Section A -Research paper

An Application-based Review of Mesoporous Silica Nanoparticles for Drug Delivery in the Biomedical Field

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ABSTRACT
Recent advances in novel drug delivery system aims to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. A number of approaches are available in delivering therapeutic substance to the target site in sustained and controlled release fashion. Recent development in drug delivery system uses a variety of carriers has resulted in a revolutionary approach towards diagnosis and therapy. Mesoporous silica nanoparticles have been a potent nanocarriers for many different therapeutic agents, i.e., the surface functionalization of silica nanoparticles with chemical agents, polymers, and supramolecular moieties enable the efficient delivery of therapeutic agents in a highly controlled system. Also, materials needed with high thermal, chemical, mechanical properties, toxicity, biosafety, and in vivo efficiency involving biodistribution, pharmacokinetics, biodegradation, and excretion of MSNs. Development of MSNs as carriers for target drug delivery systems has increased exponentially during the last few days. The present work is focused on the mechanisms, synthesis, characteristics and application of mesoporous silica nanoparticles. In this review, we summarize the facts about mesoporous silica nanoparticles drug delivery systems comprehensively. This review also provides the detailed concept of mesoporous silica nanoparticles a novel approach for drug targeting.

Keyword: Mesoporous silica nanoparticles, Drug delivery, cancer cell, surface functionalization,

INTRODUCTION
Controlling a pharmaceutical substance to have a therapeutic impact in people is known as drug delivery. Drug delivery methods that alter drug release profiles, absorption, distribution, and elimination are used in formulation development with the goal of enhancing product efficacy, safety, patient convenience, and compliance [1].

The science of nanotechnology has experienced a revolution due to recent developments in innovative drug delivery (NDDS). Many nanostructures, including polymeric, micelles, liposomes, carbon nanotubes, and silica-based nanoparticles (NPs), have been investigated in the field of nanotechnology to improve drug delivery systems. Modern nanotechnology has developed to become the most significant branch of science in the twenty-first century.

With the development of nanotechnology, materials developed at the nanoscale level have increasing attention in such fields as drug delivery, diagnostic and medical imaging [2]. Nanocarriers have an advantage due to unique features of surface modification, high drug

loading capability, high surface area to volume ratio and engineering to obtain particles of various sizes, shapes and different chemical characteristics. Nanoparticles have proven to be biocompatible, self-biodegradable and non-toxic. Compared with other porous silica nanocarriers, mesoporous silica nanoparticles (MSNs) with a pore size ranging from 2 nm to 50 nm are excellent candidates for drug delivery and biomedical applications [3].

In 2001, Vallet-Regi first reported mesoporous silica material as a drug delivery system is MCM-41, much effort has been devoted to the design of versatile MSNs for treating diverse pathologies used specially for cancer treatment. Mesoporous silica materials are considering excellent carriers because high drug loading capability. For drug delivery because of their textural properties which increase the loading amount of drug inside the pore channels. Similarly, drug diffusion kinetics can be controlled due to the functionalization of silanol group [4]. According to a recent study, MSNs are beneficial for many biomedical sciences applications, including drug delivery, diagnostics, and stem cell research, because of their low cost, surface functionalization, large surface area, simple synthesis process, adjustable pore size, biocompatibility, high loading, and controlled release capability. These nanoparticles are optically transparent and chemically and thermally stable [5].

In order to improve their cellular absorption, MSNs' surface can be easily functionalized. They also have regularly spaced pores with a constant diameter. MSNPs have a higher loading capacity than organic carriers such micelles, gels, and liposomes, and because of how well they encapsulate drugs, they have a big impact on nanobiotechnology research [6].

It has proven to be a powerful vehicle for the oral administration of hydrophobic pharmaceuticals, significantly increasing their bioavailability and rate of dissolution in comparison to normal medications. Drug delivery using nanoparticles has been shown to be capable of sustained, controlled release of treatments like antibiotics [7].

MECHANISM OF FORMATION OF MSNs

A proper understanding of the MSN formation mechanism is necessary to produce particles with the correct drug delivery capabilities. According to the described process of MSN creation, non-ionic surfactant liquid-crystalline phases are where the silica network is created. According to the stated mechanism, either the hydrolyzed silica is adsorbed around the micelles or, as is the case with SBA-15, the silica and surfactant interact at the beginning and create a core shell-like structure [8].

Since then, research teams have worked to identify the precise process that gives rise to MSNs. The development of MSNs has been assessed using time-resolved small-angle neutron scattering (SANS) in situ [9].

They were able to predict the changes occurring at the same time as formation using this technique. It has been found that the silicate ions have a tendency to adsorb around the surfactant micelles during the development phase of the early hydrolysis of the silica source tetramethyl orthosilicate (TMOS). Due to the initial hydrolysis and precipitation of the silica precursor, the charge around the surfactant is reduced. This reduction in intermicellar repulsion facilitates the further formation of small aggregates of silica [10]. contain enough discrete hexagonally ordered mesopores of silica after about ~ 400 s using this technique, which was supported by TEM studies. This is consistent with the "current bun model," which was originally put forth as the mechanism by which MSNs are formed [11]

SYNTHESIS OF MSNs

Predicted at first, MSNs synthesis, they concentrated on enhancing the synthesis of MSNs by attempting to regulate their size, pore structure, and stability. For the synthesis of spherical monodisperse micron-sized silica particles, Stober was a pioneer in developing a system of

chemical processes. Thus, Stober synthesis is the name of the technique. To produce ordered, monodisperse, nanosized silica crystals, changes have been made to the synthesis in the method [12]. MSNs can be created under basic, acidic, or neutral circumstances. The creation of liquid-crystalline mesophases of amphiphilic molecules, which act as templates for the in situ polymerization of orthosilicic acid, is the foundation for the synthesis of mesoporous silica [13]. A tetra-alkyl oxide of silane, sodium silicate, or fumed silica is all possible sources of silica. The Mobil researchers reported using micrometer-sized particles with hexagonally ordered mesopores for the construction of MCM-41 [14].

To produce stable, monodisperse MSNs, various synthesis circumstances and techniques are being continuously researched. MSNs must have uniform particle size and large pore volumes to increase loading capacity in order to be the best carrier for target drug transport. During the synthesis, the mentioned factors can be controlled by altering the temperature, pH of the reaction mixture, surfactant concentration, and silica source [15]. By using a liquid crystal template mechanism, silica is hydrolyzed and condenses on the surface of surfactant micelles to create MSNs. Tetraethyl orthosilicate, a liquid type of silica, becomes solid silica. In order to make the structure of the ordered mesophases strongly reliant on the interaction between the growing anionic oligomers of orthosilicic acid and cationic surfactant, the mesophases are subjected to MSN synthesis at low surfactant concentrations [16, 17].

1: **Stober/Sol-gel method and its modifications**

The "Stober technique" was developed by Werner Stober and is used to synthesise MSNs. This technique can be used to make monodispersed silica particles as well as non-silica particles. The diameter of the synthesised particles produced by this technique ranged from 10 nm to a few microns. The Stober technique uses ammonia as a catalyst to hydrolyze tetraalkyl silicates in a solution of alcohol and water, resulting in the production of monodispersed silica particles. Michael Grun revised this technique by altering the composition of the synthesised substance [18]. By incorporating cationic surfactant into the reaction mixture, the redesign technique produced MCM-41 spherical particles with a sub-micrometer size. The uniform MSNs with distinct pore sizes and pore structures are produced by mixing alcohol, water, and ammonia. Tetraethyl orthosilicate (TEOS) surfactant was used in various ratios by Nooney et al. to make MSNs under diluted conditions. They also used cationic (CTAB) and neutral (n-dodecylamine) surfactants as models in their investigation. Particle sizes that were produced ranged from 65 to 740 nm [19, 20].

The hydrolytic sol-gel process, which is frequently used to create silica nanoparticles, involves condensation of silicon alkoxide compounds under acidic or basic catalysis, as shown in equation 1.

The stages of the sol-gel process, a wet chemical technique also known as chemical solution deposition, are hydrolysis and poly condensation, gelation, ageing, drying, densification, and calcinations.

The sol-gel method is carried out as follows

Surfactant molecules serve as a template for the structure, and polycondensation takes place all around them, transforming precursors into an oxide network.

The network then generates a colloidal solution (sol), which is dependent on the circumstances of the reaction (the rate of polycondensation reactions through the manipulation of reaction parameters), and eventually forms a gel or discrete particles [12].

Monodispersed spherical silica particles are created under much diluted conditions, and the type and concentration of surfactants, as well as temperature, play important roles in NPs

synthesis and, consequently, in the final mesostructured of the material indicates the use of the sol-gel technique for the synthesis of MSNPs [21].

PROCESS

The surfactant is dissolved in basic water during this procedure. Next, the silica precursor [Si (OCH2CH3)4] is added drop wise to the mixture to obtain a dilute concentration of the silica precursor. The droplets eventually change into nanoparticles (NPs). MSNPs are created after the surfactant template has been eliminated using solvent extraction. The hollow porous structure is created using the template (structure-directing agent) technique [13-15]. The two sub methods of this technique are end template (soft matter templating) and exotemplate (hard matter templating). End template uses a surfactant as a template instead of a rigid template solid to create ordered mesoporous materials. In contrast, the exotemplate technique uses a porous solid as a template and fills the hollow spaces with an inorganic precursor that is then transformed at the right pH and temperature. In this process, the (MCM-41) under the size range of 60-1000 nm is formed [22].

2: Hollow silica nanoparticles synthesis

i) Soft templating method: The synthesis of hollow MSNs, which enhances the drug loading capacity and pore volume, is used in drug release and biosensing. Mesoporous silica nanoparticles, or HSNs, are a subclass of hollow MSNs. The steps involved in making mesoporous silica nanoparticles (MSNs) by using soft templates are as follows:

- Single micelle-templating.
- Vesicle-templating.
- Micro-emulsion-templating.

a) Single micelle-templating: Yang and co-workers created distinct small hollow organosilica Nanospheres and nanotubes from the MSNs created using pluronic triblock copolymer with a different hydrophobicity (EO/PO ratio) and adding a suitable quantity of organosilica precursor. Mandal and Kruk produced HSNs by using Pluronic F127 block copolymer template synthesis of ethylene-bridged organosilicas in the presence of swelling agent to produce HSNs of varying size. Cationic block copolymer micelles can also act as nanosized templates for the deposition of silicate in aqueous solution under ambient conditions. Because of the positively charged surfactant, silica-cross-linking apparently still keeps the micelle/silica isolated and resulted in nanosized hollow silica particles after pyrolysis of the organic component. Because of the limited size of micelles, HSNs produced by micelle templating are generally limited to under 20 nm in size [23].

b) Vesicle-templating: The vesicle-templating method would be ideal for expanding HSN size even more. Along with cationic and anionic co-surfactants, mixtures of silanes and silicates are used. Various aggregate microstructures are produced by this combination of cationic and anionic single-tailed surfactants with opposing charges. As meso-structural templates, silica is used to decrease the curvature even at high dilution. The cutting-edge organic models for mesostructured silica are with various amazing morphologies. MSNs with sizes ranging from 25 to 105 nm were created using the vesicle-templating technique. Co-condensation was a part of the procedure. Tetraethylorthosilicate (TEOS) and organotriethoxysilanes are co-codensated in this procedure in an alkaline aqueous solution comprising triethanolamine and the cationic surfactant cetyltrimethylammonium chloride (CTACI). A phase change from spherical micelles to cylindrical micelles to vesicles happens as the ratio steadily rises to 1.0. These mesostructural surfactants can be used to create mesoporous silica in the desired shape by

acting as a template or co-template. Then, deposition and condensation across and around the curved external surfaces of the organic structures make silica casts of the organic structures at a suitable pH where soft templates and silica species have matching interactions. For example, spherical micelles, rod like micelles, and vesicles can be used as templates to create individual silica nanofoams, mesoporous silica nanorods, and hollow spheres. The remarkable morphologies of the micelles serve as organic templates or catalysts for the synthesis of preferred MSNs forms [24, 25].

c) Micro-emulsion-templating: Hollow mesoporous silica nanoparticles were created using the reliable oil-in-water (o/w) method. With careful control of the silica shell thickness and extent of condensation of the silica framework and silica shell thickness, hollow silica nanospheres have been effectively synthesised. The hollow MSNs can be created by creating a stable microemulsion system using a combination of water, oil, surfactant, and a tiny quantity of aqueous alkaline solution[26]. The benefit of the reverse water-in-oil microemulsions is the simplicity with which other species can be encapsulated in hollow MSNs or core-shell type MSNs. Stucky's team was the first to disclose the use of microemulsion templates for mesoporous silica. 69 Hao et al. created hollow silica nanospheres with large mesopores (B8 nm) on the exterior using the triblock copolymer Pluronic F127 as a template and 1,3,5-trimethylbenzene (TMB) as a swelling agent in the presence of an inorganic salt (KCl). In an interesting discovery, Kao et al. made Kippah-like mesoporous silica hollow spheres by collapsing the encapsulated in an oil-in-water type synthesis of MSN. During synthesis, before the silica shell hardened, the oil in the centre of an oil-in-water crystal leaked out through the mesopores. Consequently, the soft exterior disintegrated to create a kippah-like structure [27].

ii) Hard templating method: Those MSNs Both discrete and monodisperse MSNs prepared by the hard-templating technique must have high colloid stability in a physiological environment and must be small enough in size to allow for prolonged blood circulation of the drug in the body. Because of their hollow interior, MSNs have a large capacity to store biomedicines, enzymes, and ligands. Because of developments in the production of polymer lattices, silica colloids, and metal oxides are used in the hard template method, the synthesis of discrete, monodisperse, mesostructured, morphology-tunable MSNs for biomedical uses remains a challenge [28]. A hard template was created Three fundamental steps are required for high-fidelity inorganic silica replicas:

• Compared to silica saturation at the surface of an organic template, self-condensation of silica species in bulk solutions is a slower process. Silicate surface must have an acceptable functional group for recognition under the suitable reaction conditions in order to make MSNs using this method [29].

MSN formation with an organic template that is steady throughout the entire condensation and deposition process of silicates. Failure of silica casting may result from the potent interplay of any of the surface activated template's components with silicates. As a result, the initial organic template was washed away and instead accumulated at the surface of silicates. Inorganic silica cast sacrificial template technique is used as a difficult templating method to remove templates without breaking them. Under mild circumstances, the internal dissolveable or combustible component can be removed following acid-dissolution, solvent extraction, and calcination [30]. Hard templating method for the preparation of mesoporous silica nanoparticles (MSNs) includes:

a) Polymer latexes-templating: Utilizing the proper functional group, the polymer latexes-templating technique enables silicification on the polymer latex surface through surface

activation. In this approach, a functional group for silica gelation, as a surface activation method, is introduced through chemical functionalization, followed by a layer-by-layer deposition technique via electrostatic attractive interaction. The leaching of the capping agents during the silica deposition can be stopped by the potent contacts between the polymer latexes and functional groups. Large-scale application of the polymer latex templating technique to create consistent silica hollow spheres [31]

b) Metal or metal oxide nanoparticles: Therefore, using cetyltrimethylammonium bromide (CTAB) as a stabiliser and mesostructural directing agent, Kim et al. show a method to produce discrete and monodisperse single Fe_3O_4 nanocrystal mesoporous silica. This produced Fe_3O_4 mesoporous silica can be used as a T2-weighting magnetic resonance imaging agent and a therapeutic agent after PEG surface modification. The Au nanorod nanoparticles embedded in MSNs have a high near-infrared (NIR) radiation absorption rate as well as the large loading capacity required to transport chemotherapy drugs [32].

3. **Mesoporous silica nanoparticles synthesis based on solution:** MCM-41, a movable crystalline material made up of cylindrical mesopores ordered hexagonally, is the material type used to create MSNs. The cetyl trimethyl ammonium bromide necessary for the production of MCM-41 is the alkyl ammonium salt that the liquid crystal is modelling. When combined with hydrophilic soluble precursors like polysilicic acid, a high quantity of amphipillic surfactant forms a spherical micelle in the water. The silica precursor is concentrated at the hydrophilic contact and forms amorphous silica, which serves as a template for the mesoporous product, in MCM-41, which is produced by electrostatic and hydrogen bonding interaction. Surfactant is present in the synthesised MSNs; the residual surfactant is removed using the calcination and extraction method [33].

4. Organically modified precursors method

The colloidal instabilities and big particle size led to the development of organically modified silica nanoparticles. Precursors that have undergone organic modification are fascinating hybrid elements. Due to an organic group that is directly attached to a silicon atom and does not require an oxygen bridge, this method's hydrolysis is avoided. The better characteristics of the organo-silica nanoparticles include their low density, large surface area, and less condensed silioxane structure. The most widely used silica sources are glycerol-derived polyol-based silanes, sodium metasilicate, orthosilicic acid, tetraethyl orthosilicate (TEOS) or tetramethoxysilane (TMOS), and tetrakis (2-hydroxyethyl) orthosilicate [34].

These NPs are easily fabricated from TEOS/vinyltriethoxysilane (VTES) and (3-aminopropyl) triethoxysilane (APTES)/mercaptopropyltrimethoxysilane (MPTMS)/diethy lenetriamine (DETA), which are inorganic and organic silica precursors, respectively, as an oil-in-water microemulsion at room temperature. The ORMOSIL NPs synthesis technique is practical and time-saving because it does not depend on surfactants or corrosive solvents35.

1. For the production of MSNs, tetraethyl orthosilicate, or TMOS, silica precursors were frequently used. Their limited use is due to their poor water solubility, which necessitates extra organic solvent and alcohol as well as extreme pH and temperature conditions.
2. To resolve the issues with TEOS and TMOS, tetrakis (2-hydroxyethyl) orthosilicate had been studied. Because it is more biocompatible with biopolymers, more water soluble than TEOS and TMOS, and can process jellification at room temperature with a catalyst, it is now used in numerous studies as the precursor to MSNs [36].

Advantages of Organically modified silica nanoparticles

The advantages of organically modified silica nanoparticles make them promising materials for biomedical uses.

i) They can be decorated with any suitable fluorophore [visible/near-infrared (NIR)] to create sturdy and fluorescent NPs because they are inert and optically transparent materials.

ii) Their size (10–100 nm) can be altered depending on the application by varying the surfactant and precursor concentrations.

iii) The SiC bond in silica precursors can be biodegraded, and they are also robust with high storage stability, which extends their shelf life and makes them ideal for long-term study.

Character of mesoporous silica nanoparticles

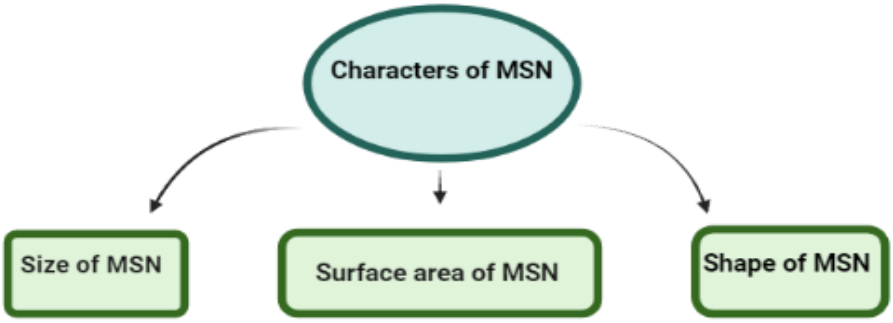

Figure 1: Characters of MSN

1: Shape

For site specificity to engage systemically with target cells and tissues, nanoparticle shape is crucial. Leachable substances or degradation byproducts from a medical device that are taken locally, transported throughout the body via the lymphatic or circulatory systems, and cause negative effects elsewhere. It has been demonstrated that MSNPs with a high aspect ratio, or AR ratio (width to height ratio), internalise cells more quickly and completely and have more noticeable effects on various cellular processes, including proliferation, apoptosis, the formation of the cytoskeleton, biodistribution, biodegradation, and biocompatibility. MSNPs with a broad width to height ratio exhibit less degradation and have less regular in vivo absorption and excretion than MSNPs with a smaller width to height ratio. MSNPs were designed in an organised nanostructural form for optimal drug delivery and biological functions [37].

2. Pore and particle size

Surfactant in aqueous solution, which may be charged or inert, can be used to synthesize MSNs. Surfactant polymerizes silicates. The rate of hydrolysis, the degree of interaction between the assembled template and the silica polymer, and the condensation of the silica source are the factors that affect regulating the pore and particle size and morphology of MSNs. The pH can be adjusted, co-solvent can be used, and various templates can be used to control this variable. The pore diameter of nanoparticles plays a significant role in drug loading and transport. To load drug molecules, MSNs need to have optimal properties like larger pore diameters than the size of the drug molecules, which also regulates the availability of adsorption sites for drug molecules. By enlarging the pore diameter from 8.2 to 11.4 nm, the

drug loading capacity of bovine serum albumin-loaded SBA-15 was raised from 15 to 27%. MSNs should be larger than 200 nm in size for target-specific tumour drug delivery to maximise tumour permeability and retention [38].

3. Surface area

The drug loading capacity of novel MSNPs is determined by the surface area of MSNs, which is a very important feature. There is currently research being done to increase particle surface area in order to control the quantity of drug load in the matrix. Different techniques are employed to change the surface area of particulates and the surface drug affinity. This demonstrated that the relationship between surface area and drug loading capacity is straightforward. MCM-41 and SBA-15 is synthesized by surface area 1157 m2 g-1, 719 m2 g-1 respectively. When alendronate is loaded in MSNs under the same circumstances, MCM-41 and SBA-15 each receive 139 mg g-1 of the medication. This demonstrates the relationship between surface area and maximal drug loading [39].

APPLICATIONS OF MESOPOROUS SILICA NANOPARTICLES

Based on their size, shape, pore type, and connectivity of mesoporous silica particles, MSNs have a variety of uses. It has been extensively used for many different things, from its use in health to therapeutic agents. Substances for imaging and diagnosis, Target specificity, adsorption of waste, chemical synthesis catalyst, toxic substances, and sensing function are all features of this substance. When compared to bulk mesoporous silica, MSNs have smaller channels, which enhance the movement of large molecules, biomolecules, and biodiesels. In order to avoid taking a long path, reactant and product molecules use nano-channels. The biological application encompasses imaging and diagnostic tools, as well as diagnostic and therapeutic molecules that can be loaded and delivered in high concentrations. Few diseases are now treated with MSNs in modern times. The MSNs primarily intended to be drug delivery carrier [40, 41].

DRUG DELIVERY

A relatively new field of medicine called drug delivery includes the use of various therapies. Therapeutic agent is delivered using nanoscience and nanotechnology within a singular system. With reports of silica nanopore membranes, porous silica-based materials for drug delivery uses first appeared in the late 1990s. Mesoporous silica nanomaterials have unique qualities that make them ideal nano-carriers for storing, safeguarding, and delivering medications to the intended location. By adding a targeting agent to the surface of the mesoporous silica, one can direct the agent to the precise injured tissue while minimising undesirable side effects. Using microfabricated PSI particles, the drug is delivered across a monolayer of intestinal Caco-2 cells using material insulin paracellular transport. MSNs are frequently used in the adsorption of toxic molecules due to their large surface area, selectivity of the adsorption substance, and minimal toxicity. While conventional MSNs can load a dose of therapeutic drug with 200-300 mg drug/1 g silica showing greater adsorption activity, the activated carbon alone showed poor removal ability when used to remove toxic chemicals. It is possible to create the multifunctional MSNs so that they work together therapeutically to treat diseased tissues. Cancer target therapy has been the main focus of study on mesoporous silica for drug delivery [42].

CELL IMAGING AGENTS

Due to its hydrophilic surface and ability to be easily distributed in an aqueous solution, MSNs are used as imaging agents. It is the perfect platform for biomedical imaging and diagnostic

applications because of the broad range and quantity of compounds that are included in them, their stability, and their manageable size. First-ever well-dispersed colloidal silica particles with dyes or fluorophores were created. Further research was conducted to produce nano silica particles with a fluorescent inner shell. These water-soluble, non-toxic particles have particle sizes between 20 and 30 nm. In this synthesis, dots are used to create biological exploratory tools with improved bio-stability, reduced energy transfer reactions, and improved dye quantum efficiency. Assuring the dye's protection from the effects of a dissolution medium or molecular quenchers, these dots have restricted rotational motility of the dye that is trapped in the C dots centre. The clinical study for Cell Imaging agents using these C dots, which were authorised by the FDA in human trials in 2011, demonstrated that the silica nanoparticles were completely harmless and left no trace after renal elimination. With mesoporous silica, the imaging pigments FITC and Rhodamine B are frequently employed. These fluorescent dyes are used to track mitochondrial transport, intracellular pH levels in the cytosol, and live-cell imaging [43].

3: TARGET SPECIFIC IN TUMOR

Mesoporous silica nanoparticles can be used in cancer therapy to enhance specific binding to receptors of target cells or tissues while decreasing non-specific binding to those same receptors. A novel and intriguing area of interdisciplinary study involving chemistry, medicine, material science, biology, and pharmacology is the use of porous silica materials for cancer therapy. The development and spread of cancer can be prevented directly by targeting specific molecules involved in tumour progression, or indirectly by using Target-specific MSNs to activate the immune system's capacity to identify and eliminate cancer cells. When treating cancer, harmful antitumor medications frequently do not dissolve before reaching the desired cells or tissues [44]. Passive and active target specialisation are crucial for boosting bioavailability. Drug permeability in tumour blood vessels is increased by passive target specificity, which also permits the build-up of nanocarriers at the tumour site. For instance, doxorubicin (DOX) is delivered using PEG copolymer-coated 50 nm MSNs, which can grow to a size of 110 nm. A KB-31 xenograft model received doxorubicin treatment by receiving weekly doses of 120 mg/kg of nanoparticles for three weeks. 85% tumour inhibition was seen during the cancer treatment using DOX-loaded nanoparticles, compared to 70% with the free medication. This highlights the significance of using permeable nanoparticles as cancer nano vaccines. The precise method to transport the medication to a cancerous cell is to surface functionalize porous silica nanomaterials with targeting moieties. Selective targeting can improve the specificity of a drug's interaction with the receptor site of binding and the internalisation of a nanocarriers [45].

BIO SENSING AND CELL TRACING

Mesoporous silica nanoparticles are used as a sensor device for the in vivo and in vitro detection of targets within individual cells. Due to their size and adaptable composition, they are used as biosensing elements. Fluorescent, self-quenching, and other diffusion-related issues do not affect MSNs. As a perfect agent for cell tracing agents, MSNs can functionalize the surface of nanoparticles with significant amounts of cell-recognition or other site-directing compounds [46].

SURFACE FUNCTIONALIZATION OF MSNs

It is possible to create organic-inorganic hybrids by surface functionalizing inorganic mesoporous materials with organic moieties. These hybrids have distinct interactions between the inorganic and organic components. MSNs made using sol-gel methods with surfactant

templates are incredibly flexible substrates for the creation of functional materials. The ability to acquire three functional domains—the silica framework, external particle surface, and internal pore surfaces—is an advantage of MSNs [48,49]. In comparison to the internal pore surface, the functional groups on the particle's exterior surface are easier to reach and can therefore be functionalized. Silanol groups on the surface, including free Si-OH and geminal Si(OH)2, serve as quick anchoring sites for organic functionalization. After the elimination of the surfactant, there must be a significant amount of surface silanols in order for the silica surface to be highly covered with functional groups. Mesoporous silica can be organically functionalized to modify its surface properties, including its hydrophilicity, hydrophobicity, and ability to bind with guest molecules. It can also modify its surface reactivity, protect the surface, and change its optical (such as fluorophores) and electrical (such as conducting polymers) properties. The surface modification of the particles should be chosen in accordance with the intended application because surface characteristics greatly influence how the particle interacts with the environment, how stable the dispersion is in the physiological environment, and how easy it is to add extra functions (like "smart gatekeeper" polymers) for a given application. In order to accomplish precise interactions with cells or tissue, targeting moieties like small molecules, peptides, or antibodies can also be added to particle surfaces. The pharmacokinetics of the particles in a physiological environment is significantly influenced by the MSN surface's overall makeup. In general, co-condensation or post-synthetic alteration can be used to functionalize MSNs (i.e., grafting or surface polymerization) [47-51].

Active surface decoration

In order to increase the uptake of MSNs by cancer cells relative to non-cancerous cells, attempts have been made to functionalize the surfaces of MSNs with cancer-specific targeting ligands. Folic acid is one such ligand, as it is known that folate receptors are overexpressed in a number of human cancers, such as ovarian, uterine, colorectal, breast, and lung. [52,53] Other small cell nutrient molecules, such as mannose and 100, were also demonstrated to preferentially enhance the absorption of MSNs by breast cancer cells in addition to folic acid.

Targeted drug delivery of mesoporous silica nanoparticles

Specific targeting is a highly appealing method for identifying the site of a disease diagnostic on its own. As a result, this technique reduces the dosage of drugs administered and lessens their toxic side effects while in circulation. [54] The creation of new MSNs-based drug delivery systems for targeted release has utilized both inactive and active surface decoration techniques [55-60].

Passive strategies

Passive methods show the increased permeability and retention (EPR) effect, which was first proposed by Matsumura and Maeda, can be used to passively accumulate MSNs in tumor tissue [61]. They proposed that the tumour microenvironment, the relatively sluggish elimination rate, and inadequate lymphatic drainage are responsible for the differential localization of macromolecules and particles of particular sizes. The particulate size, surface charge, or hydrophobicity can all affect how effective the EPR effect is [62, 63].

CURRENT AND FUTURE PERSPECTIVES

Although the FDA has only approved a small number of nanomedicines for use in treatment and in clinics, these novel technologies have successfully made a significant effect on the field of disease therapy and have the potential to alter current methods of diagnosis or treatment. Extensive research is being done to show the significance of this technology in the therapy of

numerous illnesses ever since the first discovery of the potential application of MSNs as carriers for drug delivery. Contrast to other nanocarriers [64-66], MSNs are made using a quick and cost effective procedure. Moreover, these MSNs have an additional scope of being a multifunctional nanocarrier for spatial, temporal placement of drugs and also for theranostic purpose and imaging, and also supports multidrug loading. Remarkable outcomes have been achieved in this regard in both cellular and preclinical studies. However, certain challenges lay ahead in the successful translation of this platform to bedside. Synthesis of MSNs with consistent characteristics and quality can be a major challenge. The industrial transfer of technology mainly depends on scalability and hence the synthesis of MSNs at production scale may be a barrier to its commercialization. There is a need for a better understanding and control of the manufacturing process to ensure reproducibility in the product. In addition, all drugs cannot be loaded in the same concentration and hence the amount of MSN may vary from case to case which may play a role in determining the maximum tolerated dose of MSN [67-70].

CONCLUSION

Mesoporous silica nanoparticle drug delivery systems have emerged as effective due to their remarkable structural properties, high drug loading capacity, appropriate biocompatibility, cost-effective synthesis, and use of these nanomaterials as delivery systems for biological cells and targeted releases. In order to effectively transport and distribute extremely toxic drugs, such as chemotherapeutic agents for cancer treatment, MSNPs are promising nanocarriers. They have stimuli responsive drug releases, which maximises the effectiveness of anti-cancer medications while reducing their negative side effects. The diverse nature of MSNs has a fantastic strategy for applications such as drug/biomolecule/gene delivery, targeted drug delivery for cancer drugs, as a diagnostic and imaging agent, bio-sensing and cell tracing, and many more. In conclusion, this review goes into great depth about the most recent developments in the synthesis and functionalization of MSNs.

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CONFLICT OF INTEREST

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