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Review

Multifunctional Mesoporous Silica Nanoparticles for Oral Drug Delivery

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Abstract: Nanotechnology has transformed engineering designs across a wide spectrum of materials and applications. Mesoporous Silica Nanoparticles (MSNs) are one of the new fabrications of nanostructures as medication delivery systems. MSNs have pore sizes varying from 2 to 50 nm, making them ideal for a variety of biological applications. They offer unique characteristics such as a tunable surface area, well-defined surface properties, and the ability to improve drug pharmacokinetic characteristics. Moreover, they have the potential to reduce adverse effects by delivering a precise dose of medications to a specific spot rather than the more frequent systemic delivery, which diffuses across tissues and organs. In addition, the vast number of pores allow drug incorporation and transportation of drugs to various sites making MSNs a feasible platform for orally administered drugs. Though the oral route is the most suitable and convenient platform for drug delivery, conventional oral drug delivery systems are associated with several limitations. Surpassing gastrointestinal barriers and the low oral bioavailability of poorly soluble medicines pose a major challenge in the pharmaceutical industry. This review provides insights into the role of MSNs and its mechanism as an oral drug delivery system.

Keywords: nanotechnology; mesoporous; drug delivery

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1. Introduction

Recent advancements in drug delivery systems show that drug-loaded particles are found to be the current focus of study as they are suitable for drug targeting and controlled release. Encapsulation technology also has enabled the creation of a wide spectrum of

submicron-sized drug-loaded particles. The existence of an organic shell or the arrangement of organic shells indicates that nanoparticles have a wide range of possibilities as medication vehicles [1–3]. Novel drug delivery methods, particularly porous nanostructures, to improve drug solubility, and pharmacokinetics, to optimize drug aggregation in target locations while reducing side effects, were discovered to have a potential function [4]. This novel drug delivery system has become an approachable method to accomplish the targeted drug delivery, which helps to reduce the side effect due to the accumulation of drugs [5]. Although the different types of porous nanoparticles are present, mesoporous nanoparticles (diameter of 2–50 nm) were found to be an excellent candidate in drug targeting as well as delivery in specific receptor sites to produce a desired therapeutic effect [6].

MSNs with consistent porosity and a long-range structured mesoporous structure were originally presented in 1992 by scientists at Mobil Corporation in Houston, Texas. They exhibit better surface features, such as a small pore size and large specific surface area, over other materials. A biodegradable drug carrier called MSN was developed to improve efficacy and reduce side effects. MSNs meet all of the criteria for nanoparticulate carriers: their unique structure allows for high loading capacity and a wide range of surface modifications. Fine-tuning of particle and pore sizes is possible with MSN synthesis. Furthermore, drug release can be tailored using various gatekeeper systems that are pH-sensitive or redox-sensitive, for example. Furthermore, the MSN can enter tumors passively via the increased permeability and retention effect or actively via various ligands [7]. A broad definition of supramolecular surfactant (composed of many molecules) complexes is that they are required for MSN synthesis in large quantities. Whenever the surfactant concentration is larger than the critical micelle concentration, the surfactant will frequently self-aggregate into micelles. The precursors of silica can then condense on the micelle's surface, resulting in a hybrid material that is both inorganic and organic in composition. To finish, the template surfactant can be detached by solvent extraction or calcination, which will result in the formation of pores [8]. As a result, mesoporous silica nanoparticles with an organized porous structure, a large pore volume, a large surface area, a controllable particle size, two functional surfaces, and excellent biocompatibility are produced as shown in Figure 1.

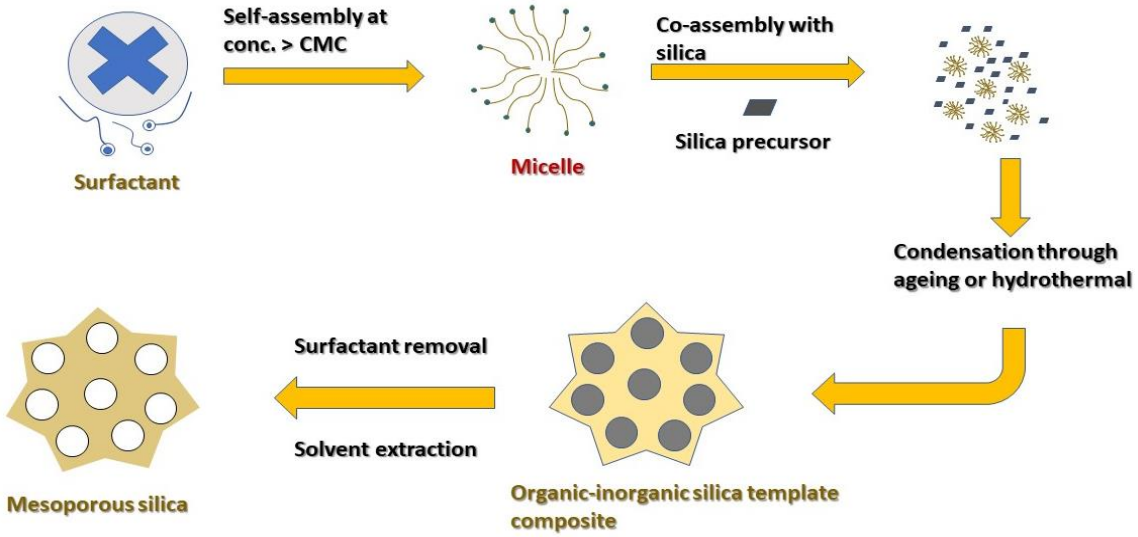

Figure 1. General synthesis of mesoporous silica nanoparticles. Modified from [9], published by MDPI, 2020.

The structure-directing agent cetyltrimethylammonium bromide was used to polymerize MSN in a two-step co-condensation process. The MSN's cellular absorption efficiency is significantly higher than that of the mesoporous particle due to its nano-size. It can also be

used as nanochannels to distribute therapeutic medicines or tracer molecules that are not easily membrane-transportable. Another feature of the MSN is that solutions may be stably halted. The MSN can also take hydrophobic medication doses into the MSN nanochannels. The MSN exterior surface can be changed using receptor ligands to enhance the efficacy of MSN internalization into the cells (folic acid and lactobionic acid). The wide internal MSN surface might be used for therapeutic purposes with cytotoxic medicines. The MSN may also integrate into in vivo cell tracking contrast agents. Mesoporous silica possesses numerous porous silanol groups (Si–OH) that make their conjugation with diverse functional groups easier to enhance the adsorption and conjugation of appropriate biological molecules [10].

Approximately 40% of recognized medicinal products available in the market are poorly soluble in water, leading to a reduction in bioavailability, particularly when taken orally, resulting in insufficient doses and poor response [11]. Through oral routes of drug delivery, many medicines, with high pH or enzymatic peptides compounds which are biodegradable, are extremely hard to manufacture and obtain effective intestine absorption. To facilitate effective systematic uptake of an active substance administered orally, the drug must be (1) in a solution in the gastrointestinal tract, (2) capable of penetrating the intestinal mucus, (3) capable of overcoming the various gastrointestinal barriers, and (4) capable of providing a successful therapeutic dose. Only a few traditional drug carriers proceeded to the commercialization stage, even though they efficiently dealt with difficulties such as poorly soluble drug transport and crystallization concerns. These difficulties motivated scientists to look for new ways to administer targeted drugs and to look for keen carriers of medication. In this perspective, MSNs seem to be potential candidates [12].

In this review, we mainly focus on the roles of MSN, mechanism, and methods to enhance the action of MSN in the drug delivery of the most frequently used oral drug delivery system. It can be obtained by incorporating the amorphous form of the drug rather than the crystalline form in a mesoporous silica matrix. It is necessary to combine more than one kind of functional group effectively with mesoporous silica nanoparticles to create more complicated MSNP-based drug delivery systems. Although two distinct organosilanes can be co-condensed with silica precursors, the ordering of MSNPs will be disrupted, and the loading quantity will be limited due to differing silane hydrolysis rates. Furthermore, the precise placement of functional groupings cannot be controlled. As a result, a multi-functionalization technique is recommended which combines co-condensation and grafting to include functional groups into the exterior and interior surfaces of MSNPs selectively [11]. These nanoparticles, on the other hand, can shield their cargos from premature release and eventual hazardous degradation in the intestines and stomach before reaching their intended destination. To this end, we can abridge that the MSN is found to be an effective carrier administering the drug orally. This carrier helps in increasing oral bioavailability of water-insoluble drugs. Moreover, it can be used with some diagnostic approaches in imaging [13,14].

The purpose of this review is to provide insight into the roles of the MSN as an oral drug delivery system. It also provides ideas about various types of MSNs for oral drug delivery, the engineering of the MSN, the fate of the MSN after administration, applications in medicine, and advantages of the MSN as a drug delivery system.

2. MSN: An Adaptive Technology for Oral Drug Delivery

MSNs offer exceptional particle characteristics compared to organic and inorganic nanostructures. This uniqueness led to a wide variety of MSN applications in several sub-areas of medicine, including diagnosis, treatment, and monitoring [15]. In the 1990s, Kuroda et al. first discovered mesoporous silica materials (MSMs) in Japan and Mobil Oil scientists in the US [4]. The mesoporous solids by aluminosilicate gels using the liquid crystal template method were initially developed by the Mobil research and development corporation in the year 1992. They classified it as MCM-41 (Mobil Crystalline Materials or Mobil Matter Composition). According to IUPAC, mesoporous materials have pores with a

2–50 nanometer diameter and an ordered arrangement of pores, resulting in an ordered structure. The pore size of these may be changed and adjusted by the surfactant employed. Cationic surfactants which act as a template and have a pore diameter of 2.5–6 nanometers are the main characteristics of hexagonal MCM-41. The most extensively studied drug delivery material is MCM-41. Moreover, by altering the reaction conditions and starting precursors, several new mesoporous materials have been produced. These may differ in terms of their pore size and structural arrangement. MCM-48 is arranged in a cubic fashion, while MCM-50 is arranged in a lamella-like fashion. Non-ionic triblock copolymers such as alkyl poly (ethylene oxide) (PEO) oligomeric surfactants and poly (alkylene oxide) block copolymers were also used as a template, with the SBA-11 (cubic), SBA-12 (3-d hexagonal), SBA-15 (hexagonal), and SBA-16 (cubic cage-structured) classifications relying on the uniformity of the mesoporous structure as well as the triblock used. Some of the commonly used MSNs are shown in Figure 2. To obtain the required symmetry in mesoporous materials, the ethylene oxide to propylene oxide ratio was changed. For biological purposes, SBA-15 is frequently utilized because of its highly organized mesoporous structure. This material was created for the first time at the University of California, Santa Barbara, and was dubbed Santa Barbara Amorphous type material (SBA). The pores are larger (4.6–30 nm), and the silica walls are thicker in comparison to MCM. Another type of mesoporous material is FSM-16, or folded sheets of mesoporous materials, which is produced utilizing a layered polysilicatekanemite and quaternary ammonium surfactant as a template as the mesoporous material. Tozuka et al. showed that FSM-16 may be utilized for medicinal purposes other than adsorption and catalysis. A large number of additional MSNs, including those dubbed Technical Delft University (TUD-1), Hiroshima Mesoporous Material-33 (HMM-33), and Centrum voorOppervlaktechemieenKatalyse/Centre for Research Chemistry and Catalysis (COK-12), were already developed with pore symmetry and shape modifications. Medications are delivered via the SBA-15, SBA-16, MCM-41, and MCM-48 which are all commonly utilized [16].

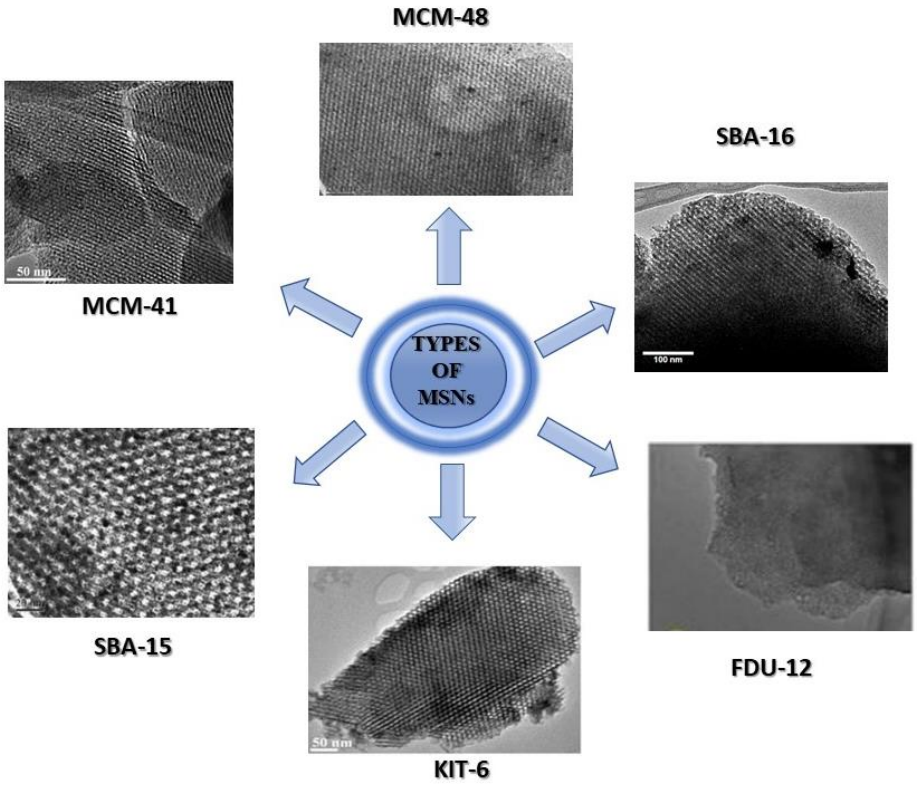

Figure 2. Types of mesoporous silica nanoparticles. Adapted from [17], published by MDPI, 2010, [18], published by MDPI, 2022, [19], published by MDPI, 2013, [20], published by MDPI, 2020.

MSNs have quite good physicochemical properties and are tunable. The high porosity of MSNs allows the lodging and release of a wide range of biomolecules and medicinal substances. In addition, the multiplicity in shape, texture, and size of MSNs boosted their use as controlled nanocarriers in drug administration. MSNs with various particle sizes, pore diameters, differentiated pores (parallel channels or radial pores) may thus be created using magnetic nanoparticles implanted in the skeleton or even the mesoporous net out of discrete metal nano part centers. Self-assembled surfactant molecules are used as condensation templates to make bulk mesoporous materials. These types of MSN can be synthesized by implanting magnetic nanoparticles in the skeleton or even the mesoporous net from discrete metal nano part centers. To create bulk mesoporous materials, self-assembled surfactant molecules are used as condensation templates. Removal of the template leads to a material filled with network cavities with orderly distribution of pores with a homogenous size ranging from 2 to 20 nm, a high pore volume (approx. 1 $cm^3 \cdot g^{-1}$), a large surface area (approx. 1000 $m^2 \cdot g^{-1}$), and a high silanol density that may promote subsequent functional activities. These characteristics make MSMs attractive as candidates for applications requiring adsorption of molecules, for example, drug delivery devices, as suggested for the first time by the Vallet–Regí group in 2001 [4,21]. MSN is considered a good drug vehicle because of its textural characteristics that enhance drug loading inside pores. Conversely, the kinetics of drug diffusion may be influenced by the silanol group functioning [22]. The unique properties of mesoporous silica nanoparticles are: readily adjustable particle size, high stability and rigid framework, pore size that is readily adjustable and uniform, high pore volume and bigger surface area, bifunctional surfaces, ease of manufacturing. [13] MSN size, surface charge, and material composition have a significant effect on the cellular permeation and efficacy of MSN-based oral administration [23].

2.1. Particle Size

Particle size is a critical aspect of MSN's biological use as drug carriers [16]. MSNPs' particle size can be easily adjusted, allowing for easy endocytosis by live animal and plant cells with little cytotoxicity [13]. The diameter of the particles may be varied according to the chemical characteristics, ranging from a few micrometers to a few nanometers. Monodisperse nanoparticles may be produced in sizes relevant to biological settings, ranging from 300 to 10 nm, for application as drug delivery nanocarriers. In this regard, the precise particle size should be tailored for the particular as well as an efficient biological application at hand [24]. Mesoporous silica nanoparticles may be produced by employing a charged or neutral surfactant in an aqueous solution. Surfactants polymerize silicates (an ester of orthosilicic acid). The rate of hydrolysis, the interaction between a constructed template and silica polymer, and condensation of the silica source are all variables that impact the size and form of mesoporous silica nanoparticles. By changing the pH, we can regulate the above variables using various templates and co-solvents [18]. Biological variables such as blood circulation time, in vivo distribution, and excretion rate can be influenced by particle size [15]. MSNs can modulate the release profile and targeting functionalities of medicines with low solubility [25–28]. According to Zheng et al., MSNs with particle sizes smaller than 100 nm enhance the oral bioavailability of poorly soluble medicines. Interestingly, recent investigations mainly focused on particle size transition, offering little information on the impact of particle shape on oral absorption. As a result, it is crucial to look into using MSNs with a favorable shape as medication carriers for efficient oral delivery [23]. Low solubility seems to be the most significant factor impeding oral bioavailability among the other variables. To improve solubility, drug modification (for example, salt generation), the use of a complexation agent or a surfactant, solid dispersion formation, and particle size reduction are some of the approaches that have been developed. Moreover, it is recognized that the solubility of a compound indicates the particle size property; for example, the smaller the particle sizes, the greater solubility due to a larger surface area per volume. Thus, nano-formulations offer drug dispersion to a high degree and allow drug stabilization in its non-crystalline state by improving medication bioavailability. As a

result, encapsulating the medicines in porous matrices, such as mesoporous silica carriers, may create a nano-sized environment, increasing drug solubility even more. Because of the interactions between the drug and the carrier, the nano-encapsulation operation not only reduces the size of the particles of the drug to the nanometer range but also changes the physical nature of the drug, which is referred to as the amorphization process. Due to the well-organized and structured nanoscale porous form of mesoporous silica materials (i.e., MSNs), drug molecules may be easily trapped and stabilized in a non-crystalline form within the mesopores, hence increasing the drug dissolving rate [14].

2.2. Particle Shape

Some studies reported that particle shape can be a factor that determines oral drug delivery which gets inspired by the fascinating fact that the majority of microbial residents in the gastrointestinal tract are rod-shaped. Biocompatibility, biodistribution, and clearance are affected by MSN structure. According to Yu et al., in the intestinal mucus, rod-shaped nanoparticles diffuse faster than spherical counterparts, resulting in a longer retention period in the GI tract and deeper mucus penetration [29]. Banerjee et al. showed that nanorods had substantially greater intestine cellular absorption than spheres [30]. According to other research, cellular uptake efficiency and processes are shape-dependent, with MSNRs outperforming MSNSs in terms of cellular absorption efficiency [19].

2.3. Pore Size

The size of the pores has a significant effect on the drug release rate. The dissolving rate is most likely determined by the final porosity of a delivery vehicle. The more porous a delivery system is, the more the dissolving medium can permeate and break it down, allowing the release of the drug [31,32]. The surfactant species chosen has a significant effect on the mesostructure ordering of the nanoparticles and the pore size [16]. The factors that regulate the pore shape of MSNs are the source of silica, surfactant concentration, and surfactant packaging capacity. The surfactant accumulation in the solution relies on pH and solution concentration. MSNs are either acidic and basic pH produced with distinct pore shapes. For example, the high pH lamellar mesophases are created (>12), the basic pH (10–12) being used as hexagonal structures. A study by Lin et al. shows that changing the pore size can offer different antibacterial effects using MSN. The hydrothermal treatment method is the most commonly used method to adjust the pore size. The size is dependent on the materials selected and includes the length of the hydrophobic chain or by employing mesitylene, a volatile organic solvent as a swelling agent. Pore enlargement may be accomplished via the introduction of chemicals during synthesis, although further tuning is needed due to the additives' ability to alter the hydrophobic-hydrophilic balance. Mesitylene is utilized to increase the pores of MSNs by 3–5 nm without affecting their particle size, and these MSNs with enlarged pores are employed as a vehicle for the delivery of membrane-impermeable proteins to cancer cells [22] so that we can assume that the size of the pores affects the loading and release rates of molecules. By increasing the size of the pores, more molecules may be placed within, increasing release rates [33].

2.4. Pore Volume

The volume of pores is an essential component in the loading of drugs. A high number of pores may thus prevent strong interactions between drugs which facilitate drug pores' inter-molecular interactions resulting in large-scale mesopore canals. The kind of pores may also affect loading and release rates [33]. When the size of the pore is less than 15 nm and the surface area is about 1000 $m^2 \cdot g^{-1}$, the pore volume is typically in the 2 $cm^3 \cdot g^{-1}$ range. Drug interaction with mesopores is a surface event, while poor drug-drug interactions may result in pore filling. Pore volume may be used to calculate the quantity of medication adsorbed. Many successive drug loadings in ordered mesoporous material induce significant filling of mesopores, increasing drug-intermolecular interactions inside the pore width. It means that the pore volume and the quantity of medication loaded are proportionate to each other [22].

Increased pore volume can help to avoid strong interactions between drugs, facilitating drug-pore wall intermolecular interactions and resulting in a large filling of the mesopores channels. The arrangement of pores can also affect cargo loading and release rates. Heikkilä et al. evaluated three different pore arrangements, MCM-41, TUD-1, and SBA-15 materials, in processes on ibuprofen loading and release processes [15,24]. Andersson et al. evidenced that comparable hexagonal mesostructured pores (SBA-1) showed quicker release than unconnected pores (SBA-3). Similar amounts of drug loading were detected for these systems [34].

The surface area of MSNs is the most important element in influencing the number of pharmaceutical products absorbed. Two distinct techniques are utilized to regulate the number of incorporated drugs in the matrix: raising or lowering the surface area and altering the surface drug affinity. This shows that the amount of drug absorbed is directly proportional to the surface area [22]. High surface area is also an important factor in the material dispersion process from MSNs. For MCM-41 systems, the Vallet-Reg group discovered 2-D hexagonal mesoporous silica vehicles which have greater drug adsorption values than SBA-15 systems [33].

Thus, MSNs with a tuning pore size and structural properties, the constrained particle size of about 50–200 nm, monodispersed spherical particles, high volume of the pore, surface area and high stability, and a rigid framework make them an adaptive technology for oral drug delivery [14].

3. Various Barriers in Oral Drug Delivery of MSN and Approaches to Overcome

The oral pathway is the most prevalent form of drug administration, as it offers primacy such as the comfort of oral dosing, patient preferences, cost-effectiveness, and easiness to manufacture large-scale oral dosage forms even though medication, especially high pH or enzyme biodegradable peptide drugs, are extremely hard to propagate and attain good intestinal absorption. The oral route has attracted the most attention among the various routes of drug delivery because of its distinctive advantages, which include long and controlled delivery, proficiency of administration, viability for sound formulations, and amiability with patients. A recent pre-clinical study by Qi et al. shows that oral administration of salecan-based hydrogels, a controlled drug delivery for oral insulin, is 10 times more effective as compared to pharmacological availability of free oral insulin solution [35,36]. A wide area (>300/m^2), lined with a viscous mucous layer, also lays the groundwork for drug adjustment and subsequent absorption. In addition, drug molecules that are trapped in mucus are protected from the shear stress caused by fluid gastric juices. Due to the presence of a large number of enterocytes in different parts of the intestine, especially microfold (M) cells covering the Peyer's patch, the small intestine lymphoid segment, the human intestinal epithelial cell is quite absorbing. Compared to other routes, however, oral drug absorption mechanisms are more complex. The route to oral medicine still appears to be the most efficient, less intrusive, and most efficacious way of distributing drugs, particularly from the point of view of patients. To circumvent these constraints, various formulation strategies and delivery mechanisms have been investigated. Although numerous conventional drug carriers have effectively addressed concerns associated with the transport of poorly soluble medicines, only a few have reached a specific point of commercialization. These challenges prompted the scientific community to seek other methods to target medication delivery systems and to begin searching for intelligent drug delivery vehicles. MSNs as oral drug delivery are used in this setting. This nanoparticle in the form of the oral formulation can overcome certain barriers, offers incredible ease of administering the drug, correspondingly improved patient comfort, and is usually less expensive compared to other formulations, and thus MSN as an oral method portrays a novel method to the scientific world. In addition, numerous benefits of MSNs, including easy replicating methods, variable pore and particle sizes, efficient and simple functionalization, a large surface area, and a large pore volume adequate for significant drug loadings, make them suitable candidates for drug nanocarriers. Moreover, mesoporous

silica nanoparticles have been shown to increase the oral bioavailability of weakly water-soluble medicines significantly. Additionally, it was demonstrated that by coating MSNs with sensitive functions, premature drug release in the GI tract can be inhibited, resulting in increased bioactive molecule concentrations in targeted organs [2,3,14].

3.1. Barriers of MSN for Oral Drug Delivery

Biological barriers, physicochemical barriers, metabolic and biochemical barriers are the main four types of barriers present in oral drug delivery. Most of the orally administered drugs get absorbed from the upper part of the intestine, that is, the duodenum and jejunum. One of the greatest challenges for absorption of the drug in the GI tract as a biological barrier is the epithelial lining of the intestines among lumen, mucus, and tissues [2,3]. The GI tract's anatomy is consistent across all segments. Smooth muscle cells encircle the lumen, which is coated by the serosa, muscularis, submucosa, and mucosa layer. Epithelial cells, muscularis mucosae, and lamina propria make up the mucosal layer that lines the inner GI tract, and they all play important roles in food and drug molecule transport, as well as GI immunity. Absorption of drugs usually occurs in the small intestine due to a wide absorption area and a lengthy residence period [3]. Epithelial cells are layered in a single column, and the building blocks are present at the apical surface, which are interspersed with enterocytes and connected by zonula occludens or close intersections known as tight junctions. The tight joints are primarily responsible for the transition of hydrophilic molecules through the paracellular route. The apical epithelium projects with the lamina propria to form microvilli. The small intestine approximately consists of 3000–7000 microvilli per cell, foldings called kerckrings, and about 10–40 finger-like projections called villi of 0.5–1.5 mm that offer a large surface area for absorption and drug interaction [37]. While the microvilli structures enhance the amount of surface area in the small intestines for absorption, they also act as an enzymatic barrier, because their brush border is densely packed with digestive enzymes [38]. To reach the mucosa, epithelium, and blood or lymph capillary walls, drugs must pass through numerous layers of the GI tract lumen, including the mucous-rich layer, pericellular matrix, and gastric juice [2] other than this biological barrier; some factors such as GI pH, GI transit time, food, GI fluids, a usual distance of the segment, mode of absorption also play a crucial role in the bioavailability and absorption of drugs that are orally administered [2]. The stomach's extreme acid condition (pH 1–2.5) is considered as an important biological barrier to any orally delivered medicine, denaturing the maximum of the supplied molecules and extremely reducing their effectiveness. Apart from these, osmotic pressures throughout the GI tract, peristalsis of the GI muscles, and shear stresses caused by the flow velocity of gastric juice inside the lumen are also variables that limit drug efficacy owing to the lumen's mechanical degradation. Flowing gastric juice may potentially shorten the contact time between medication molecules and the epithelial layer, hindering drug absorption. Mucus is considered as another biological barrier. It is sticky and viscous and composed of water, mucins, salts, bacteria, carbohydrates, and also a proteoglycan coating. Mucins are large molecular substances composed of disulfide bonds and form the mucosal layer. The mucosal layer is of two types: the inner thick adherent layer is composed of glycoprotein and glycolipids, and the outer layer is a thin loose layer. The thicker layer is considered as a barrier for drug transport to the submucosal layer [3].

In the context of physiochemical barriers, drug absorption is of major concern. The drug dose must be released from the dosage form for it to be absorbed in the GI tract; the drug part of the delivery should be in a solution or dissolve in the GI liquid. In addition, the medicine must penetrate through the intestinal wall. As a result, drug hydrophilicity and intestinal epithelial membrane permeability are important factors of GI absorption. The major physiochemical barrier includes hydrogen–bonding potential, charge, size, drug metabolism, hydrophilicity that alter the membrane partition and permeation. The hydrogen bonding potential of peptides to water molecules has proven to be a major component in peptide penetration. In vivo and cell culture studies of the intestinal mucosa show that hydrogen bonding potential affects peptide penetration. The idea underlying

the concept of hydrogen bonding potential is the energy required to dissolve the peptides' polar amide bond for it to penetrate and pass through the cell membrane. According to the Lipinski rule, a therapeutic molecule with more than ten hydrogen bond acceptors or five hydrogen bond donors and a molecular weight greater than 500 Da has a lower chance of crossing biological barriers. Even though the molecular weight of a hydrophobic molecule is more than 500 Da, it is projected to have trouble passing the intestinal mucosa's biological membranes [2,39].

The intestinal enzymes as well as brush bordered enzymes act as metabolic and biochemical barriers. The pancreas produces digestive enzymes, such as peptidases, amylase, and lipases, as well as trypsin and chymotrypsin, and those originating from the intestinal flora of the colon, which is primarily situated in the lower area of the GI tract, normally stimulate intestinal metabolism. Furthermore, enzymes residing within the brush border membrane perform first-pass metabolism on the enterocyte surface, which encompasses intracellular and brush-border metabolism. Brush-border metabolism takes place primarily in the small intestine. Brush border metabolism is aided by alkaline phosphatase, isomaltase, sucrose, and other peptidases. First, pass metabolism, phase I metabolizing enzyme, and phase II conjugating enzyme, influx and efflux transporter also affect the drug absorption [2,39].

3.2. MSN as a Drug Carrier: Mechanisms to Overcome Oral Barriers

Drugs can be administered to patients as semi-solid, solid, or liquid formulations, with the nature of the formulation varying according to the patient category, i.e., age, sex, patient health status, and route of administration. Patients are most frequently prescribed solid medications, which are administered orally as soft and hard capsules. Typically, hard pills include the medication in a solid state, whereas soft pills contain the medication in a liquid or semi-liquid state. To aid in tablet penetration into the GI tract, the pills contain lubricating and flavoring additives as well as excipients such as sugar or film coatings that do not dissolve in an acidic environment and only disintegrate in the intestine. Liquid systems and semi-liquid are more absorbable than solid forms, and their final formulations include an organic solution that transports the active molecules while also aiding in GI tract absorption. Unfortunately, these modified dosage forms also show some hazardous and toxic disadvantages and lead to limited uses. To accommodate the growing demand for pharmaceutical oral medicines, researchers are concentrated on creating oral delivery devices with reduced adverse effects, good stability, controlled release, and MSNs were found to be among them. Many scientific studies evidence the positive role of the MSN as a drug carrier in oral drug delivery.

A mechanism-related study related to the mesoporous silica nanorods and nanoparticles shows dual strategies that can overcome the oral barriers. In the case of the MSN, clathrin depends on the pathway for endocytosis and caveolae-mediated endocytosis for nanorods. In a study, the drug doxorubicin was loaded along with Caco-2 cells. Then, the mechanism of absorption was studied. It is conducted by incubating Caco-2 cells for 1 h at 37 °C in PBS containing particular inhibitors and then exposed to MSNs for two hours at 37 °C. A control group was conducted in PBS lacking MSN inhibitors. To deplete cholesterol, 10 mmol/L methyl-b-cyclodextrin in the presence of lovastatin of 1 g/mL were utilized, which was shown to impede caveolae-independent and clathrin-independent endocytosis. Chlorpromazine was utilized at a concentration of 10 μg/mL to suppress clathrin-interceded endocytosis. By incubating cells with 10 μg/mL nystatin, we were able to inhibit caveolae-dependent endocytosis. Then, they concluded that MSNR gets more easily absorbed MSN, and the cellular internalization occurs by caveolae-mediated endocytosis. Nanoparticles absorbed employing clathrin-intervened endocytosis will be converted into the endosome, where a portion of the internalized particles may be returned to the cell surface. In any case, caveolae-mediated endocytosis transports nanoparticles either via the endosomal pathway, where they are internalized, or through the caveosome pathway, where a fraction of the particles may be intercalated to the endoplasmic

reticulum/Golgi body (Figure 3). Thus, in comparison to clathrin-mediated endocytosis, caveolae-mediated endocytosis may be more effective at internalizing MSNRs. Likewise, the apparent permeability coefficient values of MSNRs loaded with doxorubicin hydrochloride were approximately 1.8-, 3.2-, and 6.3-fold greater than those of Dox-laden MSNs. The in vivo pharmacokinetics investigation revealed that Dox-loaded MSNRs obtained an area under the plasma concentration-time curve (AUC) that was 1.9-, 3.4-, and 5.7-fold greater than the equivalent values for Dox-loaded MSNSs. Taken together, our findings indicate that fine-tuning the geometry of nanoparticles may influence their biological fate, such as increased cellular uptake and oral bioavailability [23].

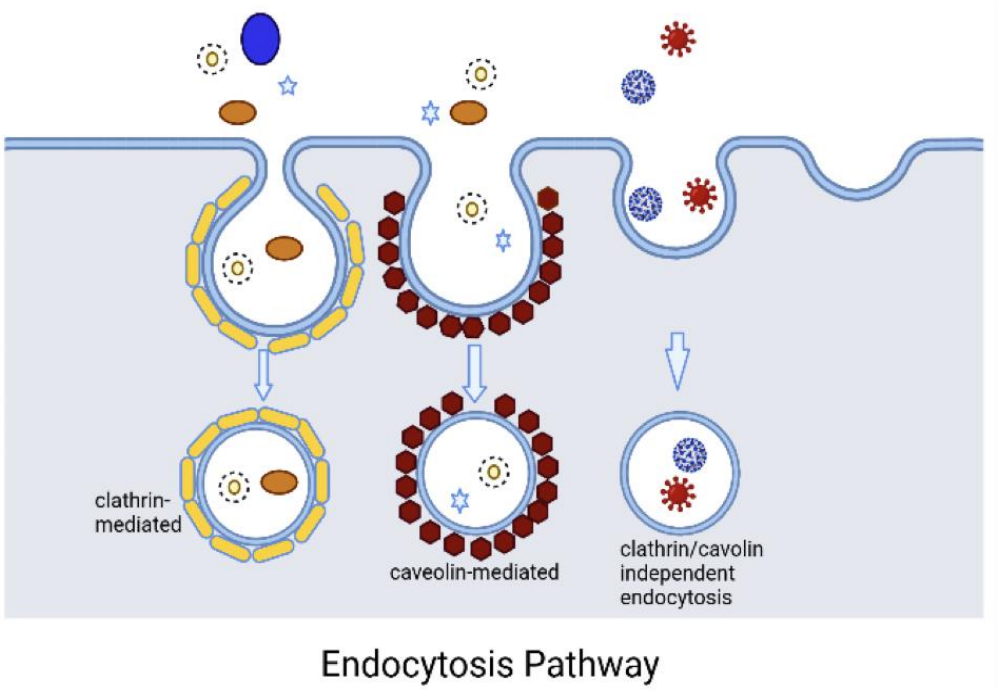

Figure 3. Types of Endocytosis pathway to overcoming GI barriers.

Lipid-coated nanoparticles are found to be effective in overcoming epithelial barriers [40]. The particle absorption takes place due to their strong interaction with cell lipid bilayers. In any case, their hydrophobicity would make them cooperate hydrophobically with lipophilic portions of mucin, so restricting their dispersion through the layer of mucus. Additionally, adsorbing or covalently attaching certain absorption enhancers to the exterior of the nanoparticles can boost the nanocarriers' cellular uptake. These enhancers are typically engaged in processes of recognition or adhesion. The surface charge of the particles (i.e., their zeta potential) also affects their absorption. Positively charged constituent parts have been shown to have an advanced endocytosis rate than a negatively charged constituent. Therefore, the ability of a negatively charged constituent part to change their zeta potential to a positive value on one occasion, through the mucus and reaching the epithelium, may be a capable technique for efficiently passing through both the mucosal and cellular restrictions [14]. E.g., an in vitro study shows that a lipid-coated MSN was found to be effective in eliminating the Salmonella pathogen. In this study, particle size was determined to be between 50 and 100 nm, with a lipid coat thickness of roughly 5 nm. The lipid coating was generated by sonicating liposomes with MSN particles and was characterized using CLSM and FTIR. L-MSN particles were found to be less cytotoxic than pure MSN particles. Ciprofloxacin antibiotic demonstrated improved antibacterial activity when loaded onto L-MSN particles in in vitro experiments. Confocal microscopy studies revealed that the lipid coat aids in intravacuolar targeting of the medication cargo. Additionally, we noticed that employing the L-MSN oral delivery system, a lower dose of antibiotic was adequate to eliminate the infection from mice and boost their survivability [41]. So, we can

draw a conclusion that modifying the surface of the MSN with lipids can easily permeate the epithelial layers as shown in Figure 4 given below.

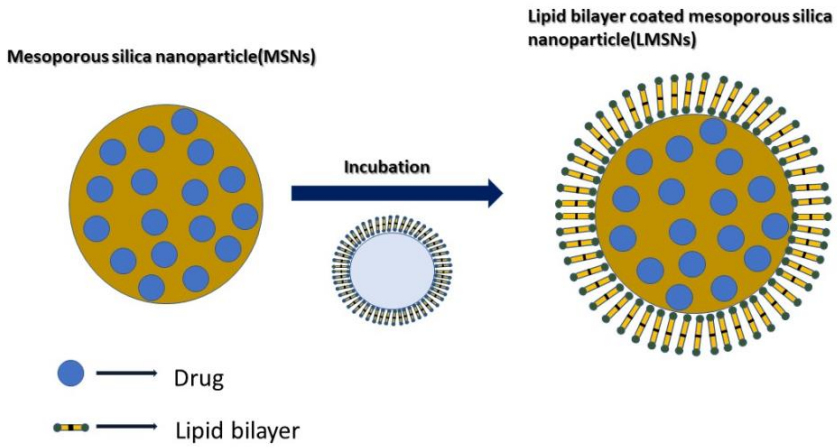

Figure 4. Figure showing the mechanism of lipid coating in the Mesoporous Silica Nanoparticles.

As mentioned above, the alkaline nature of the gut, bacterial content, transit time, fluid volume, presence of various enzymes act as a barrier for drug absorption. Studies show shreds of evidence that we can overcome these barriers by coating or encapsulating the drug surface with various polymers. These polymers help in the release of drugs at specific GI sites. The coating can be conducted through two methods. In the initial technique, pure MSNs are coated with a polymer and then loaded with drugs, and that in the second method, drug-loaded MSNs are generated first and then coated with polymer. The selection of polymer hangs on the physicochemical properties of the drug, polymer coating procedure, and attributes of the polymer. Natural polymers such as chitosan and poly(dopamine), and synthetic polymers, such as poly(ethyleneimine) (PEI) and poly(ethylene glycol) (PEG), are being broadly used for coating applications. The choice of a polymer for coating is frequently determined by the preplanned features essential for the intended result, for example, biocompatibility, sustained release, targeting, or stimulus-sensitive product release from MSNs. The Figure 5 represents the polymeric coating of MSN [42]. Many studies evidence the beneficial role of polymeric-coated MSN drug delivery for crossing biological barriers. One of the examples is a study by Song et al. They created SBA-15-type MSNs covered with PDA comprehending silver as an antibacterial agent to expand the restraint of bacterial development through in situ produced silver nanoparticles. PDA-coated MSNs limit the discharge of silver particles; also, a persistent repressive effect with *Escherichia coli* (60 h) and *Staphylococcous aureus* (36 h) bacterial strains was found [43]. As a metronidazole carrier system, whisker-like SBA-15 particles covered with 10 percent tannic acid were employed in the treatment of trichomoniasis. Tannic acid was coated on the exterior of nanoparticles with the help of glutaraldehyde. Tannic acid increased the metronidazole drug loading volume by 7 percent and facilitated pH-sensitive drug release. In vitro, the coated MSNs limit protozoal development 100 percent for 180 min, outperforming metronidazole solution [44].

The effect of spherical mesoporous silica nanoparticles as an oral dosage form on the oral absorption and bioavailability of telmisartan, as well as their cellular absorption and cytotoxicity can be observed. They compared the efficacy of drug absorption of bioavailability of the MSN and MSM. Spherical mesoporous silica nanoparticles and APTES-modified mesoporous silica nanoparticles (AP-MSNs) were synthesized using the standard process by Zhang et al. MSNs were matrix-labeled with the fluorescent dye FITC for fluorescence detection. AP-MSNs were resuspended in 10 mL of carbonate buffer solution at a concentration of 200 mg/mL at a pH 9.0. The AP-MSNs were then combined with a FITC solution of 1 mg/mL. After 10 h of stirring at 4 °C, the suspension was centrifugated at 12,000 rpm to bring together the FITC labeled MSNs. Following thorough washing with

carbonate buffer, the labeled materials were dried under vacuum and kept as dry powders. FITC-MSNs were the names given to the dried composite samples. Then, the MSN was loaded with telmisartan. It is conducted by direct compression that is the physical blending of microcrystalline cellulose, mannitol, TEL-MSNs, and cross-linked polyvinylpyrrolidone of MSM which is prepared by transferring it to a 100 mg/mL acetic acid solution of TEL. The loading solution had a 5:3 ratio of MSMs to TEL (*w*:*w*); the mixture became frothy. This study reported that the MSNs utilized in this investigation were not harmful. MSNs depend on time, concentration, as well as size in their cellular binding, association, and transit. Additionally, MSNs can dramatically increase TEL permeability and decrease the rate of P-gp-mediated drug efflux, and the TELMISARTAN-MSN formulation exhibits improved in vivo pharmacokinetics (increased Cmax and bioavailability) when compared to either a commercial formulation or a TEL-Mesoporous silica micro-nanoparticle formulation. A faster rate of drug release and the accompanying increased concentration gradient betwixt gastrointestinal fluids and blood, as well as increased drug permeability across biological membranes, are the primary processes by which MSNs promote greater oral absorption of poorly soluble medicines. This work illustrates the enormous potential for using spherical MSNs as a novel delivery mechanism for medications that are insoluble in water. Additionally, we may deduce from this work that further particle reduction to the nanoscale region will accelerate the drug's liberate profile and hence boost the dissolving rate. Surprisingly, the TEL discharge of the two drug-loaded assays from the TEL-loaded MSN tablet was seen to be faster. The difference in release rate between MSN and MSM tablets loaded with TEL could be explained by the carrier pore channel length. TEL molecules adsorbed in two-dimensional cylindrical MSM pore systems had a higher chance of escaping and diffusing into the release medium than those trapped in short MSN pore channels (pore channel length smaller than the MSN radius) (pore channel length greater than 1 m) [45].

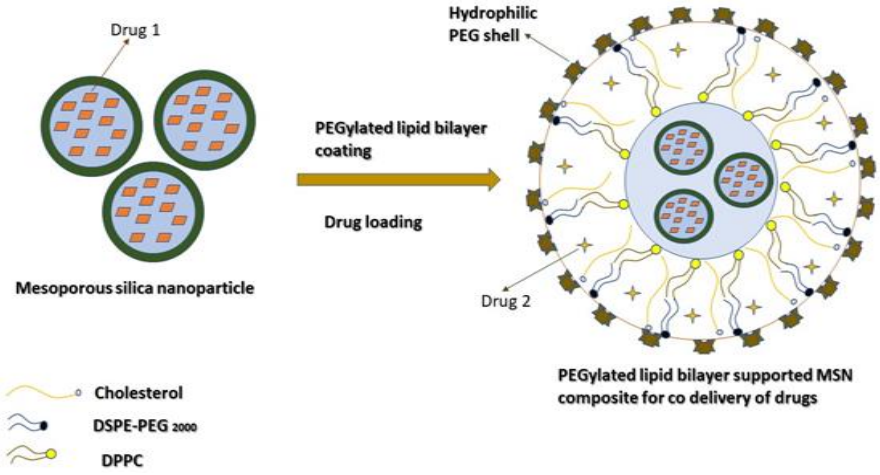

Figure 5. Representative picture of polymeric coating of MSN.

The encapsulation of drugs into the MSN can increase the drug solubility. This is accomplished by shrinking the medication's particle size to the nanoscale scale and altering the drug's physical state, i.e., the amorphization process. Drug molecules can be easily trapped and fixed in a non-crystalline state within the mesopores due to the well-organized and structured nanoscale porous structure of mesoporous silica materials, hence increasing the dissolving rate of the drug [14].

Stimulus-responsive hydrogels were largely examined as sealing materials to give MSNs target-specificity. Various stimulus types (i.e., magnet, pH, heat, and light) were used for MSN systems to date. Stimulation response can be accomplished by different principle strategies: (1) clinical and covalent bonding/crosslinking between the carrier and the medication in response to stimuli, such as cleavable binding at pH levels lower than plasma

pH and (2) functioning of the surface or coating of the channels, which can switch the conformation according to the neighboring properties Figure 5. To prevent any early release, doxorubicin has been connected to the inner walls of MSN channels via pH-sensitive hydrazine bonds. This means that the acidic situations of the lysosomal/endosomal environment when absorbed into the cell through endocytosis can stimulate drug release due to the binding protonation [2,37]. Another example is the light-responsive MSNs; Mekaru et al. used photoactivatedazobenzene to create light-responsive MSNs; when excited, it triggered the release of light from an external source. One of the most common cancer therapy carriers is light-responsive MSNs. Later, the magnetic-responsive MSNs replaced them for the same objective, as the light connected to the inner walls of MSNs via pH-sensitive hydrazine bonds that can prevent the medicinal product from being released prematurely. They were later replaced by magnet-responsive MSNs for the same purpose, as light could not pierce deep enough into the tissue, while magnetic fields could address any type of tissue that cannot penetrate into the tissue deep enough, while the magnetic field could tackle every type of tissue at any desired depth. Iron oxide was one of the greatest possibilities for magnetic induction at the desired depth. These systems were not primarily targeted towards the administration of oral drugs but were responsive to MSNs, but these systems demonstrate diverse stimuli-responsive features that can be incorporated into materials that benefit oral medication provision [3]. Another study shows that pH-responsive protein, i.e., the succinyl β-lactoglobulin (BL) when combined with the MSN, can mutually diminish the gastro-sensitive release of omeprazole (OMP), and improve the dissolution in the intestinal pH. They reported that the drug-inducible mesoporous silica nanoparticles combined with succinylated β-lactoglobulin (BL) provide an alternative to the existing formula as this system protects the medicinal product throughout the GIT, increases the intestinal solubility in pores, and enables other features to be anchored to the free surface of the medicinal product [46].

From all the above-cited scientific studies, we can conclude that by encapsulating the MSN surface with lipid layers or polymers, transport processes such as clathrin-mediated and caveolae-mediated endocytosis, the apparent permeability coefficient of about $4.6 \pm 0.78 \times 107$ cm/s, increased permeability, decreased efflux transportation, accumulation in the targeted site, short pore channel length, increased dissolving rate, and susceptibility to stimuli mediating responsivity make Mesoporous Nano Particles an excellent drug delivery carrier by surpassing all the barriers in oral drug delivery [19,45].

3.3. Engineering of MSN for Oral Delivery

Various groups patented the synthesis of porous silica in the 1960s, resulting in hollow fibers as well as porous particles containing a crystallized phase, causing low density with exposure to surfactants [44,47]. This exploration was not completely acknowledged until the 1990s and the start of the nanotechnology transformation, starting with Tsuneo et al.'s synthesis of microporous-material in 1990 [48] and later by Mobil Corporation research facilities, which was designated MCM-41 [47,49].

Silica nanoparticles, also known as nano-silica, are vital components of nanoparticle research; due to their low toxicity and body stability, they are mostly used in biomedical applications. Mesoporous silica nanoparticles are a common term for silica nanoparticles (MSNs) because of their mesoporous property or containing pores with diameters of a range of 2 to 50 nm [50]. MSNs have a SiO_2 structure and can be made in several different methods, resulting in a wide range of features. The MSN needs four main constituents for the synthesis which are silane (silica precursor), surfactant, solvent, and catalyst [51,52]. Even though only these four components are required for synthesis, MSNs with varying properties such as surface area, diameter, shape, and pore size can be obtained [50].

The various methods, as well as the material used for the synthesis of MSNs, are mentioned below. Synthesis of MSN can be conducted by various methods which are sol-gel, hydrothermal synthesis, microwave synthesis, soft and hard templating methods, template synthesis, fast self-assembly, modified aerogel methods, etc. [47,53].

3.3.1. Sol-Gel Process

The production of silica nanoparticles is usually conducted by the sol-gel process as shown in Figure 6 given below, a soft chemistry procedure that occurs at room temperature under basic or acidic conditions. In an aqueous solution, a silane such as tetramethylorthosilicate (TMOS) Si (OMe)4 or tetraethyl orthosilicate (TEOS) Si (OEt)4 is used as a precursor [50]. The reaction takes place via a condensation and hydrolysis reaction in the existence of a base or acid catalyst such as NH_3 or HCl [51,52]. The speed of hydrolysis and condensation depends on whether the catalyst is an acid or a base. Hydrolysis is much quicker than condensation in an acid-catalyzed reaction, resulting in a large number of small silica particles. These particles have a gel-like consistency. In contrast to the hydrolysis stage, the base-catalyzed reaction has a quicker condensation step, resulting in bigger silica nanoparticles [50,54].

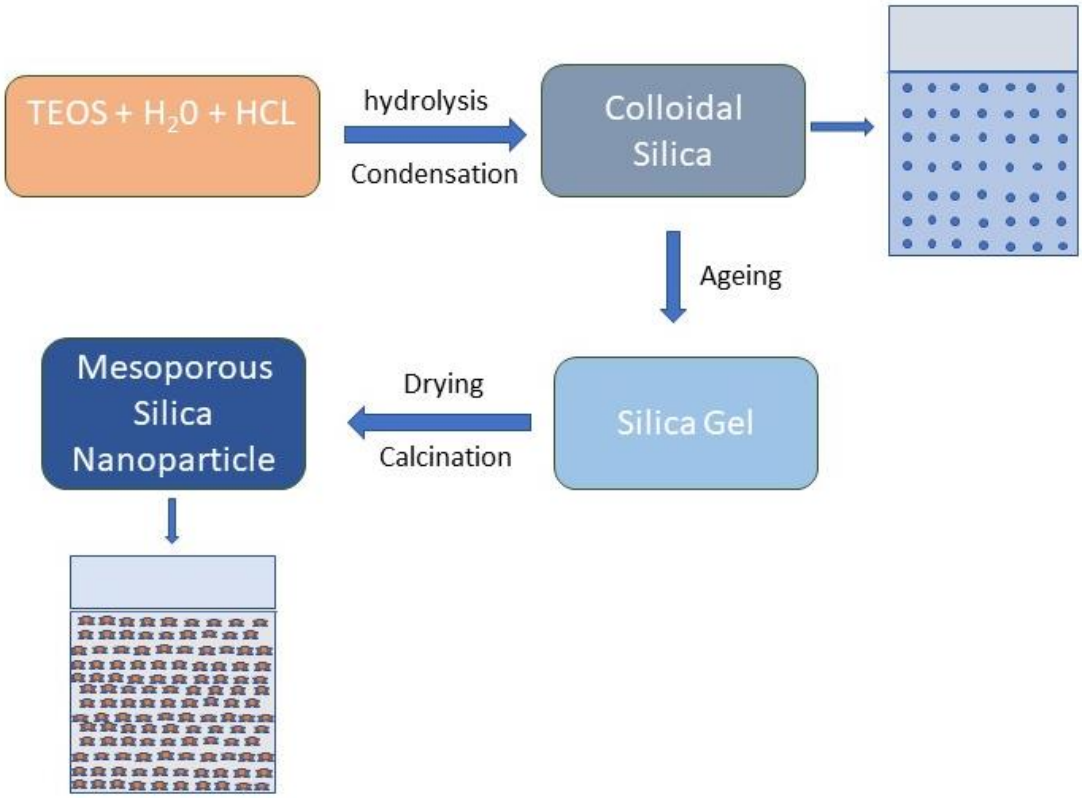

Figure 6. Sol-Gel process for the synthesis of Mesoporous Silica Nanoparticles.

3.3.2. Hydrothermal Synthesis

A surfactant is typically used as a templating agent in hydrothermal synthesis, along with an acid or basic catalytic agent [55]. To the solution, an inorganic material is added to create a hydrogel, which then is autoclaved [56]. In general, temperatures and high pressure are used when dealing with the reaction precursor. Organic matter will be removed, and the precursor will be separated. This procedure necessitates more time for reaction [47].

3.3.3. Microwave Synthesis

Microwave synthesis will take place in an electromagnetic field with a rapid speed of heating. When compared to the hydrothermal method, this method is easier to use and takes less time [47]. Various synthetic strategies were developed based on the usage of hard and soft templates, as well as template elimination. Templates are categorized as soft or hard, and they serve as an integral part of the construction of structures, ensuring repeatability [47].

Surface modifications are very useful in mesoporous nanoparticles because they can enlarge the scope of biomedical applications for mesoporous silica nanoparticles. There is the physical and chemical type of surface modification. The advantages of surface modifications are the increase in biocompatibility, prevention of particular adsorption as well as the provision of functional groups for biomolecule conjugation. Layer by layer self-assembly is a physical method for changing the surface of MSNs, and chemical surface functionalization is a chemical method [6,57]. Additional factors affecting MSN biocompatibility include surface features such as functional groups, charge, and molecule presence. When compared to neutral and anion species, positively charged nanoparticles can elicit a stronger immune response and cause cytotoxicity. Serum opsonin has been linked to MSNs with a negative zeta potential. Macrophages in the reticuloendothelial (ER) systems swiftly eliminated them from ambient or intracellular settings [58]. The amount of (-SiOH) groups at the outer surface of MSNs is just another crucial factor. These functional groups have the potential to react negatively with biological components such as cellular membrane lipids and plasma proteins, resulting in their loss of structure. As a result, surface modification is a vital step in altering the surface reactivity of MSNs to increase their biocompatibility and biological utility [6,7].

The need for surface modification of MSNPs is that they alter the physicochemical characteristics of the nanoparticles, which is important for future medicinal applications. Hydrophobic drugs do not penetrate the mesoporous silica [13]. The functionalization of the hydrophobic functional group can solve this problem; this allows the loading of a variety of hydrophobic drugs. To delay the release of the drug into the aqueous medium from the mesoporous channels, the functionalization of the surface can be utilized [13,17]. Generally, surface modification is used to enhance the physicochemical properties, improve semiconducting, decrease hydrophobicity, enhance luminescent properties of the material and increase stimuli responsiveness. The most common type of MSNs is organically modified silica, which enriches organic molecules by covalent bonding to the inorganic network of Si NPs. Surface modification can be accomplished using either the post-synthesis or co-condensation methods [7,59].

(1) Co-condensation Process (one-pot synthesis)

Organosilanes are directly condensed with a combination of silica precursors and surfactant templates in a process known as co-condensation [13]. The co-condensation method allows for the uniform distribution of organic groups across the whole inner pore surface without causing pore shrinkage or blockage [60,61]. Moreover, by introducing different organosilanes, the morphology of MSNPs can be influenced. The interaction between organosilanes and surfactant molecules can cause variation in particle morphology such ase hydrogen bonding or electrostatic interaction. They discovered that hydrophobic groups on organosilanes interact with the hydrophobic tails of surfactants, causing intercalation of organic groups of organosilanes with surfactant micelles. These outcomes are in the adjustment of long round and hollow micelles and the arrangement of rod-shaped MSNPs. Hydrophilic organosilanes, then again, do not collaborate with surfactants and do not further stabilize micelles, bringing about circular particles with randomly arranged pore structures [62]. To save the pore structure and long-range pore ordering of MSNPs, the measure of the functional group consolidated by the co-condensation strategy does not typically surpass 25% of surface inclusion because of the distinction in condensation rates among organosilanes and silica precursors. The loading efficiency is determined by the nature of organic functional groups. Functional groups with a greater capacity to compete with the silicate anions in surfactant molecule binding would be more likely to seem to be on MSNP surfaces than those with a weaker ability, which are typically encased in silica frameworks and thus are inaccessible. The degree of surface modification can be altered based on their findings by selecting appropriate organic functional groups [13].

(2) Grafting method (Post synthesis modification)

Grafting is a post-synthesis method that involves the attachment of functional groups to the material surface after the removal of surfactant which is the method of modification of

the surface of the prefabricated inorganic mesoporous nanoparticle. Surface silanol groups (SiOH) of mesoporous silica nanoparticles, which are usually found in high concentrations, provide anchoring points for the functionalization of organic groups [63]. The grafting method involves functionalization at the pore opening and the exterior surface of MSNPs. Grafting has the disadvantage of inhomogeneity in surface coverage due to the external surface's easier accessibility for kinetic action than the interior pore wall. As a result, the majority of the organic functionalities that were grafted accumulates at the mesoporous opening, thus hampering the ability of penetration to the interior locations of pores [64]. Given the benefit, the use of functional groups helps in selective functionalization at the interior and exterior MSNP environment. MSNPs that have been grafted with organosilane are more thermally stable and have better-retained pore structures than MSNPs that have been co-condensed. The degree of functionalization achieved by the grafting process is often lower than that achieved by the co-condensation process due to the limited number of free surfaces of silanol groups [13,61].

In the post-synthesis grafting procedure, changing amino silane functions as well as managing aggregation kinetics are both problems.

(3) Multifunctionalization

For the development of perplexed drug delivery systems based on MSNPs, consolidation of more than one functional group to the MSNPs can be considered as an option. Although two distinct organosilanes can be co-condensed with silica precursors, the ordering of MSNPs will be disrupted, and the loading quantity will be limited due to different silane hydrolysis rates. Furthermore, the precise location of functional groups cannot be controlled. As a result, a multifunctionalization method was developed that combines co-condensation and grafting to incorporate functional groups onto the inner and outer surfaces of MSNPs selectively [58]. The MSNPs are first manufactured using the co-condensation method, and the free silanol groups are then functionalized in a supercritical fluid medium using the grafting method. An alcohol acidic extraction method is then used to remove the surfactant, resulting in the development of a mesoporous structure [13]. Acidic conditions weaken the template-silica backbone interaction. Proton exchange and solvent extraction are used to remove the surfactant. As a result, organic functional groups are uniformly monolayer covered on both the inner and outer surfaces. This method produces spherical NPs, and the addition of alkoxysilanes did not affect the final product's morphology [13].

The co-condensation strategy was utilized to make the mercaptopropyl functionalized MSNPs, which came about in 90 percent of the complete thiol groups within the pore channels. Then, with 43 percent surface coverage, the outermost layer of thiol-functionalized MSNPs was grafted with 5,6-epoxyhexyltriethoxysilane (EHTES). The mercaptopropyl groups were modified to o-phthalic Hemi thioacetal (OPTA) groups, and the PLA coating was made with the 5,6-dihydroxyhexyl groups. This assembly was described as an amino-containing neurotransmitter detector. The MSNPs' external and internal surfaces were both altered in this study without interacting with one another [65]. A trifunctional zed MSNP composed of three different domains was designed: hexagonal pores, silica framework, and outmost surfaces, each of which was functionalized with biomolecular ligands for tumor cell targeting, contrast agents for imaging, and drug payloads for tumor therapy. To allow optical tracking of MSNPs, TEOS was coupled with a near-infrared fluorescent contrast agent. After removing the surfactant templates, the nanochannels were grafted with a palladium-porphyrin-based photosensitizer for photodynamic therapy. The final functionalization event lead to the formation of cRGDyK peptides on the outer surfaces of cancer cells, which particularly bind to overexpressed integrins [13,66]. Various studies of msn for oral drug delivery are summarized in Table 1 [67].

Table 1. Reported studies of msn for oral drug delivery.

Various Reported Studies with Examples	Result
Supercritical CO_2 was utilized by He et al. to load the poorly aqueous soluble medicine clotrimazole into mesoporous silica of the MSU-H type, which is a form of MSU.	Clotrimazole was evenly distributed in mesoporous and is not crystalline, according to experimental and theoretical findings. In turn, it will increase the oral bioavailability of the drug [8,68].
He et al. used paclitaxel-loaded mesoporous silica nanoparticles which were compared to paclitaxel-free mesoporous silica nanoparticles. The MTT experiment revealed that paclitaxel-free mesoporous silica nanoparticles were cytotoxic to HepG2 cells.	The results show that solubility is increased for paclitaxel after loading into MSNs, thus increasing oral bioavailability of the drug [8,69].
Paclitaxel-loaded MSNs were created by Jia et al., with pore diameters ranging from 3 to 10 nanometers.	The in vitro drug discharge test revealed that the discharge rate dropped as pore sizes decreased from 10 to 3 nm, which could be attributed to the fact that paclitaxel stacked in relatively small pores has a lower possibility of escaping and diffusing into the release medium [8,69].
Ibuprofen was loaded into the amino-modified SBA-15 by Ahmadi et al.	According to the findings, the release rate of amino-modified SBA-15 is much slower than that of SBA-15. This has been attributed to the interaction of Ibuprofen's carboxyl groups with the amino groups of the amino-modified SBA-15. Drug release from mesoporous silica nanoparticles has also been observed to be hindered by hollow structure, which reduces drug bioavailability [8,70].
Chen et al. developed a liquid-solid preparation in which liquid polyethylene glycol400 (PEG400) and the model drug carbamazepine were absorbed into mesoporous silica to achieve increased adsorption capacity and high drug loading. The resulting liquisolid system was granulated and packed into gelatin capsules after being mixed with starch slurry.	The in vivo study showed that there is an increase in the bioavailability of the liquisolid capsule, and it was increased up to 182.7 percent when compared with the commercial carbamazepine tablets [8,71].
Wang et al. reported extrusion/spheronization-based production of instant release carbamazepine pellets using mesoporous silica SBA-15.	The incorporation of drug-loaded SBA-15 into pellets did not affect in vitro release behavior, according to the dissolution results. Furthermore, in dogs, pellets had a 1.57-fold higher oral bioavailability than fast-release commercial tablets ($p < 0.05$) [71].

4. Fate of Oral Mesoporous Silica Nanoparticles

The physiological barrier function that prevents ghosts from entering the body is directly related to the absorption of nanoparticles in the body at first. Skin and the gut, as two of the body's principal natural physiological barriers, can efficiently protect the body from harmful infections and chemicals. Nanoparticles, on the other hand, are largely believed to be absorbed by the gastrointestinal epithelium. Furthermore, numerous prior research has found that the particle sizes of nanomaterials that enter the body through the intestine have a significant impact on their penetration [72]. MSNs are a promising nanomaterial for biomedical applications; however, their interaction with the body remains poorly understood. The absorption, distribution, and excretion of MSNs following oral administration, which are the two primary methods for MSNs to be used in biomedicine, are illustrated in the Figure 7. Furthermore, MSNs can be coated with other biocompatible materials. MSNs may be combined with other materials to form hybrid nanoparticles capable of medication delivery. However, the rapid growth of MSNs has expanded the gap between their fabrication and the relatively sluggish progress in understanding their biological impacts, which must be addressed in the future.

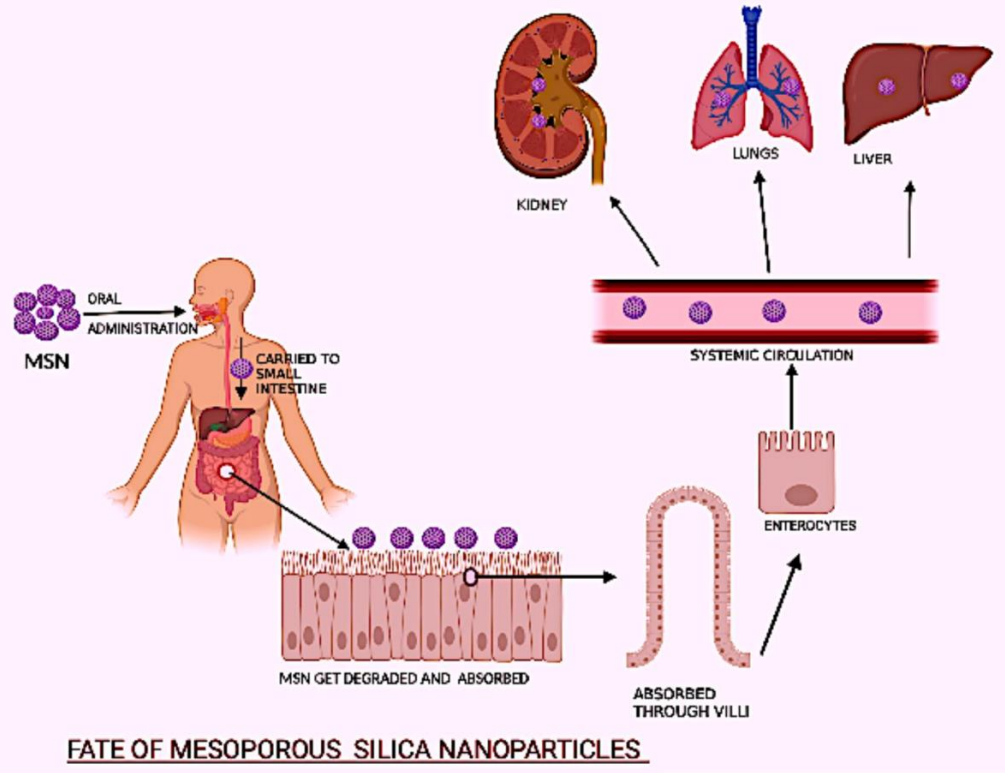

Figure 7. Fate of mesoporous silica nanoparticles.

MSN absorption and distribution are highly variable depending on the route of administration. Unlike IV administration, oral administration of MSNs resulted in their absorption into the blood via the gastrointestinal system. Mesoporous silica nanoparticles with a regular size of 110 nanometers persisted in the liver following oral delivery (Table 1), and the absorption takes place via the intestinal tract, as validated by transmission electron microscopy and inductively coupled plasma-optical emission spectrometry analysis. It is likely that following oral administration, MSNs were partly absorbed into the portal vein via the colon and subsequently delivered to the liver. The MSN content of the liver increased initially and gradually declined over the next seven days [73]. One key reason is that the liver, which has a large number of sinusoidal endothelial cells and Kupffer cells, is the primary organ responsible for the removal of circulating macromolecules and bacteria. The amount of SNs in the liver, on the other hand, was not constant following oral delivery. For example, the amount of SNs in the liver increased initially and then dropped over seven days following oral consumption [72].

The gastrointestinal system could only absorb polystyrene nanoparticles with a mean size of 50 nanometers. The gut barely absorbed smaller or larger particles. However, TEM and inductively coupled plasma analyses indicated that SNs with a diameter of 110 nm were absorbed into the body within 24 h after oral administration in the current investigation. One explanation for this event is that SNs introduced via the oral route were absorbed into the portal vein via the intestine and subsequently transferred to the liver via the portal vein. Furthermore, this procedure was quick and could be completed in a few hours [72].

In the case of the distribution of MSN, particle size plays an important role. The brain, kidneys, spleen, liver, lung, and testes/ovaries were all studied for silica nanoparticle biodistribution. As mentioned previously, total Si concentrations in tissues were measured by comparing increases in total Si levels in silica-treated rats to untreated controls. Regardless of dose, sex, or particle size, Si levels were found to be considerably greater in the kidneys, lungs, spleen, and liver of treated rats. Furthermore, 6 h to 3 days after injection, high Si concentrations were found in the livers and kidneys, whereas raised Si levels were

found in the lungs and spleens 6 h to 2 days after administration. Silica nanoparticles did not accumulate in the ovaries, brain, or testes in substantial amounts. Furthermore, regardless of particle size or gender, tissue distributions were identical. There were no changes in Si concentrations in the gastrointestinal tract 7 days after injection (stomach, esophagus, and intestine). Thus, these study insights show that the kidney, liver as well as spleen were found to be the targeted organs of drug distribution [74].

Before their implementation in biomedicine, it is critical to examine nanoparticles' excretion from the body. MSNs are primarily removed via urine and feces following delivery via various routes. Additionally, the majority of MSNs was observed to be excreted 24 h after oral delivery. However, no intact MSNs were detected in urine 24 h after oral treatment [73]. Because the concentration of Si in the blood and its distribution in vivo have a significant effect on the excretion of SNs from the body, numerous previous studies hypothesized that silica nanoparticles excreted through the renal system caused damage to the glomerular and then increased the glomerular permeability. Histological examination of tissues in the current investigation revealed no evident histopathological abnormalities of the kidney. However, when alternative exposure methods were used, the Si content in urine assessed by ICP-OES rose at 24 h in comparison to the control group. These findings indicated that SNs might be eliminated successfully via urine without affecting the kidney microstructure [72].

Oral silica nanoparticles of two distinct diameters were given to female and male rats (20 and 100 nm, respectively). Transmission electron microscopy and elemental analysis were used to investigate tissue, excretion profiles, distribution kinetics, and tissue fates. This study concluded that the smaller 20-nanometer particles were shown to be removed more quickly than the larger 100-nanometer particles, indicating size-dependent excretion kinetics. Even though urine removed 7%–8% of silica nanoparticles, the majority of nanoparticles was expelled via feces, regardless of particle size or segregation. Thus, for excretion, it is concluded that the removal of silica nanoparticles is aided via urinary and fecal excretion channels [74]. Thus, we can summarize the ADME of the MSN from various reported pre-clinical studies.

Pathological examinations demonstrated that SNs were biocompatible with the tissues following oral and intravenous injection. These findings indicated that oral dosing was a relatively safe mode of delivery for potential biological applications. This study may aid in the selection of appropriate exposure pathways for nanoparticles that are employed as effective medication delivery vehicles.

5. Bio-Medical Application of MSNPs

MSNs have very unique properties that make them perfect nanocarriers for hosting, protecting delivering of the drug to the specific site. The mesoporous silica surface is loaded with targeting agents which is viable for transporting them to the defective tissues which also increases the targeting and will reduce the unwanted side effects [75]. The majority of studies using mesoporous silica nanoparticles concentrated on cancer treatment [12].

The first study was conducted on silica type MCM-41 for ibuprofen controlled release, and the study was performed by Vallet-Regi et al. and his group. The ibuprofen liberation profile revealed a divergent pattern that is dependent on how the active substance is loaded in the silica but unaffected by pore size. The in vitro tests were carried out in a constant state, with the mixture not being stirred while the drug was released, restricting diffusion at the surface of the particle [75]. After that, another study was performed on the pore size effect from the MCM-41 on the release rate of ibuprofen; this study showed that in a stimulating body fluid solution, it decreases directly proportional to the size of the pores in the 2.5–3.6 nm domain [12,76].

MCM-48 also gained attention as a therapeutic delivery system and also for its matrix, which contains unique penetrating bi-continuous channels that can be used when easy molecule accessibility and rapid transport are required. The study was conducted on

MCM-48 by loading ibuprofen and erythromycin; the rate of therapeutic release decreases as the pores' widths and surface chemical modification increase.

5.1. Cancer Therapy

Efficient therapy is not achieved by anticancer drugs due to the narrow therapeutic window, drug instability, poor solubility, poor cellular uptake of various anticancer drugs, and also the continuous side effects. For effective cancer therapy, delivery methods that allow for a large drug payload, preserve the drug from degradation, and promote cellular absorption with target specificity must be created. However, using MSNPs can fulfill all the requirements which are needed for efficient cancer treatment [77].

Many researchers looked into MSNPs as a way to deliver anticancer drugs. Le et al. and his group found out that DOX-originating ex vivo fluorescence and apoptosis in collected tumor cells 48 h after injection when doxorubicin is delivered to the cancer sites were observed. MSNPs showed better DOX intracellular absorption and therapeutic effectiveness. When DOX is loaded into MSNPs, it will increase the efficacy. DOX-loaded MSNPs were introduced into Hep-A-22 liver cancer and resulted in much higher tumor regression than the free drug. The increase in the retention (EPR) effect and permeability, which has been regarded as the essential premise for passive NP targeting, accumulated MSNPs in tumor locations. It is very difficult to distribute the nanoparticle uniformly to all areas of cancer tissue even with EPR effect. A lack of convection, a thick extracellular matrix, increased intratumoral interstitial fluid pressure, and the presence of hypoxic zones that are ineffectively perfused are the main difficulties found while distributing NPs and therapeutic drugs uniformly in cancer tissues Figure 8. The problems caused by the passive targeting promoted the idea of the development of more enhanced active targeting [13].

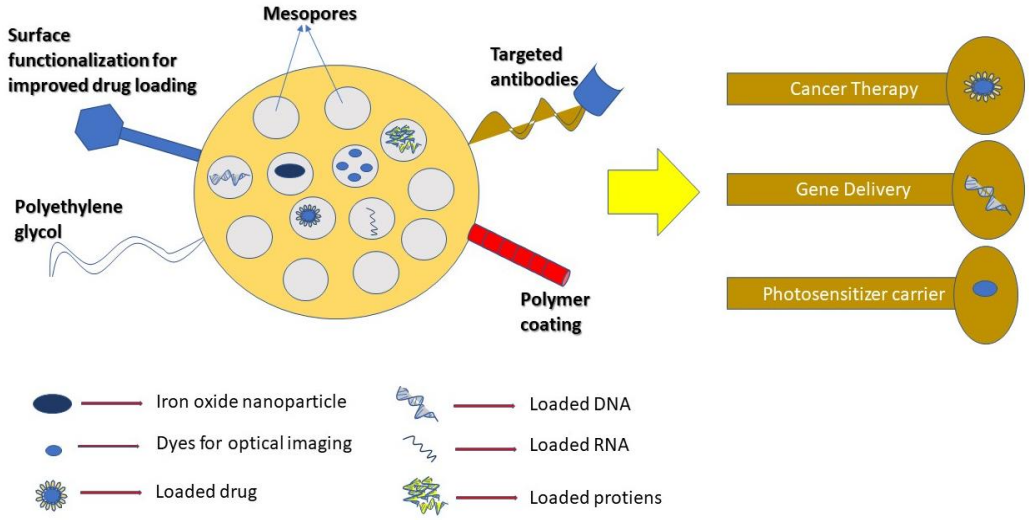

Figure 8. Diagram representing the various applications of MSN in medicine.

5.2. MSNs in Cell Imaging and Photosensitizer Carrier

The study, depiction, and quantification of biological processes at the molecular and cellular levels in humans and other living systems are known as molecular imaging, and it is critical for gaining a deeper understanding of life's mysteries. The advantages of bifunctional fluorescent nanoparticles-based bioimaging and sensing techniques include their high stability, in-situ, and real-time capabilities [78].

The two methods of preparing dye-doped SiNPs are the reverse microemulsion method and Stöber method. To prepare monodispersed solid Silica nanoparticles with a wide range of diameters from 50 nm to 2 µm, the Stöber method is used. Water, surfactant, and oil are used to prepare a dye-doped nano-silica particle in case of a reverse microemulsion method [79]. At the surfactant-oil interface, the silica precursor undergoes condensation, hydrolysis, and the production of dye trapped nanoparticles, resulting in

fluorescent nanoparticles. Quantities of 30–60 nm of monodispersed silica nanoparticles were obtained by using this method [12].

Mesoporous silica nanomaterials are used as a carrier for fluorescent agents. Because of their nanoscale particle size, they are optically clear and do not interfere with fluorescent agent emission. The quantum dots are readily oxidized and produce fluorescence; PEGylated liposome coated quantum dots-mesoporous silica was created to avoid oxidation and increase dispersion stability [80]. In vitro studies of cadmium ions as quantum dots, for example, revealed that liposome-modified mesoporous silica inhibited quantum dots' degradation.

Magnetic resonance imaging (MRI) is a useful biological technique that allows for the noninvasive acquisition of high-resolution anatomic and functional data [80]. Due to their high specific surface, mesoporous silica nanomaterials-based magnetic resonance contrast agents have enhanced sensitivity, allowing for larger payloads of active magnetic centers. MSNPs' surface is modified with targeted ligands and delivered to damaged tissue for diagnostic purposes [80]. Because of its matrix capacity, porosity, flexible synthesis, and absorbed light, MSNPs are also utilized as vectors in photodynamic treatment [12,78].

5.3. MSNPs in Vaccine Delivery

Inducing a robust and cost-effective immune-protective response in the host is the main issue in vaccine development. Mesoporous silica nanoparticles can be utilized as an antigen carrier because of the antigen retention and transport to the presenting cell [78].

The SBA-15 type nanoparticle has increased immune reaction and immunogenicity more than $Al(OH)_3$. In vitro macrophage investigations revealed that silica enhanced phagocyte intake while interacting with the cells little. Furthermore, the greatest concentration of SBA-15 caused a substantial rise in the number of cells, resulting in the production of interleukin(IL)-4 and interleukin(IL)-13, as well as a heterogeneous response of Th1- and Th2-type cytokines. Mesoporous silica rods were used to modify immune cells and to see whether they might be used as a vaccination matrix to produce an adaptive immune response [12,78]. In vivo experiments revealed that mice vaccinated with the complete mesoporous silica rods vaccine had significant Thy 1.2+ leukemic cell proliferation, as well as enhanced expression of the peripheral blood CD4+ CXCR5+ T helper cell clonal and T follicular helper cell differentiation [12].

DNA vaccines were also delivered using silica nanoparticles, depending on the transitory nature of the targeted antigen in the host cells [81]. In contrast to DNA, which had lower immunogenicity when compared to a traditional vaccination, the immunogenicity of silica nanomaterials-DNA was significantly increased. Silica-based vaccinations elicited enhanced proliferative responses, suggesting that silica nanoparticles can be used as effective delivery methods for DNA vaccines, promoting both humoral and cellular responses. Because of the benefits of mucosal vaccination, including simplicity of administration and immunological profiles, this viewpoint for distribution via mucosal channels represents an important goal [12].

5.4. MSNPs in Gene Delivery

Mesoporous silica can be used as a carrier for gene transfection in addition to traditional medication delivery. Because naked nucleic acids have a limited ability to penetrate cell membranes, carriers are widely established to play a significant role in gene delivery. Viral and nonviral systems are the two main gene delivery systems. Immunogenicity, gene recombination, and non-specificity are all major safety concerns with more powerful viral systems. In recent years, non-viral systems such as cationic chemicals, recombinant proteins, polymeric and inorganic nanoparticles were extensively explored. Cationic materials, on the other hand, are frequently associated with severe toxicity, and recombinant proteins have a low cost-performance ratio [82]. Liposomes received a lot of publicity and can enable effective gene transfection, but their primary disadvantage is their instability. Compared to other forms of nanoparticles, inorganic nanoparticles offer several benefits,

including ease of synthesis and surface functionalization, high physicochemical stability, and strong biocompatibility. MSNs are particularly appealing among diverse materials because of their unique features. As a result, MSNs are thought to be a viable gene delivery vehicle for increasing cell uptake and transfection efficiency [8].

6. Advantages of MSN

Mesoporous silica nanoparticles are silica-based nanoparticles that provide wide opportunities for the treatment of various challenging diseases. The MSN is having a well-defined surface area, large pore size, large pore volume, and is non-toxic and biodegradable as well as biocompatible in nature. It also allows homogenous distribution of molecules in porous space, the ability for surface charge control, and free dispersion throughout the body. The Figure 9 represents the advantages of MSN [7].

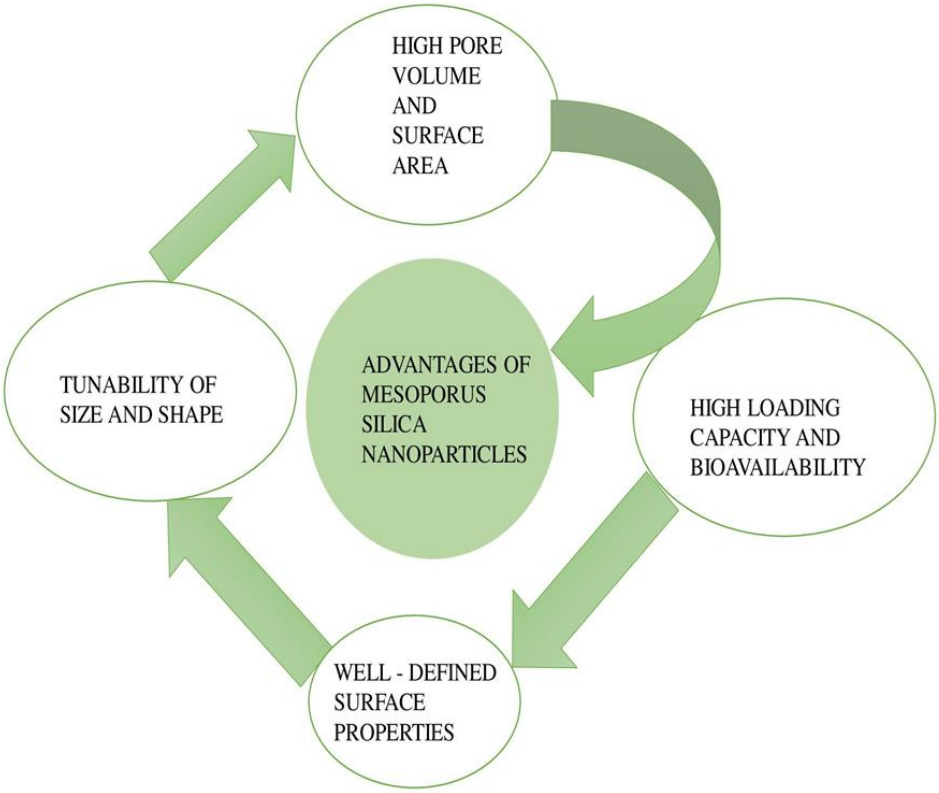

Figure 9. Advantages of mesoporous silica nanoparticles.

7. Comparison of Oral Carriers and Delivery Method

Nanocarriers for oral drug delivery are a developing area. Oral nano drug delivery improves encapsulation capacity and release of the drug. Loading of drugs with nanocarriers can improve the membrane permeability and absorption through the membrane. It is mainly used to protect the drug from various hydrolytic enzymes, improve residence time, increase the absorption as well as the bioavailability. Various nanocarriers for oral drug delivery include polymeric nanocarriers, inorganic nanocarriers, solid lipids as nanocarriers, mesoporous silica nanoparticles, and metallic nanoparticles [4,17,30,32,34,37,40,52,62,64,83]. Silica based nano carriers for delivery of drugs, biomolecules, and food are an emerging highlight. The silica based oral delivery system includes non-porous silica nanoparticles, mesoporous silica nanoparticles, hybrid silica nanoparticles, and diatom silica nanoparticles [12,18,30,63,68,72,78,80]. Of these, the mesoporous silica nanoparticle is most commonly used. One of the most important advantages of this system is it is resistance to microbial action Figure 9. Of all the varieties of silica, amorphous silica is used for oral drug delivery as it has low toxicity and increased dissolution [2,25,37,45,49,59,75,79,81]. A comparison of silica based oral carriers (Table 2) with other oral nanocarriers (Table 3) [18,67,84–89].

Table 2. Comparison of oral carriers and other delivery methods.

	Oral Carriers [30]
Microspheres	Enhanced drug release and drug loading
Hydrogel	High drug loading and controlled drug release
Liposome	Synergistic drug loading and efficient delivery of poorly soluble drugs
3D printed deliveries	Nanosize ink suspension
Microneedle	Protective carrier and possibility of antigen and IgG
-	Other delivery carriers [79]
Pulmonary	100% bioavailability and faster body response
Topical	Non-invasive, self-administered, and long release time

Table 3. A comparison of silica based oral carriers with other oral nanocarriers.

Silica	Resistant to microbial action, Can synthesize easily Feasible at low temperature, Neutral in aqueous phase Tunable pore size, Large surface area	[67]
Nanoparticles	Poor bioavailability, Low tissue absorption Loss of drug during transport	[84]
Nanotubes	Lack of solubility, Small size, Expensive	[90]
Dendrimers	Low hydro solubility, Highly toxic, Cellular toxicity Difficult to synthesize	[85,86]
Liposomes	Trigger immune response, Poor stability	[85,87]
Hydrogels	Non-biocompatible, Non-biodegradable, Response to stimuli is very slow, Possibility of drug deactivation	[89]
Micelle	Poor drug-loading efficiency, Poor physical stability, Insufficient cellular interaction, Low encapsulation efficacy	[89]

Silica based nanoparticles have many advantages, and we can easily adjust the sizes of pores of silica nanocarriers. Silica with a pore size greater than 50 nm is macroporous silica; 2 to 50 nm is mesoporous silica; smaller than 2 nm is microporous silica. The wide range of pore size can be used for the encapsulation of various drugs. The ability to adjust the size of the pore is of great advantage in oral drug delivery. Pore size can be used for adjusting the kinetics of drug. Highly porous substance can make silica an ideal agent for gastro-retention [81]. These nanocarriers protect the drugs from various enzyme action by confinement or a steric hindrance. This nanocarrier can address the main limitation of oral drug delivery such as solubility and bioavailability as compared to other nanocarriers. A recent pre-clinical study shows that silica nano carriers can be used for the effective release of drugs for managing obesity. Another study shows that encapsulation of the MSN with certain BCS (biopharmaceutical classification system) class ii drugs such as celecoxib, fenofibrate, telmisartan, and BCS IV drug furosemide increased intestinal permeability [81,82].

8. Conclusions

Mesoporous silica nanoparticles have appealing properties such as a wide-reaching discrete surface area, homogeneous as well as tunable pores, low mass density, and enhanced pore volume. Based on the following characteristics, MSNs are shown to increase the dissolution rate and bioavailability of water-insoluble drugs: (1) non-crystalline medication entrapped in mesopores; (2) high dispersibility with vast surface area; (3) increased wettability due to MSNs' hydrophilic surface. Hypothetically, all these advantages can decrease the drug dose and increase the effectiveness of the drug. In this case, the drug's peculiar phase behavior in the existence of mesoporous materials can be considered advantageous in the formulation of poorly soluble molecules, especially in terms of reaching larger oral availability doses. MSNPs also have high drug stability, have high drug loading capacity,

and also can incorporate various functional groups by surface modification and linkage methods. These materials can also be delivered by a different route of administration.

Many studies show that employing MSNPs as a vehicle can deliver the majority of medications to the desired location, also by allowing surface modification they can significantly increase the specificity. For cancer therapy, mesoporous nanoparticles show various advantages such as endocytic behavior and high loading capacity. In terms of gene delivery, MSNs with large pores have been engineered to encapsulate a large number of genes while also protecting them from nucleases. MSNs can bind with genes and be successfully transfected into diverse cells thanks to cationic modification. For vaccine delivery, MSNs significantly increased immunogenicity.

New and innovative methods are required to combat many diseases. Here, we try to provide insight into the role of the MSN as a good carrier for delivering the drugs orally. The MSN as a drug delivery vehicle can reduce the side effects and improve efficacy of various drugs. It has the ability to surpass all the barriers associated with oral drug delivery. These nanocarriers have the capacity to load large amounts of drugs and can easily modify its surface. One of the most important advantages of the MSN is that they are highly biodegradable and have high biocompatibility. However, clinical translation is still a challenge so there is a need for more studies to address this. In the future, this system can be used as a smart tactic for improving effective drug delivery. However, one need is to tackle the challenges of scale up and make the system more accessible and affordable.

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