figure 2 depicts the mechanism by which MCM-41 forms. Since then, research teams have been working to identify the precise mechanism that leads to MSN production.

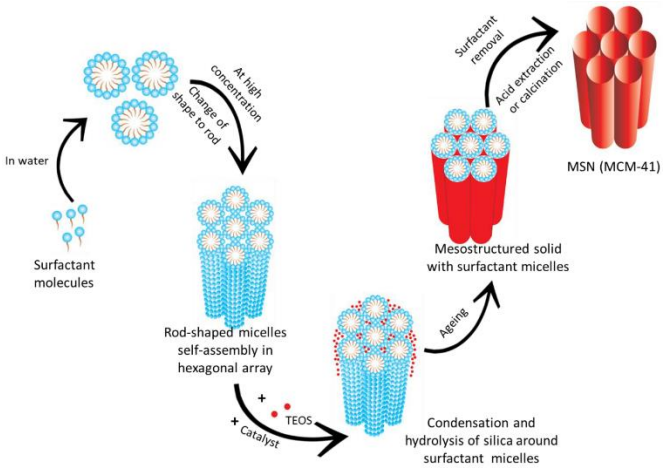


Figure 2. Mechanism of formation of Mobil Crystalline Materials No.41 (MCM-41) (33)

The generation of MSNs has been studied in-situ using time-resolved small-angle neutron scattering (SANS). They were able to forecast the alterations that would occur in tandem with the formation process by using this strategy. It was noted that the silicate ions have a tendency to adhere around the surfactant micelles during the development phase during the early hydrolysis (~40 s) of the silica source tetramethyl orthosilicate (TMOS) (34). Small silica aggregates can continue to form as a result of the intermicellar repulsion decreasing as the charge surrounding the surfactant decreases as a result of the first hydrolysis and the condensation of the silica precursor. Transmission electron microscopy (TEM) examinations indicated that the reaction mixture included sufficiently distinct hexagonally organised silica mesopores after around 400 s. The "current bun model," which was previously proposed (35), describes the mechanism of MSN production.

A different mechanism, known as the "swelling-shrinking mechanism," was put out to explain how MSNs originate using time-resolved synchrotron small-angle X-ray scattering (SAXS) technology. When tetraethyl orthosilicate (TEOS) is utilised as the precursor in isolation, without the usage of any other solvent, such as ethanol, this method works well. TEOS, an oil-like monomer, demonstrated phase separation while the mixture was static, but an emulsion-like system was produced when the mixture was vigorously stirred (36). At first, the hydrophobic tail of cetyltrimethylammonium bromide (CTAB) generates an inner core that forms ellipsoidal micelles. The addition of TEOS causes it to dissolve in the hydrophobic core, expanding the micelles and changing their shape from ellipsoidal to spherical. The monomers in TEOS hydrolyze to become hydrophilic and are discharged into the surrounding aqueous medium. Electrostatic attraction causes the negatively charged hydrolyzed monomers of TEOS to be adsorbed onto positively charged CTAB micelles (37). The micelles contract and becoming smaller after the TEOS inside the hydrophobic core is fully consumed. The micelles continually contract as a result of the simultaneous processes of hydrolysis and condensation until all of the TEOS has been hydrolyzed and a silica shell has formed around the micelles. As the nearby micelles combine, a mesoporous structure is formed by the development of particles (38).

THE RAW MATERIALS UTILISED AND THE VARIABLES INFLUENCING MSN CHARACTERISTICS

A silica precursor (tetraethyl orthosilicate, tetramethyl orthosilicate, tetramethoxyvinylsilane, sodium meta-silicate, and tetrakis (2-hydroxyethyl) orthosilicate, THEOS), a surfactant (non-ionic or cationic surfactant) acting as a structure directing agent (SDA), and a catalyst are the three main components that make up the core of MSN (39). Depending on the needs, other additives such as cosolvents and anti-aggregation chemicals may also be added. Natural perlite materials as pumice rock, rice husk, and renewable biomass could also be investigated for the synthesis of MSNs in order to guarantee the scale-up of MSNs at an affordable cost (40). Changes in temperature and reaction conditions (amounts of catalyst, water, and alkoxysilane) can effectively control the particle size, pore size, and shape of MSNs (41).

REGULATION OF PARTICLE SIZE

For MSNs to be used as drug carriers in biomedicine, particle size is a crucial component. Therefore, precise particle size tailoring is necessary for efficient medication delivery. The size of MSNs is mostly controlled by the pH of the reaction media. By using appropriate additive agents, such as alcohols, amines, inorganic bases, and inorganic salts, the particle size can be efficiently regulated. These substances change the silica precursor's hydrolysis and condensation. They cause the kinetics of the reaction to speed up, resulting in smaller particles. Triethanolamine (TEA) was utilized by Moller et al. in place of the often utilized base catalysts sodium hydroxide (NaOH) and ammonium hydroxide (NH4OH). It not only imparts a basic pH but also functions as a complexing agent to produce distinct nanoparticles (42).

DRUG LOADING AND RELEASE OF DRUGS FROM MSNPs

MSNPs are a popular drug delivery carrier because of their special qualities, which include a high loading capacity resulting from their large pore volume and surface engineering properties on both the interior and external surfaces for improved drug targeting (43).

DRUG LOADING

The primary basis for medication loading is the adsorptive characteristics of MSNs. It is possible to integrate both hydrophilic and hydrophobic cargos into MSN holes. Compared to other carriers, MSNs have a higher loading capacity by nature because of their huge pore volume. However, a lot of effort has been put into improving the drug loading even more. One such method to improve MSN loading is the synthesis of HMSNs. By functionalizing the surface silanol groups with various silanes, such as octadecyltrimethoxysilane (OTMS), 3-aminopropyl triethoxysilane (APTES), and 3-

cyanopropyltriethoxysilane (CPTES), She et al. aimed to boost the loading of 5-fluorouracil (5-FU) into hollow MSNs. A higher loading of 28.89% was noted for amine-functionalized HMSNs as opposed to 18.34% for plain HMSNs. The positively charged amino modified HMSNs and the negatively charged 5-FU may interact electrostatically to do this. By changing the type of functionalization, a similar method might be applied to increase the loading capacity of medications through electrostatic attractions (44). Wang et al., however, presented a different idea in their publication, arguing that loading a medication before surface grafting produced a carrier with higher loading than grafting followed by loading. Because of their hollow cavities, HMSNs turned out to be a better carrier than MSNs in terms of cargo capacity. Drug loading was shown to be 3–15 times higher in HMSNs than in MSNs. Furthermore, it was possible to accomplish dual loading of pharmaceuticals with the same carrier (45). Using polymer gatekeeping to catch hydrophobic medicines could further increase the loading capacity of MSNs (46). Improved drug loading may also result from a consecutive drug loading procedure that strengthens intermolecular interactions (47). It was also discovered that an increase in the medication feeding ratio had a significant impact on MSN loading capacity. The primary component that determines how much of the medicine is loaded is the pore volume of MSNs. Therefore, a method of pore expansion can be used to introduce and retain a lot of cargo. Pore enlargement is aided by pore swelling agents such as alkanes/ethanol, N,N-dimethylhexadecylamine (DMHA), trioctylamine (TOA), decane, and triisopropyl benzene (TIPB) (48).

RELEASE OF DRUGS FROM MSNPs

Drug release profiles from MSNs are mostly determined by how well the medications diffuse from the pores, which can be adjusted by changing the MSNs' surface to better meet biological requirements. The interaction between the drug molecule and the surface groups on pores is the key component governing release control (49). In contrast to systems that were functionalized first and then loaded with the drug, it was found that drug loading followed by surface functionalization with amine groups significantly contributed to maintaining the drug release. This may be explained by the medications being loaded into the pores and then sealed with APTES to stop the drugs from releasing. There could be issues if the surface was functionalized first and then loaded MCM-41 (50). Consistent with these findings, the surface alteration was found to have a significant impact on the release of ibuprofen from SBA-15. When using a one-pot synthesis to create amino-functionalized SBA-15, the full drug release was seen after 10 hours, whereas ibuprofen was released from post-synthetically modified SBA-15 for up to three days (51).

TARGETED ANTITUMOR THERAPY USING MSNPs

In order to improve the site-specific administration of medications and prevent adverse effects, the surface functionalization of MSNs is a characteristic that is actively investigated. It is an adaptable carrier that allows medications with various physicochemical characteristics to be loaded and further functionalized for efficient treatment. Because of the enhanced permeability and retention (EPR) action, they have the potential to greatly accumulate within the tumour (52). Optimising the uptake of actives into the cells is made possible by active targeting. Appropriate receptors that are overexpressed on tumour cells are chosen based on the distinctions between normal and tumour cells, and ligands specific to those receptors are conjugated on the surface of the MSNs. Targeting ligands can be used to anchor MSNs in order to achieve specific medication delivery. One well-known ligand that enhances folate is folic acid (FA). An amide bond between the carboxyl group of FA and the amine group of aminopropyltriethoxysilane (APTES) causes the FA conjugation on the surface of MSNs. Ma et al. (53) conjugated folic acid on the surface of HMSNs against B16F 10 skin cancer cells, delivering 5-aminolevulinic acid for photodynamic treatment. It was found that the created formulation exhibited a high level of photocytotoxicity towards cancer cells. Similar findings have been reported, demonstrating that amine functionalization on the surface facilitates folic acid's covalent binding to receptor surfaces to guarantee doxorubicin (DOX) uptake in breast cancer cells that is selective. Comparing FA-MSN-NH2-DOX to MSN-NH2-DOX, the apoptosis and cellular

uptake experiments demonstrated that FA-MSN-NH2-DOX showed stronger internalisation into the cells (54). Another extensively researched ligand for CD44 receptors that are overexpressed on cancer cells is hyaluronic acid (HA). An HA functionalized DOX-MSN that exhibited both receptor-mediated and enzyme-responsive behaviour was described by Zhang et al. Biodistribution and in vivo tumour growth suppression tests demonstrated the drug's low in vivo toxicity and enhanced absorption by colon cancer cells. Hyaluronidase, an enzyme found in the tumour microenvironment, also contributed to the release of DOX in addition to receptor-mediated absorption (55). Gary-Bobo et al. (56), who created HA-MSNs for photodynamic therapy against colon cancer, reported similar outcomes. The studies were carried out on HCT-116 colon cancer cell lines, which demonstrated the increased efficacy of HA-MSNs over plain MSNs due to their action targeting the CD44 receptor. The construction of lactosaminated (Lac) MSNs is another unique strategy for the active targeting of hepatoma cells that has been disclosed. The capacity of these innovative delivery methods to be endocytosed by asialoglycoprotein (ASGPR) receptors on the surface of hepatocytes demonstrated a promising result. The results of tests on cellular uptake in ASGPR-positive cells (HepG2 and SMMC7721) revealed that Lac-MSNs outperformed plain MSNs in terms of cellular uptake. These findings corroborated the findings. The data also revealed an intriguing fact: lactose, the ligand, was only identified in its conjugated form with MSNs, not in its free form (57). To improve the absorption by tumour cells, analogues for targeting the mannose-6-phosphate receptor, which is overexpressed in cancer cells, were grafted onto MSNs. Prostate and colon tumors were reported to respond favorably to these treatments (58). It has been shown that αvβ3 and αvβ5 integrin receptors, which are overexpressed in a variety of tumors, preferentially absorb arginine-glycine-aspartic acid (RGD). The treatment efficacy was increased as a result of the drug-loaded surface-engineered RGD-MSNs being absorbed by the liver cancer cells and thwarted by normal cells (59). Apart from molecular targeting, attempts were also made to combine chemotherapy and positron-emission tomography (PET) imaging into a single carrier. The MSNs were loaded with sunitinib, a model anticancer medication, and surface-engineered using polyethylene glycol and cyclo-(Arg-Gly-Asp-D-Tyr-Lys) peptide (cRGDyK). The effectiveness of the receptor uptake was verified through investigations using flow cytometry, PET imaging, and histopathology. U87MG human glioblastoma cells were used in the trials, while a thymic nude mice were employed for in vivo testing. It was found that the tumor absorption of the nanoconjugates was decreased when cRGDyK conjugated HMSNs were utilised in place of plain HMSNs (60). Numerous positive effects have been demonstrated by grafting a wide range of ligands onto the surface of MSNs to make it target selective.

RECENT PATENTS FILED IN THE FIELD OF MSNS FOR BIOMEDICAL APPLICATIONS

Since MSNs were first produced, multiple patent applications have been made thanks to synthetic adjustments intended to regulate the particle size and pore volume. Patents pertaining to MSNs are mostly focused on their investigation for biomedical applications, biosensors, imaging, and as adsorbents due to their diverse nature of loading medicinal compounds that are both hydrophilic and hydrophobic. An innovative method of coating MSNs with lipids known as "protocells" has drawn a lot of interest in the creation of medication delivery systems. These combine the benefits of MSNs (tunable size, shape, and loading capacity) with liposomes (low toxicity, long circulation durations) (61).

CONCLUSION

We have discussed some fascinating research using mesoporous silica nanocarriers as drug delivery platforms in this review. They are extensively used as nanocarriers due to their special abilities, which include high loading capacity, pore volume, and variable pore size. By adjusting the reactant type, molar proportion, and reaction conditions, MSNs with varying pore volume, shape, and size can be produced. Customising MSNs' pore size and surface characteristics improves loading and changes the drug release profile. Since MSNs are easily functionalized, much research on them focuses on using them to treat cancer. A wide range of ligands can be fixed onto the surface of MSNs. These intelligent

technologies can also be utilised for medication delivery at the place of interest by a variety of internal and external stimuli, including light, chemicals, pH, temperature, and ultrasound, among others. According to a review of the submitted patents, most research focuses on investigating the potential application of supported lipid bilayer-coated protocells (MSNs) for the transport of drugs and macromolecules. It is feasible to accomplish "zero" premature discharge and safeguard the cargo from the outside environment with these kinds of technologies. However, these carriers' pharmacokinetics and biodistribution differ based on their properties and the mode of administration. There are still questions about the long-term effects of using MSNs. This flaw prevents the technological platform from progressing to the next degree of clinical application.

FUTURE PERSPECTIVES

While the FDA has only licenced a small number of nanomedicines for use in treatment and clinical settings, these innovative systems have had a significant impact on the area of illness therapy and have the potential to alter standard diagnosis or treatment methods. Extensive research has been conducted since the potential use of MSNs as drug delivery carriers was first recognised, demonstrating the significance of this technology in the treatment of various diseases. The majority of the research focuses on using these carriers to deliver chemotherapeutic drugs to targeted sites. However, the safe and effective translation and regulatory approval of these goods are restricted by technological and regulatory barriers. MSNs are easy and inexpensive to fabricate, in contrast to other nanocarriers. These innovative technologies have had a significant impact on the field of disease therapy and have the potential to alter standard diagnosis and treatment protocols, despite the FDA having only licenced a small number of nanomedicines for use in treatment and clinic settings. Extensive research has been conducted to demonstrate the significance of MSN technology in the treatment of various diseases, ever since it was originally recognised as a possible drug delivery vehicle. The utilisation of these carriers for site-specific delivery of chemotherapeutic drugs is the main focus of the research. However, technical and regulatory barriers prevent these goods from being translated safely and effectively or from receiving regulatory approval. The synthesis of MSNs is an easy and affordable procedure, in contrast to other nanocarriers. Additionally, these MSNs can be used as multifunctional nanocarriers for theranostic purposes, imaging, and the geographical and temporal placement of pharmaceuticals. They can also facilitate multidrug loading. In this approach, remarkable results have been obtained in preclinical and cellular research. But before this platform could be successfully implemented at the bedside, there were a few obstacles to overcome. The synthesis of MSNs with reliable properties and high quality might be very difficult. Since scalability is a key component of technological transfer to industry, commercializing MSNs may be hampered by their production-scale synthesis. To guarantee product reproducibility, a deeper comprehension and management of the manufacturing process are required. The amount of MSN may differ from case to case even with the same concentration, which could influence the maximum dose of MSN that can be tolerated. Batch-to-batch variance might be decreased by using specific process analytical instruments, such as size exclusion/gel permeation chromatography (GPC) combined with custom-built fluorescence correlation spectroscopy (FCS), as used by Chen et al. (62). These tools would help monitor particle size and long-term stability.

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