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Review

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Exploring Mesoporous Silica Microparticles in Pharmaceutical Sciences: Drug Delivery and Therapeutic Insights

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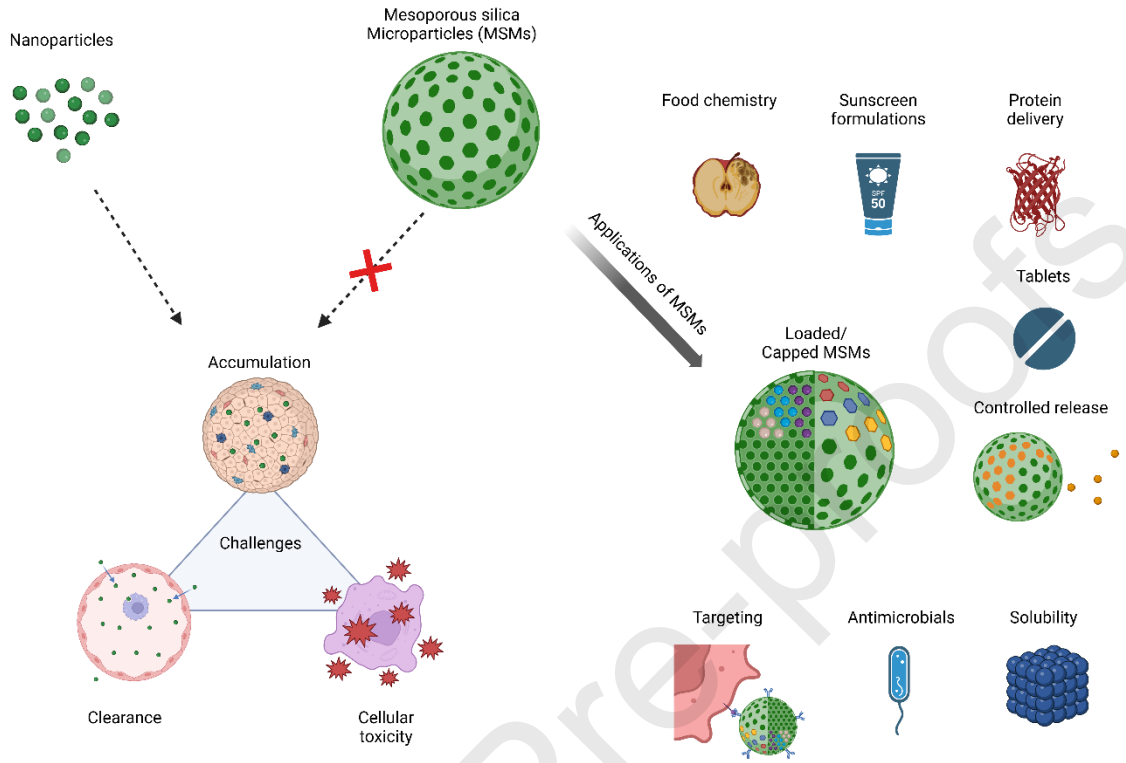
Graphical Abstract



Abstract

Nanotechnology has revolutionised pharmaceutical sciences, with mesoporous silica nanoparticles (MSNs) extensively studied as drug carriers. However, their clinical translation is hindered by challenges such as toxicity, tumour accumulation, and uncontrolled endocytosis. Mesoporous silica microparticles (MSMs) have emerged as a safer alternative, offering enhanced drug loading, controlled release, and improved formulation properties. MSMs facilitate protein delivery, solubility enhancement, and bioavailability improvement through pore size modulation, amorphous drug loading, and surface functionalisation. Additionally, they aid in overcoming multi-drug resistance and enable organ-specific targeting using aptamers or magnetic nanoparticles. Beyond drug delivery, MSMs enhance pharmaceutical formulations, with commercial products such as SYLOID®, Aeroperl®, and Neusilin® improving tablet performance and drug stability. Their role in controlled release systems further underscores their pharmaceutical potential. As research advances, MSMs offer promising strategies for precision medicine and optimised drug delivery, reinforcing their potential for future clinical applications.

Keywords:

Mesoporous silica; Nanoparticles; Microparticles; SYLOID; Targeting; Drug delivery.

1. Introduction

The term "Nanotechnology" was first introduced in 1974 by Professor N. Taniguchi, and shortly thereafter, Drexler expanded on Feynman's ideas. Drexler articulated the concept in his 1986 book, *Engines of Creation: The Coming Era of N* In recent decades, nanotechnology—particularly in medicine—has emerged as a transformative and commercially significant technology, enhancing healthcare strategies. Despite certain limitations, many pharmaceutical and medical device companies have embraced medical nanotechnology. For instance, it enables the safer administration of highly toxic drugs, such as cancer chemotherapeutics, by improving their safety profiles. Various nanocarriers are now widely used in biomedical applications and drug delivery [1].

Petros and his colleagues highlighted significant advancements in nanotechnology dating back to the mid-19th century. They documented that the first controlled-release polymer device was developed in 1964, following the conjugation of polymers with drugs in 1955. Furthermore, liposomes were first introduced by Bangham in 1965, while albumin-based nanoparticles (NPs) were developed in 1972. By 1973, liposome-based drugs had been formulated, and in 1983, the first approved micelle was introduced. The FDA further advanced the field by approving its first controlled drug formulation in 1989, followed by the market introduction of the first polyethylene glycol (PEG)-conjugated protein in 1990. These milestones have paved the way for innovative treatments across various medical fields [2-4]. According to Afzal et al., the evolution of NPs in both their types and applications began with poly(alkyl cyanoacrylate) NPs in 1991 and has since progressed significantly [4, 5]. The timeline of NP development, as detailed by Afzal et al., is shown in Figure 1.

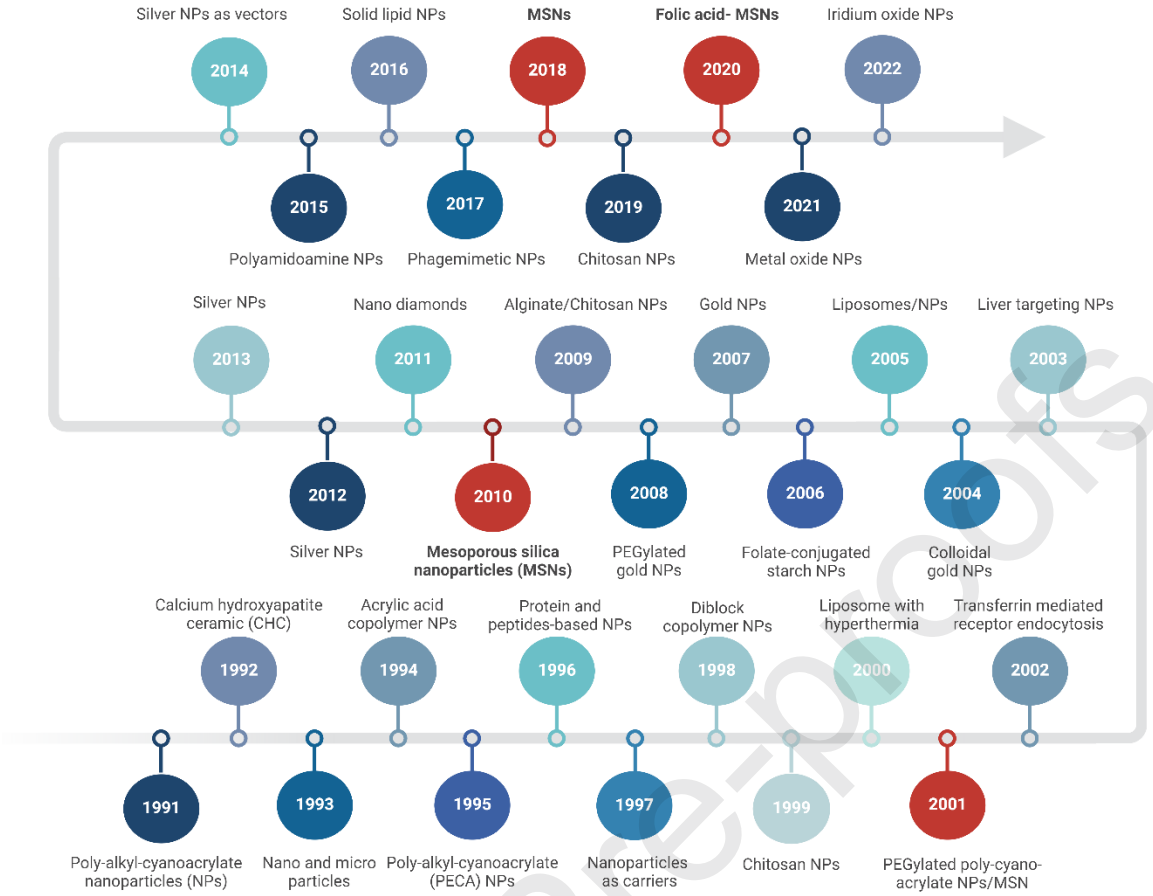


Fig. 1. The evolution of nanoparticles highlights a growing focus on carrier systems each year.

2. Mesoporous silica nanoparticles

Since the discovery of mesoporous silica-based materials in 1992, these materials have been extensively studied for their potential applications in material separation [6], catalysis [7], hybrid material preparation [8], and drug delivery [9]. These materials are synthesised through the derivatisation of silicon, a naturally occurring element in the human body, which plays a critical role in various physiological processes, particularly in the maintenance of bone and connective tissue health [10]. While they share the non-biodegradable nature of other nanoparticles, such as liposomes, mesoporous silica are characterised by their exceptional biocompatibility [11].

Mesoporous silica nanoparticles (MSNs) are considered among the most promising nanoparticles for drug delivery, owing to their large surface area, porous structure, biocompatibility, and the ease with which their surfaces can be functionalised, primarily due to the presence of silanol groups. These properties enable the formation of organic-inorganic hybrid carriers [12]. Furthermore, the incorporation of gatekeepers, or capping materials, allows for the entrapment of drug cargo within the porous structure, with release occurring in a controlled manner in response to specific stimuli, as opposed to liposomes, where drug release predominantly occurs through diffusion [13, 14].

In comparison to other drug delivery systems, particularly liposomes, MSNs offer several distinct advantages. Their stability in non-aqueous solutions facilitates the efficient loading of hydrophobic drugs using organic solvents. Additionally, their large and easily functionalised surface area permits the loading of hydrophobic drugs in aqueous environments, where the

surface acts as an effective reservoir for these compounds [15]. Moreover, mesoporous silica has emerged as a promising platform for mitochondria-targeted drug delivery, employing strategies to enhance both precision and therapeutic efficacy. Surface modifications with targeting ligands, such as triphenyl phosphonium, enable selective mitochondrial uptake by exploiting the organelle's negatively charged membrane. Stimuli-responsive systems, such as the use of gold nanoparticles or chitosan to cap pores, further facilitate controlled drug release at the mitochondrial site, thereby improving therapeutic outcomes [16].

In biological environments, MSNs offer superior stability relative to other nanoparticles, providing enhanced protection for encapsulated drugs. The rigid silica framework acts as a barrier against enzymatic degradation, which is particularly important for sensitive therapeutics, such as proteins and peptides, which are susceptible to breakdown in complex biological fluids. MSNs are particularly well-suited for the delivery of therapeutic proteins in oral drug delivery systems, where they shield proteins from enzymatic degradation and protect them from pH fluctuations in the gastrointestinal tract, thereby improving bioavailability. This dual protection ensures that therapeutic agents remain intact and stable until they reach their target site, thereby enhancing the overall efficacy of the treatment [17, 18].

Mesoporous silica particles are widely utilised in pharmaceutical applications, including drug delivery and detoxification. Functionalised MS, such as ethylenediaminetetraacetic acid-modified MS (MS-EDTA) for copper detoxification and amino-functionalised MS (MS-NH2) for methotrexate (MTX) removal, have demonstrated high adsorption efficiency. In vivo studies confirm their ability to mitigate toxicity safely, highlighting their potential for long-term therapeutic use and improved treatment strategies [19-21]. Despite their advantages, MSNs and other nanoparticle-based systems face challenges related to biocompatibility, long-term safety, and large-scale production. Understanding these limitations is crucial for optimising their clinical translation and ensuring their effectiveness in real-world therapeutic applications. This will be addressed in the following section.

2.1. Mesoporous silica preparation methods

As mentioned prior, MSNs are highly versatile materials that have drawn immense interest due to their ordered pore structures, high surface area, tuneable size, and ease of surface functionalisation. These properties make MSNs particularly suitable for applications in drug delivery, imaging, catalysis, and separation. Numerous synthetic strategies have been developed to tailor MSN features such as particle size, pore diameter, shape, and surface chemistry. Broadly, these synthesis methods can be categorised into conventional chemical methods**,** templating approaches**,** energy-assisted techniques**,** and aerosol or spray-based processes**.** Each category offers unique advantages in controlling the physicochemical characteristics of MSNs, enabling their customisation for specific applications. The preparation methods are highlighted in Figure 2 and reported in the following sections.

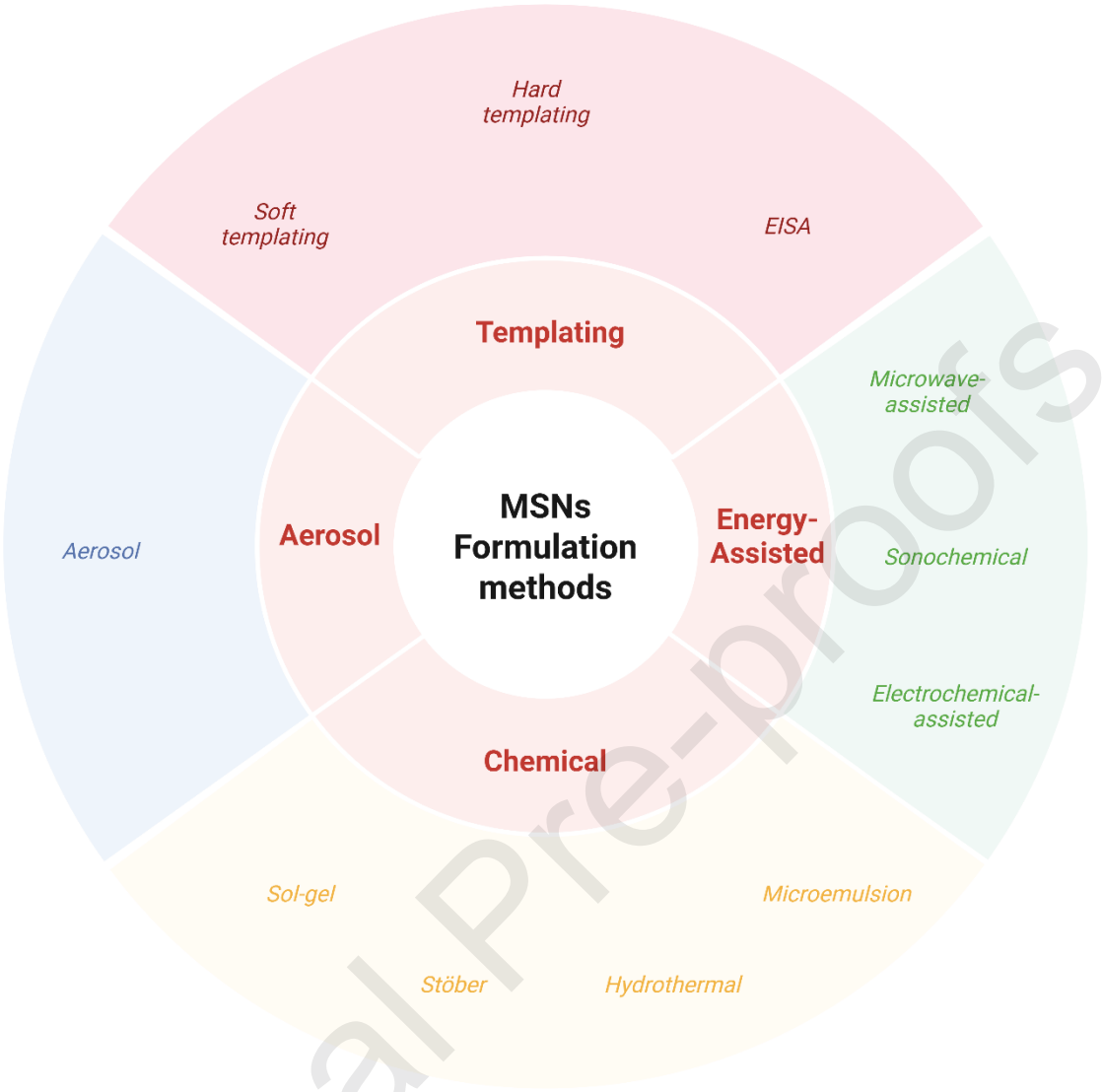


Fig. 2. MSN preparation methods. EISA refers to Evaporation-Induced Self-Assembly.

2.1.1. Chemical methods

Among the most established techniques for synthesising MSNs are conventional chemical methods. One of the most widely used approaches is the *sol–gel method*, which involves hydrolysis and condensation of silica precursors such as tetraethyl orthosilicate (TEOS) in the presence of surfactants like cetyltrimethylammonium bromide (CTAB). The surfactants self-assemble into micelles that act as templates, around which silica condenses. This method enables precise control over pore size and particle morphology by adjusting reaction parameters such as pH, temperature, and surfactant concentration [22]

A notable variation of this technique is the Stöber method, a classic sol–gel process that synthesises monodisperse silica nanoparticles by hydrolysing TEOS in an alcohol medium with ammonia as a catalyst. Recent advancements have adapted this method for MSN production by incorporating surfactants like CTAB to introduce porosity. These modifications enable precise control over particle size, pore structure, and surface properties, rendering MSNs ideal for drug delivery and biosensing applications [23].

The microemulsion method presents another chemical approach, utilising water-in-oil microemulsions as nanoreactors. Here, the aqueous phase containing silica precursors is dispersed as minute droplets within an oil phase stabilised by surfactants. These droplets provide a confined space for controlled hydrolysis and condensation reactions, resulting in uniform MSNs with tuneable sizes and morphologies. The method's flexibility lies in adjusting parameters such as surfactant concentration, oil-to-water ratio, and reaction conditions [24].

Similarly, the hydrothermal method synthesises MSNs by exposing silica precursors to high temperature and pressure within a sealed autoclave. This technique allows for precise control over particle morphology and pore architecture. Importantly, the cooling rate post-reaction significantly influences the final particle characteristics, making this method particularly suited to applications in drug delivery and catalysis [25].

2.1.2. Templating methods

Beyond conventional methods, templating approaches offer further sophistication in MSN design. These include both *hard* and *soft templating* strategies. In hard templating, rigid structures such as polymer latex or silica beads act as moulds around which silica precursors deposit. Subsequent removal of the template yields MSNs with well-defined structures and controlled porosity. In contrast, soft templating employs surfactants or block copolymers, which guide the self-assembly of silica into mesoporous architectures under milder conditions. This approach affords greater flexibility in tuning pore size and morphology [26].

The Evaporation-Induced Self-Assembly (EISA) method, a variation of soft templating, is particularly effective for synthesising mesoporous films. It involves co-assembly of surfactants and inorganic precursors during the solvent evaporation process. EISA enables the fabrication of highly ordered mesostructures, often crack-free and with controllable thickness, and is especially useful for energy and environmental applications [27].

2.1.3. Energy-assisted methods

Recent innovations have introduced energy-assisted methods to enhance MSN synthesis efficiency. The microwave-assisted method offers rapid and uniform heating, significantly reducing reaction times from hours to minutes. In one example, the sol–gel synthesis of spherical mesoporous SiO_2 and SiO_2–TiO_2 particles under microwave irradiation produced materials with a surface area of 800 m²/g and a pore size of 1.6 nm, demonstrating high mesoporosity and uniform morphology [28].The sonochemical method for preparing porous nanomaterials employs ultrasonic irradiation (20 KHz–10 MHz) that triggers cavitation, creating hot spots with high temperatures (up to 5000°C) and pressures (over 500 atm). This accelerates rapid nucleation and facilitates the formation of porous structures. The process includes primary sonication, which breaks bonds, and secondary sonication, which promotes chemical reactions leading to porous nanomaterials. Ultrasonic horns are primarily used for synthesis, with cleaning baths applied for specific applications [29].

The electrochemistry-assisted approach employs the electrochemical generation of hydroxide ions at the substrate–solution interface to synthesise mesoporous silica nanoparticles in a rapid and cost-effective manner. This method promotes the self-assembly of surfactant micelles and catalyses the polycondensation of silica precursors, resulting in nanoparticles with uniform pore sizes and high surface areas [30].

2.1.4. Aerosol methods

Finally, aerosol and spray techniques provide a scalable route to synthesising MSNs with advanced functionalities. The aerosol-assisted method involves the direct co-condensation of silicate and organosilicate species—bearing nonhydrolysable functional groups—in the

presence of surfactants such as CTAB and P123. This process produces organically modified mesoporous silica particles with a range of mesostructures, controlled pore sizes, tailored surface chemistries, and varied morphologies. As such, this method holds significant promise for catalyst and filler applications [31].

2.2. Preparation methods of mesoporous silica microparticles (MSMs)

In contrast to the synthesis of MSNs, which typically involves methods like sol–gel, micro-emulsion, and hydrothermal synthesis, the preparation of mesoporous silica microparticles (MSMs) often employs techniques such as spray-drying or precipitation. A spray-assisted method has been developed to synthesise MSMs, involving the preparation of a silica sol via a carbonation reaction, rapid gelation at high temperature, and subsequent rapid solvent removal. This approach allows for precise control over particle size and porosity, resulting in uniform microparticles suitable for applications like adsorption and chromatography [32, 33]. Furthermore, a wet chemistry method has been patented for synthesising mesoporous silica microparticles, involving the preparation of a sol by mixing silica precursors with water and a solvent, followed by gelation and drying processes. This method offers advantages such as simplicity and scalability, making it suitable for industrial applications [34].

According to Johansson [35], the synthesis of mesoporous silica particles can be tailored to produce either microscale rods or nanoscale particles, depending on specific reaction parameters. For instance, reducing the stirring time from 20 hours to just 5 minutes, followed by a static condensation period of 20 hours, facilitates the formation of monodispersed silica rods approximately 1–1.5 μm in length and ~0.5 μm in diameter [36]. This morphology arises due to the absence of shear flow and a lower rate of precipitation during static conditions. Similarly, using sodium metasilicate as a silica precursor and stirring for as little as 30 seconds can yield monodispersed rods, whereas continuous stirring throughout the synthesis results in fibre-like morphologies where rods act as building blocks [37]. The composition of the synthesis, particularly the HCl concentration plays a crucial role in determining the final morphology. Both TEOS and sodium metasilicate as silica precursors can produce rods of similar sizes (1–2 μm), with pore sizes tuneable between 5.5–12.5 nm by varying hydrothermal treatment times. Notably, sodium metasilicate reacts faster than TEOS, which may account for the shorter stirring times required [38]. Alternatively, the addition of inorganic salts such as KCl, combined with stirring for 8 minutes followed by static condensation for 20 hours, results in the formation of 1–2 μm long straight rods [39]. In contrast, the synthesis of MSNs typically involves extended stirring and high shear conditions, which promote the formation of smaller, spherical particles due to increased nucleation rates and shear-induced fragmentation. Higher surfactant concentrations, such as CTAB, facilitate the creation of smaller micelles, leading to nanoparticles with uniform pore structures. Accelerated reaction kinetics favour the generation of numerous nucleation sites, resulting in smaller particle sizes. Additionally, incorporating stabilisers or capping agents can prevent particle growth and aggregation, maintaining nanoscale dimensions [33].

Additionally, when designing mesoporous microparticles instead of nanoparticles, several key factors need to be considered. Synthesis methods such as spray-drying or precipitation are commonly used for microparticles, whereas sol-gel and hydrothermal methods are more typical for nanoparticles. Stirring time and conditions play a significant role, with shorter stirring times (minutes versus hours) followed by static condensation helping to achieve monodispersed microparticles. The selection of silica precursors, such as TEOS and sodium metasilicate, influences particle size and morphology, with sodium metasilicate reacting faster and requiring less stirring. Surfactants like P123 and CTAB, along with additives such as glycerol and ethanol, help control particle size, pore structure, and uniformity. Hydrothermal treatment duration also affects pore size, with longer treatments leading to larger pores. Finally, the concentration of reaction components, including HCl, silica precursors, and surfactants, determines the size, morphology, and uniformity of the microparticles. In

summary, designing microparticles involves carefully controlling these factors to achieve larger, uniform particles with specific pore structures, in contrast to the finer control needed for nanoparticles [35].

2.3. Challenges with MSNs and NPs

Despite the significant advantages of MSNs and NPs in general, their application as carriers for drug delivery is not without several notable challenges, which primarily include issues related to their safety, stability, and overall efficacy [40]. Nanomaterials designed specifically for biomedical applications must undergo thorough assessments to evaluate their cytotoxicity. According to ISO/TR 10993-22:2017, such evaluations should assess potential genotoxicity, which may cause DNA damage [41], and consequently lead to carcinogenicity, particularly in the case of metal-based nanomaterials [42]. Additionally, the reproductive toxicity of nanomaterials must be examined, as the accumulation of nanoparticles within tissues can result in the destruction of Sertoli cells [43]. Furthermore, immunotoxicity is a crucial concern, especially for metal oxide nanomaterials, which may provoke undesirable immune responses [44]. Hemocompatibility, referring to the interactions between nanomaterials and blood cells, is another vital aspect that requires consideration due to potential adverse effects stemming from the nanomaterials' surface chemistry [45]. Additionally, systemic toxicity must be addressed, as ultra-fine particles (<50 nm) may be absorbed into the bloodstream through the alveolar vasculature, presenting significant concerns for their biocompatibility and safety [46]. Furthermore, potential complications related to the implantation of such particles should also be assessed in preclinical and clinical studies [47, 48].

The cytotoxicity of nanomaterials is determined by various factors, including their composition, molecular structure, and notably, their size. Nanoparticles that exceed a certain size threshold (100 nm) may exhibit increased toxicity due to their potential to trigger stronger immune responses. These responses can lead to the activation of antibodies, which may result in immune clearance of the particles, causing inflammation and tissue damage. This can negatively affect the therapeutic efficacy of the nanoparticles and increase the risk of adverse effects in the body. [49]. According to Adabi et al., the biocompatibility of nanomaterials is influenced by several interrelated parameters, including the nanomaterials' shape, surface chemistry, and size [50].

The shape of nanomaterials plays a critical role in determining their biocompatibility. Acicular (needle-like) nanomaterials, for example, are known to induce higher toxicity, likely due to the more pronounced physical damage they inflict upon direct contact with biological tissues [51]. Rod-shaped particles are particularly prone to increased toxicity, as their orientation results in stronger Van der Waals interactions, which in turn facilitate heightened cellular interactions and potentially harmful effects. In contrast, spherical nanoparticles typically experience weaker interactions with biological systems and are generally better tolerated [52]. The shape of nanoparticles also has a notable impact on their internalisation by cells. Spherical nanoparticles tend to be more readily absorbed into the cell membrane, while elongated particles are more likely to align parallel to the membrane, owing to their higher length-to-radius ratio [53].

Surface charge is another critical factor influencing the biocompatibility of nanomaterials. The charge on the surface of nanoparticles profoundly affects their interactions with biological systems, including cell membrane interactions, penetration, protein adsorption, and stability in biological fluids [54]. Neutral nanoparticles typically undergo slower opsonisation compared to charged particles, which can impact their longevity and bioavailability. Interestingly, nanoparticles with a slight negative charge tend to accumulate more effectively in tumour tissues, owing to their ability to navigate biological barriers more efficiently. Positively charged nanoparticles, conversely, are more readily internalised by cells due to electrostatic

interactions between the positively charged nanoparticles and the negatively charged cell membranes [55-57].

In addition to shape and surface charge, size is a key determinant of nanoparticle behaviour and toxicity. Nanoparticles, due to their small size, possess the unique ability to penetrate cell membranes, enter the bloodstream, and reach organs, allowing them to target areas within the body that are otherwise inaccessible to larger particles [58]. As the size of bulk materials decreases below a critical threshold, the surface area increases exponentially, leading to a higher number of chemical molecules bound to the surface, which in turn enhances reactivity. This increased reactivity may contribute to the toxic effects of nanoparticles, which are often more pronounced than those associated with larger particles [59-61]. The size of nanoparticles also influences their distribution and accumulation within the body. Nanoparticles within the size range of hundreds of nanometres tend to accumulate in organs such as the liver and lungs, where their size facilitates retention. Moreover, nanoparticles in the size range of 20 to 150 nm are more likely to accumulate in tumour tissues via the enhanced permeability and retention (EPR) effect [62]. The EPR effect is a result of the rapid and disorganised angiogenesis typically observed in tumour tissues, which leads to an increase in the permeability of blood vessels and the disruption of vascular integrity within the tumour's neovasculature. This leaky vasculature allows nanoparticles to extravasate into the tumour interstitium more easily than they would in healthy tissues [63]. While the EPR effect benefits tumour targeting by facilitating the accumulation of anticancer agents, it can also present challenges, particularly due to the inconsistent accumulation of nanoparticles in tumour tissues as compared to other organs [64].

While MSNs possess remarkable characteristics for drug loading and delivery, they are not without limitations, particularly when it comes to their size, which directly impacts their therapeutic use. One of the major limitations associated with MSNs is their tendency to accumulate in the liver and spleen. For instance, spherical nanoparticles are predominantly found in the liver, while rod-like particles tend to accumulate differently Furthermore, particle size plays an important role in the extent of accumulation. Larger MSNs tend to accumulate in the liver and spleen in higher concentrations, especially following intravenous administration in ICR mice. However, smaller MSNs, particularly those below 80 nm, tend to escape degradation in the liver and exhibit slower degradation rates [65]. This slower degradation, while beneficial in some respects, raises concerns regarding the toxicological implications of prolonged retention in vital organs.

To assess the potential toxic effects of MSNs, studies have been conducted, particularly on hollow MSNs, in which the LD_{50} was determined in rats. The study found that at doses of 1280 mg/kg, the rats did not survive. However, when administered at a lower concentration of 20 mg/kg intravenously over a period of 14 days, no significant haematological or pathological changes were observed [66, 67]. Despite these findings, a significant drawback of nanoparticles for drug delivery remains their rapid clearance by the reticuloendothelial system (RES). The RES, which comprises phagocytic cells like macrophages, actively eliminates nanoparticles from circulation following systemic administration. This rapid clearance reduces the bioavailability of nanoparticles, significantly limiting their ability to reach the intended target site. Moreover, the accumulation of nanoparticles in the RES, particularly in the liver and spleen, can lead to off-target effects and potential toxicity, further complicating their clinical application. This rapid clearance poses a significant challenge to the sustained release and efficacy of nanoparticles for drug delivery [68, 69].

The challenges associated with nanoparticles and their effects, including MSNs, are summarised in Figure 3.

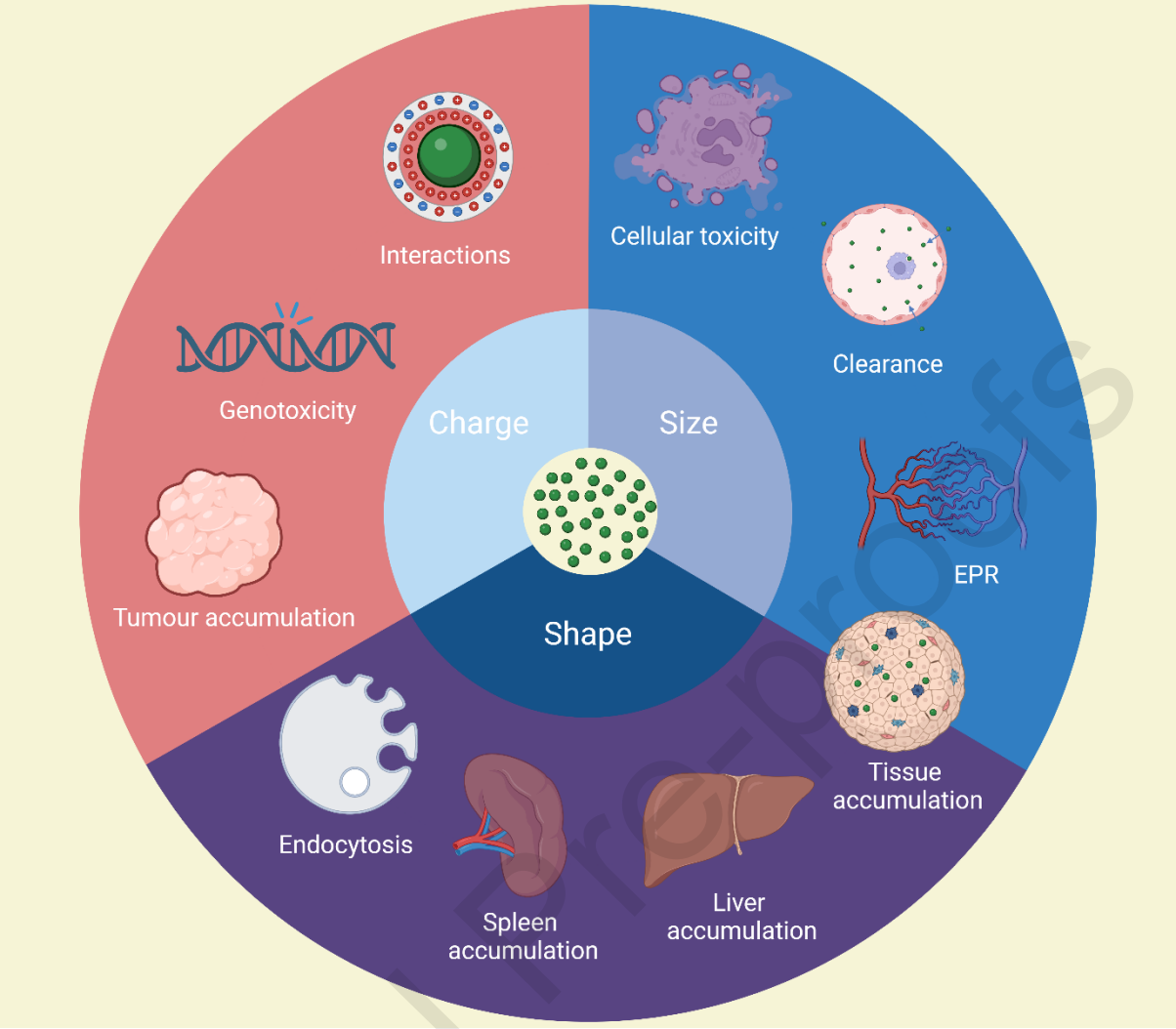


Fig. 3. The challenges associated with the use of nanoparticles depending on their size, charge, and shape.

3. Advantages of mesoporous silica microparticles

Microparticles are promising drug delivery systems (DDSs) where the size and shape of the particles play a crucial role in determining their interaction with cancer cells, ultimately influencing cellular uptake. Shapes with sharp features are particularly beneficial, as they enhance adhesion and internalisation, highlighting the importance of optimising microparticle design for targeted and efficient drug delivery [70]. One significant advantage of microparticles over NPs is their ability to provide localised drug delivery. Particles larger than 100 nm typically do not penetrate the interstitial space, remaining contained within the site of administration and being transported via lymphatic pathways. This localisation helps to reduce systemic distribution, thereby ensuring the safe encapsulation of potentially toxic compounds. Additionally, drugs can be handled more effectively as dried solid microparticles, which offer improved stability compared to their liquid counterparts. Moreover, the larger size of microparticles significantly reduces the foreign body response compared to smaller particles, minimising immune activation. These attributes make microparticles ideal for applications requiring sustained, localised drug release, while ensuring safety, stability, and minimal inflammatory responses in DDSs [71, 72].

The size of microparticles is also crucial in pulmonary drug delivery, as it determines where the particles will target within the tissue. For instance, particles smaller than 20 μm will undergo phagocytosis by macrophages once they enter the bloodstream. Particles smaller than 10 μm will reach the pulmonary alveolar region, where tissue permeability is high and favours gas exchange, optimising drug delivery to this area [73, 74]. In contrast, NPs used for transdermal drug delivery are transported by the lymph across the interstitium if their size is below 100 nm. This results in more systemic effects, which can be a disadvantage when aiming for a better retention profile in the skin, as it leads to less localised effects [71, 75].

Microparticles are generally designed for the controlled release of active agents through various routes of administration. However, intravenous application is restricted for microparticles, depending on their size, as larger particles may block blood capillaries, causing adverse effects [76]. On the other hand, NPs, due to their smaller size, can be administered via all known routes, including intravenous delivery, where their size-related limitations are less of a concern. The smaller size of NPs enables intracellular drug delivery, potentially allowing targeting of the cellular nucleus. This makes NPs particularly well-suited for intravenous applications aimed at specific cellular or subcellular sites. Microparticles, however, excel as reservoir systems for controlled release, making them ideal for the delivery of polypeptide or protein-based drugs [77].

Despite these advantages, the degradation and biodistribution of porous carriers are critical factors affecting their performance. Controlling the size and porosity of the carriers is essential to achieve tight regulation over drug release kinetics and carrier degradation [78]. Fuentes et al. studied the degradation of different-sized porous carriers under simulated physiological conditions [79]. The study focused on three types of mesoporous silica, comparing nano- and microsized porous MCM-41 (a type of MSM). They found that the size of the carriers remained unchanged after functionalisation, with the loaded silica carriers maintaining their structure after treatment with artificial lysosomal fluids (ALF). This suggested that the loading and functionalisation process helped preserve the particles' structure. While MSNs can cross intestinal barriers and reach cellular and subcellular compartments, they tend to accumulate in these areas after oral ingestion, potentially causing toxic effects [80]. This issue, however, was not observed with microparticles, which tend to be eliminated without significant accumulation, thereby reducing the risk of toxicity [79].

Another notable advantage of MSMs is their relatively lower cytotoxicity compared to NPs. Santos et al. assessed the toxicity of mesoporous silica carriers against Caco-2 cells [81]. They found that the cytotoxicity of silica carriers was size-dependent, with larger mesoporous

microparticles (those exceeding 38 μm) showing a lesser decrease in metabolic activity. This observation was attributed to the surface chemistry of the particles, as smaller particles tend to generate more reactive oxygen species (ROS), resulting from their increased cell-particle interactions. Furthermore, longer incubation times exacerbated the cytotoxicity of smaller particles, leading to mitochondrial ATP depletion and increased ROS production, which causes cell apoptosis and membrane damage. Another study focused on the cytotoxicity of porous silica-based carriers, aiming to assess their toxicity for ocular drug delivery [82]. Korhonen et al. found that the surface treatment of microparticles was critical to ensuring cell tolerance. They reported that thermally oxidised porous silicon particles maintained the viability of human lens epithelial cells, in contrast to non-treated particles. Moreover, both negatively and positively charged porous silicon particles were tolerated by human corneal epithelial (HCE) and retinal pigment epithelial (ARPE-19) cells at concentrations not exceeding 200 μg/ml. Furthermore, particles with hydrophilic properties, particularly those amino grafted, enhanced drug dissolution and improved interaction with negatively charged cells [82].

Overall, while microparticles provide distinct advantages in controlled and localised drug delivery, their performance is influenced by several factors, including size, shape, surface chemistry, and degradation behaviour. These characteristics determine not only their interaction with target tissues but also their toxicity and ability to reach specific sites of action. As such, optimising these factors is crucial for maximising the potential of microparticles as drug delivery systems, particularly in applications requiring sustained release, targeted delivery, and minimal toxicity.

4. Mesoporous silica microparticles applications

Given the aforementioned limitations of NPs, particularly MSNs, research has increasingly focused on MSMs, which have been widely explored in the literature for various applications using different carrier systems. For instance, SYLOID, an MSM available in multiple grades and pore sizes, has been reported to enhance the solubility of lumefantrine a fluorene derivative used in malaria treatment [83]. Additionally, SYLOID has been utilised as a filler in dental composites, in ecotoxicology applications [84], and for improving the dissolution of carvedilol [85]. Another notable example of MSMs is Neusilin®, a series of amorphous magnesium-alumino-metasilicate-based MSMs, which have been employed to enhance powder properties and tablet properties [86]. Neusilin® has been reported to convert liquid self-nanoemulsifying drug delivery systems (SNEDDS) into solid-SNEDDS [87], , improve the tabletability and solubility of atorvastatin calcium [88], and investigate solid-state interactions with ibuprofen [89]. The applications and carriers of MSMs are summarised in Figure 4 and elaborated upon in the subsequent sections.

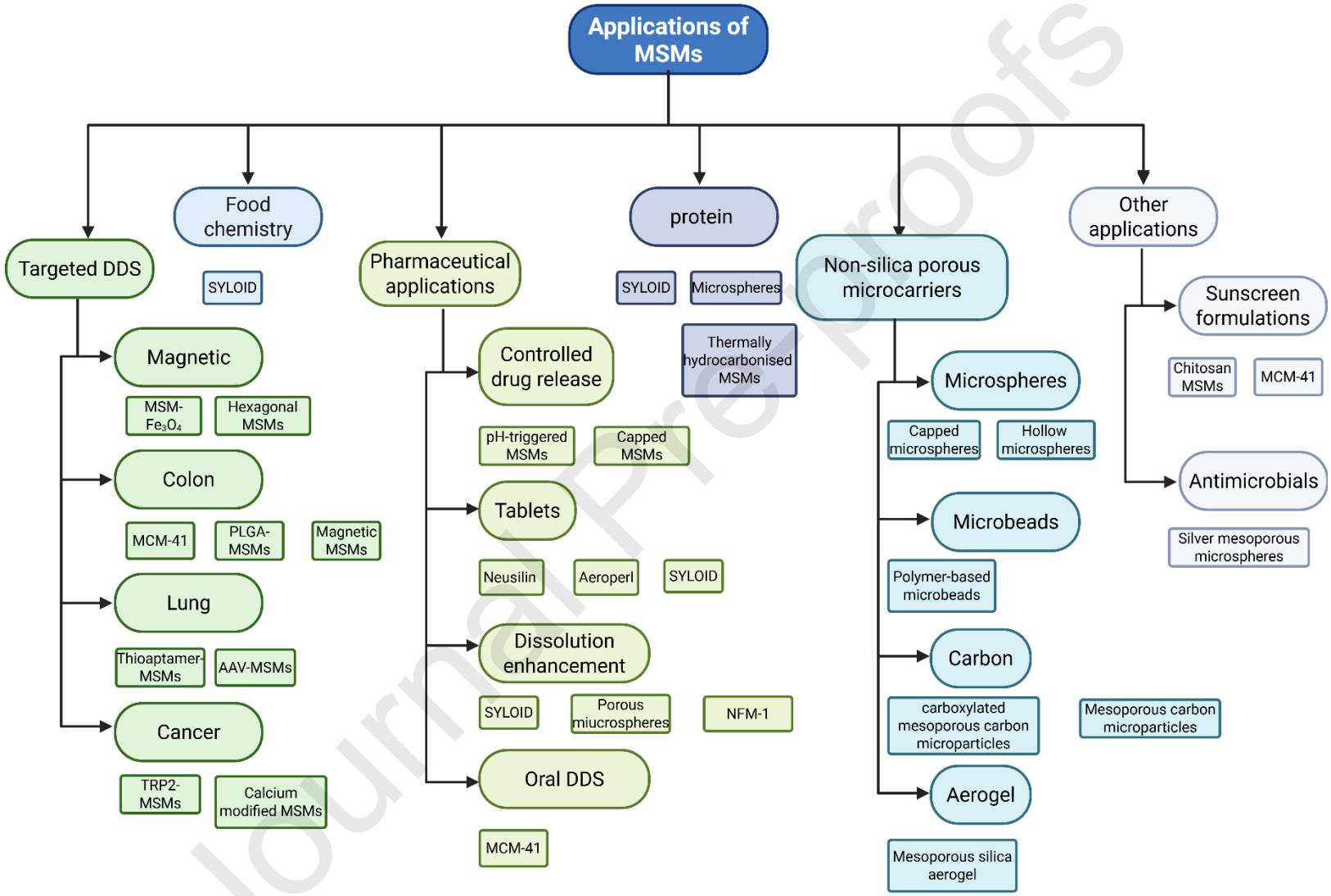


Fig. 4. The uses of MSMs in numerous applications, highlighting the used carrier in each use.

4.1. Food chemistry and related applications

One of the notable applications of MSMs is in food chemistry, where they have been utilised to enhance the properties of food products. A notable example involves the use of folic acid-loaded pH-responsive MCM-41 to fortify yoghurt and regulate the bioaccessibility of folic acid [90]. This approach facilitated the controlled release of folic acid under conditions closer to neutral pH rather than acidic environments. Importantly, the incorporation of MSMs did not alter the physicochemical properties of the yoghurt or compromise the viability of lactic acid bacteria, thereby preserving the product's quality.

Another significant application of MSMs involves their role in improving the antimicrobial efficacy of plant-derived compounds in sugar-based food products such as fruit juices [91]. In this study, the antimicrobial activity of vanillin, eugenol, and carvacrol-loaded MCm-41 was evaluated against Escherichia coli and the yeast *Zygosaccharomyces rouxii* (*Z. rouxii*). The researchers aimed to immobilise these antimicrobial agents on MSMs to enhance their interaction with bacteria, given their lipophilic properties. This immobilisation improved their efficiency by promoting sustained release and interaction with microbial cells. The results demonstrated that combining eugenol and carvacrol exhibited an additive effect in grape juice and a synergistic effect in apple juice against *Z. rouxii*, indicating the potential of MSMs in enhancing food preservation strategies.

Beyond food-related applications, silica microparticles have been investigated for their potential use as insecticides [92, 93] offering a safer alternative to chemical insecticides for controlling arthropods in food crops [94]. Faliagka et al. assessed the insecticidal properties of various grades of SYLOID MSMs by evaluating their desiccation effects upon contact with arthropods. The study tested three pest species—*Sitophilus oryzae*, *Tribolium confusum*, and *Aphis fabae*—using three types of MSMs: SYLOID ED3, SYLOID ED5, and SYLOBLOC S200. The findings revealed that mortality rates increased to 90% after seven days of exposure to silica particles, highlighting the potential efficacy of MSMs in insect pest management, particularly for storage protection [94].

4.2. Sunscreen formulation

Prolonged exposure to sunlight has detrimental effects, including skin burns, premature ageing, DNA damage, and skin cancer, primarily due to ultraviolet (UV) radiation [95]. To mitigate these harmful effects, UV filters are employed to enhance protection, with their efficacy depending on their nature—whether organic or inorganic. However, their effectiveness is often compromised by issues such as incompatibility and photocatalysis-induced degradation. Consequently, various strategies have been explored to improve filter compatibility, including nanoparticle entrapment. Despite these advancements, challenges persist, including leakage and polymer degradation, which limit the long-term stability and efficacy of UV filters [96, 97]. In this regard, porous carriers offer a promising alternative due to their biocompatibility, chemical stability, and thermal resilience [98].

MSMs have demonstrated the potential to enhance the stability and photoprotective efficacy of octyl methoxycinnamate (a widely used sunscreen agent) by mitigating photochemical degradation and reactive oxygen species (ROS) generation through a chitosan-modified MSM platform [99]. This novel approach significantly improved the stability of the sunscreen agent, reducing degradation to 20% after three hours, compared to 80% degradation observed within one hour in the absence of MSMs. Additionally, the incorporation of chitosan-MSMs effectively suppressed ROS generation by 99% and enhanced the viability of fibroblasts exposed to UV light. These beneficial effects were attributed to the presence of chitosan on the surface of MSMs, where the formation of a protective layer was facilitated by interactions between protonated amino groups of chitosan and hydroxyl groups present on the silica surface.

Another MSM-based strategy for improving the delivery and stability of octyl methoxycinnamate was reported by Ambrogi et al. [100]. In their study, MCM-41, an ordered mesoporous silica material with a high surface area and hexagonal pore structure, was utilised as a carrier. Octyl methoxycinnamate was loaded into MCM-41, followed by the application of a cosmetic ingredient as a pore-capping agent, using a hot-melt method with several candidates, including tristearin, ceresin, and stearyl alcohol. The results demonstrated that the release of octyl methoxycinnamate was significantly prolonged, with 60% and 21% release after 480 minutes from unloaded and MCM-41-loaded formulations, respectively. Additionally, the formulations incorporating capping materials exhibited even lower release values, indicating further controlled release.

4.3. MSMs as drug delivery carriers

Over the past two decades, there has been growing interest from both scientists and the pharmaceutical industry in MSNs and MSMs as drug delivery systems. These systems, designed to enable controlled release and targeted delivery, are highly regarded for their distinctive physicochemical properties. Porous silica carriers provide a high drug-loading capacity, facile functionalisation, and excellent biocompatibility, making them well-suited for enhancing the therapeutic efficacy and safety of various pharmaceutical formulations [101].

Several factors influence the loading efficiency of MSMs, including the method of drug incorporation and the nature of interactions between the carrier and the active pharmaceutical ingredient (API) [102]. Additionally, certain factors are specific to the physicochemical properties of the API itself. Salonen et al. investigated these parameters by loading five model drugs into MSMs to assess their loading efficiency and release characteristics in oral drug delivery [103]. Their findings demonstrated that surface properties govern API interactions, thereby influencing loading affinity and efficiency, with values ranging from 9% to 45%. Furthermore, the release profile was dependent on the dissolution behaviour of the API, where drugs with a high dissolution rate exhibited delayed release from the porous structure. The following sections will explore the application of MSMs as drug carriers in more detail.

4.3.1. Protein delivery

MSMs, such as SYLOID, have been extensively explored for protein loading in various applications. Al Tahan et al. investigated the loading efficiency of SYLOID XDP 3050 with two proteins, octreotide and bovine serum albumin (BSA), using three different solvents [18]. Their findings demonstrated that octreotide exhibited higher recovery and diffusion into the porous structure due to its smaller molecular size and greater solubility compared to BSA. The primary mechanism governing protein loading was diffusion, as described by the Stokes-Einstein equation, which is influenced by factors such as protein size and solvent viscosity. Larger proteins, such as BSA, displayed lower diffusion rates due to their greater hydrodynamic radius, while solvent viscosity further influenced protein movement within the porous network. Both protein size and solvent properties played a crucial role in determining the efficiency and uniformity of protein encapsulation. Additionally, interactions between the solvent and silica surface were found to impact loading efficiency, as highly polar solvents reduced loading due to competitive interactions with the charged silica surface [18, 104].

Another study reported the use of SYLOID for protein delivery, focusing on the development of novel capped silica carriers [105]. In this approach, SYLOID XDP 3050 was functionalised with stearic acid at different loading concentrations, leading to the formation of needle-like structures on the silica surface. These structures were attributed to the recrystallisation of stearic acid due to the loading process while maintaining its crystalline structure. According to the authors, this platform holds significant potential for enhancing the oral delivery of proteins. The presence of a hydrophobic stearic acid coating is expected to facilitate oral protein delivery by improving membrane permeability and overcoming gastrointestinal barriers [106].

Beyond drug delivery, mesoporous silica has also been investigated for protein separation. Li et al. developed a novel nickel oxide (NiO)-decorated submicrosphere system, incorporating a magnetic core and a mesoporous shell to facilitate the efficient separation of histidine-tagged proteins [107]. The inclusion of NiO provided a selective affinity for histidine residues, while the magnetic core conferred strong magnetism, allowing for rapid separation in the presence of an external magnetic field. Additionally, the mesoporous shell exhibited a flower-like structure, enhancing the particle's surface area and pore volume, thereby improving protein loading capacity. The results demonstrated that the newly developed system exhibited exceptionally high affinity for histidine-tagged proteins, achieving a separation efficiency of 93% from mixed protein solutions.

Given the recognised biocompatibility of mesoporous silica, MSMs have been increasingly explored as carriers for protein delivery. A novel electrochemically designed MSM-based device was recently developed for the controlled release of proteins, incorporating chitosan as a functional modification [108]. This approach utilised MSMs loaded with insulin and BSA as model proteins, demonstrating a strong affinity for both biomolecules. The inclusion of chitosan played a pivotal role in modifying the in vitro release profile, as the cumulative release decreased from approximately 75% to 55% at pH 7.4. Furthermore, chitosan functionalisation provided additional advantages, including enhanced mucoadhesion and improved permeation, making this platform highly promising for mucosal drug delivery applications.

MSMs have also been employed for the delivery of peptide-based drugs, including agonists and antagonists. Kilpeläinen et al. investigated the use of thermally hydrocarbonised MSMs for the in vivo delivery of lys-GHRP6, a ghrelin antagonist (GhA) used to modulate food intake and blood pressure in mice [109]. Their results demonstrated that GhA was successfully incorporated into the MSMs, achieving a loading efficiency of 20% w/w while maintaining its pharmacological activity. Moreover, the loaded carrier exhibited a controlled and sustained release profile without eliciting an acute cytokine response following a single administration, highlighting its potential for safe and prolonged therapeutic use.

Another study explored the application of thermally hydrocarbonised MSMs for the delivery of melanotan II, a peptide hormone involved in skin pigmentation [110]. The findings indicated that the loaded peptide exhibited a sustained release profile while preserving its pharmacological activity in vivo. Notably, melanotan II is known to induce tachycardia and suppress water intake as part of its pharmacological effects. However, these effects on heart rate were observed to diminish after 8 hours in the case of the unloaded peptide, whereas the loaded MSM formulation extended this effect to 12 hours. This prolonged action suggests that MSM-based delivery systems can effectively modulate peptide pharmacokinetics, potentially reducing dosing frequency and improving patient compliance. Collectively, these studies underscore the versatility of MSMs in protein and peptide delivery, demonstrating their ability to enhance bioavailability, prolong release, and improve targeting. By leveraging their high surface area, tuneable pore structure, and functionalisation capabilities, MSMs represent a promising platform for the advancement of protein-based therapeutics. Figure 5 provides a summary of the MSM-based carriers that have been reported for protein delivery.

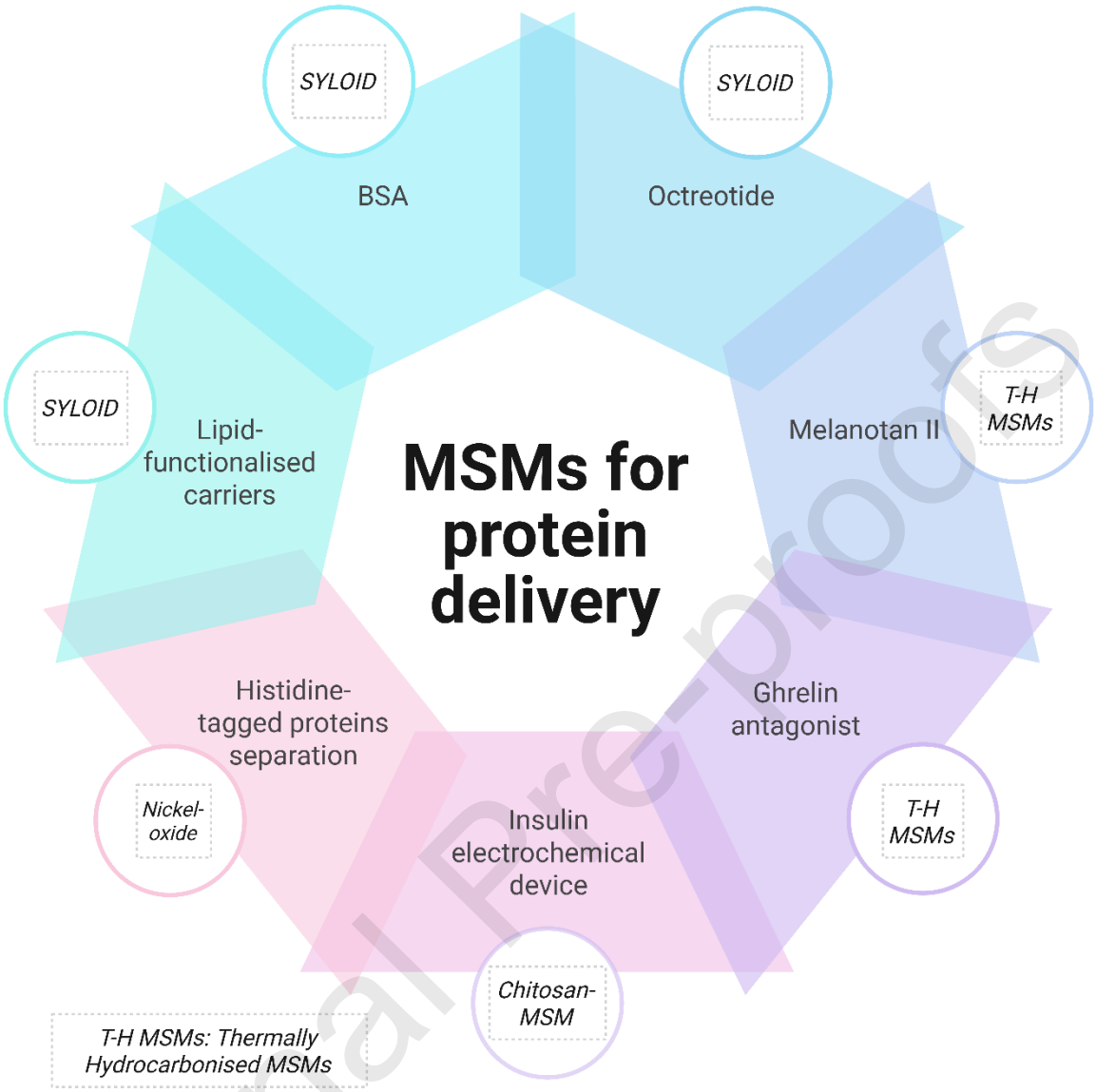


Fig. 5. MSM-based carriers for protein delivery.

4.3.2. Controlled release

Controlled drug delivery is an advanced approach designed to enhance therapeutic efficacy by maintaining localised drug concentrations at a steady level over an extended period, particularly in hard-to-reach areas of the body. This method enables sustained drug release, improving treatment precision while minimising systemic exposure and reducing potential adverse effects [111]. Several controlled DDSs have been developed, including capped DDSs, in which capping materials regulate drug release, preventing premature leakage and ensuring controlled delivery [14]. Another widely utilised approach involves pH-responsive materials, which detect pH variations and undergo polymeric chain transformations to facilitate targeted drug release. This mechanism is particularly beneficial in stimuli-responsive systems, as it ensures drug delivery in specific physiological environments, such as acidic tumour sites or the gastrointestinal tract, thereby enhancing therapeutic efficacy while minimising unintended

systemic distribution [112]. The following section focuses on the use of MSMs as controlled DDSs.

MSMs have been investigated as triggered-release carriers due to their tuneable surface properties and ability to incorporate responsive modifications. Samart et al. developed a poly(acrylic acid)-grafted mesoporous silica system designed as a pH-triggered drug carrier, using indigo carmine as the model drug [113]. This approach exploited the swelling behaviour of poly(acrylic acid), which shrinks at pH 2 and expands at pH 4. The modified MSMs exhibited pH-controlled release, with less than 10% of the drug cargo being released at pH < 2, whereas drug release increased to 90% at pH > 5 due to polymer expansion. The authors suggested that this novel carrier could serve as a stable drug delivery system for the lower gastrointestinal tract by protecting the loaded drug in acidic environments.

Another study explored controlled drug release from MSMs using capped systems for the delivery of rhodamine B via an amino-functionalised oligonucleotide 5′ containing a K^+ aptamer [14]. In this approach, gold nanoparticles (NPs) served as pore capping agents, preventing premature release. The system exhibited zero drug release in the presence of K+, whereas release was triggered when K+ was introduced into the solution. The authors attributed this effect to the detachment of gold NPs from the MSM surface, caused by the self-assembly of single-stranded DNA into a G-quadruplex structure upon K^+ binding, ultimately enabling controlled drug release.

4.3.3. Tablets

Tablets remain the most widely utilised drug delivery systems (DDSs) due to their ease of manufacture, cost-effectiveness, and patient compliance. However, despite their widespread use, fewer than 20% of pharmaceutical products are formulated as tablets [114]. This limitation arises because APIs and excipients must possess sufficient compactability and compressibility to withstand the mechanical stress of compression without compromising stability or dissolution properties [114-116]. To overcome these challenges, various additives and carrier materials are incorporated into tablet formulations to enhance their physical and mechanical properties, ensuring optimal performance in terms of stability, bioavailability, and drug release kinetics. Among these materials, mesoporous silica has gained significant attention due to its excellent biocompatibility, high surface area, and non-toxic nature, making it a valuable component in pharmaceutical formulations [117]. The MSM-based carriers used in tablet formulations are illustrated in Figure 6 and discussed in the following sections.

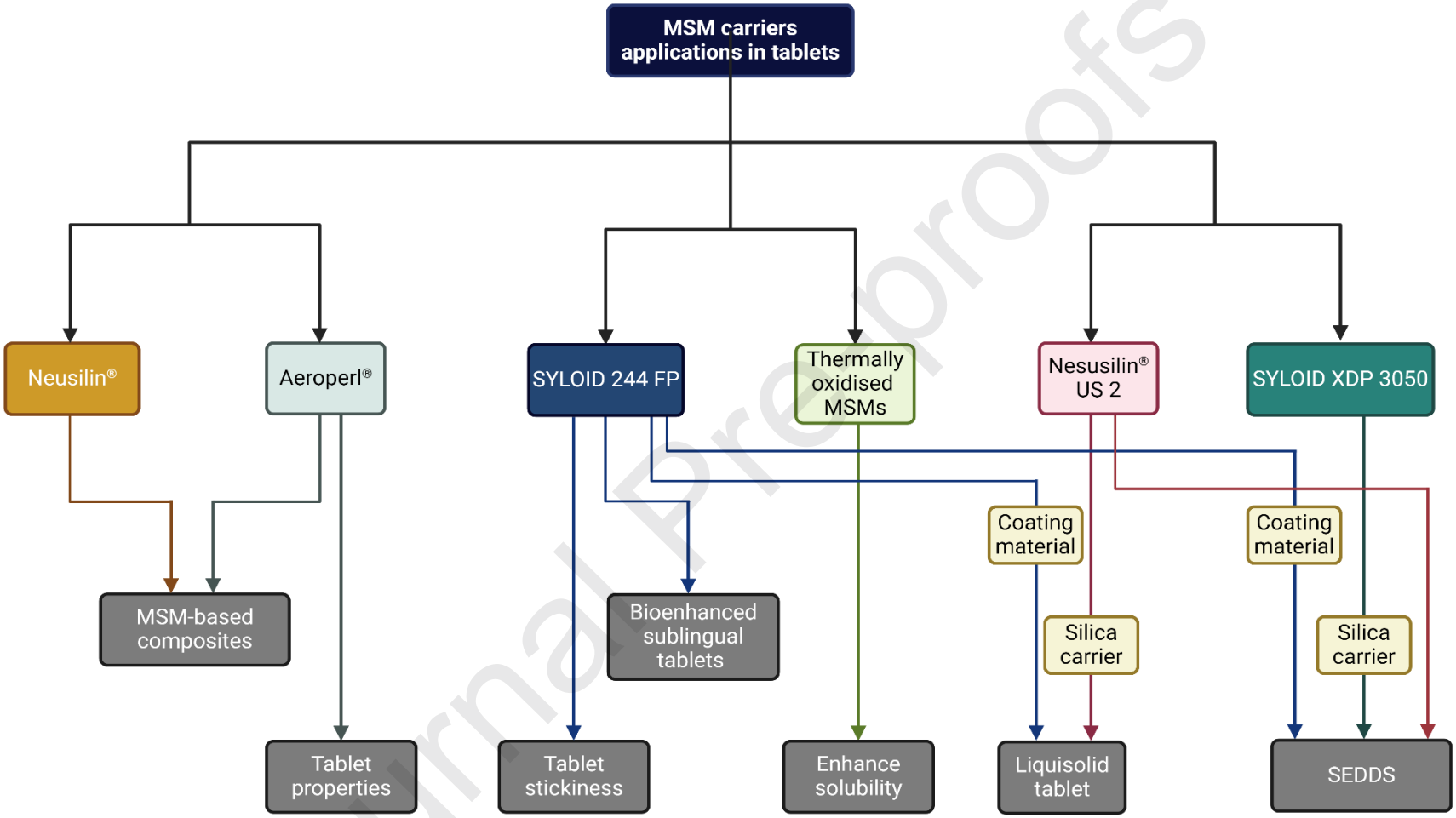


Fig. 6. The MSM carriers in tablets with each carrier accompanied to its specific applications. SEDDS refers to self-emulsifying drug delivery system.

The incorporation of MSMs in tablet formulations serves multiple functions beyond their primary role as carriers for active pharmaceutical ingredients (APIs). MSMs have been extensively employed to improve powder flowability, tablet disintegration, drug dissolution, and content uniformity while also addressing formulation challenges such as tablet sticking and poor compressibility. Their application extends to advanced drug delivery systems, including self-emulsifying drug delivery systems (SEDDS) and liquisolid tablets, thereby enhancing the bioavailability of poorly soluble drugs.

One prominent application of MSMs is their role in optimising the properties of bioenhanced sublingual tablets. A notable example is the commercially available SYLOID 244 FP, which was incorporated into a tablet formulation for zolmitriptan, a drug with limited permeability [118]. The results demonstrated that SYLOID 244 FP significantly enhanced the flowability of the powder blend by absorbing substantial amounts of liquid while maintaining the blend's dryness. Additionally, its inclusion facilitated tablet disintegration by improving the capillary wetting of granules, reducing interparticle aggregation, and forming a silica coating around other excipients, thereby optimising tablet performance.

Beyond their impact on powder flow and disintegration, MSMs have been employed to enhance the content uniformity of powder blends prepared for direct compression [119]. Sun et al. investigated the integration of different APIs into Neusilin® and Aeroperl® (commercially available MSMs) to develop MSM-based composites. Excipients were subsequently added before the tableting process. The findings indicated that tablets prepared using Aeroperl® exhibited superior physical stability compared to those formulated with Neusilin®. This difference was attributed to Aeroperl®'s higher surface area and the monolayer area of the drug molecule. It was observed that the monolayer area of the drug was smaller than the surface area of Aeroperl® but larger than that of Neusilin®, thereby reducing the likelihood of crystal nucleation. This feature was particularly advantageous, as it contributed to enhanced dissolution and improved content uniformity upon drug loading into the porous carrier [119].

Tablet sticking to the compression punch is a prevalent issue in pharmaceutical manufacturing, affecting the efficiency and quality of tablet production. MSMs have been investigated for their ability to mitigate this challenge. Parekh et al. examined the influence of MSM-based glidants—specifically Aerosil®, talc, and SYLOID 244 FP—on the stickiness of ketoprofen tablets [120]. Their results revealed that increasing the MSM concentration effectively reduced tablet stickiness by minimising the contact surface area of ketoprofen, reducing electrostatic interactions, and forming a protective coating around drug molecules. These factors collectively altered the cohesion properties of the formulation, improving its manufacturability.

However, while MSMs offer distinct advantages in preventing tablet sticking, their inclusion can significantly influence tabletability, particularly in formulations lacking diluents. For instance, when Aeroperl® was used in direct compression formulations without diluents, the resulting tablets exhibited poor mechanical strength. This was attributed to the large particle size and poor compaction properties of Aeroperl®. The addition of diluents markedly improved compressibility and mechanical integrity, underscoring their necessity in silica-based tablet formulations [119, 121].

The modification of MSMs has also been explored as a means to enhance drug solubility and permeability. A study focusing on indomethacin-loaded thermally oxidised MSMs demonstrated that such modifications significantly improved drug dissolution and permeability [122]. The modified MSMs facilitated an increase in the dissolution rate, with approximately 85% of the drug dissolving in comparison to only 40% for the unmodified formulation. Furthermore, permeability was enhanced, likely due to the thermally oxidised MSMs increasing the local drug concentration and inducing drug supersaturation, leading to improved absorption.

Another noteworthy application of MSMs is their use in liquisolid-based compacts, where they serve as both loading and coating carriers. SYLOID 244 FP and Neusilin® US2 have been employed in such systems to enhance drug solubility and tablet properties [123, 124]. This approach involves the incorporation of a water-insoluble drug into a porous carrier, followed by a coating material to optimise powder flow and prevent adhesion during compression. One specific application of this technique was in the formulation of progesterone with polyethylene glycol (PEG) 400 dispersions to improve solubility and bioavailability [123]. Given that progesterone exhibits polymorphism, the liquisolid formulation facilitated enhanced dissolution by improving wettability, enabling molecular dispersion of the drug, and stabilising progesterone in both its amorphous form and the more stable β-form.

Further research by Vraníková et al. investigated the impact of the SYLOID-to-carrier ratio on the successful formulation of liquisolid-based tablets [125]. Their study revealed that the choice of MSMs significantly influenced powder flow properties. Notably, SYLOID-based materials negatively affected powder flow compared to Aerosil®, a phenomenon attributed to the larger particle size of SYLOID. At high carrier-to-coating ratios, SYLOID's larger particles resulted in incomplete coverage of the primary carrier surface, leading to an increased presence of unattached coating particles. These particles exhibited stronger adhesive forces, causing greater cohesion within the powder blend. Additionally, the irregular morphology of SYLOID contributed to this effect, as non-spherical particles were less effective as glidants compared to the more spherical Aerosil® particles, which provided better surface interaction without requiring extensive rearrangement.

MSMs have also been employed in the development of solid self-emulsifying drug delivery systems (S-SEDDS) to enhance the oral bioavailability of poorly soluble drugs such as cabazitaxel [126]. SEDDS formulations are designed to self-emulsify upon contact with gastrointestinal fluids, forming emulsions, microemulsions, or nanoemulsions depending on the composition of the oily phase and surfactant [127-129]. In this approach, SYLOID XDP 3050 and SYLOID 244 FP were utilised as the SEDDS carrier and coating material, respectively. Cabazitaxel was initially loaded into the SEDDS, followed by the addition of the two silica types. SYLOID XDP 3050 was selected due to its optimised particle size and pore size, which facilitated efficient drug loading and tablet formulation. Subsequently, SYLOID 244 FP was employed as a coating material to facilitate SEDDS adsorption onto the surface of SYLOID XDP 3050, ensuring uniform morphology. In vivo studies in rats demonstrated a significant increase in cabazitaxel bioavailability when incorporated into the SEDDS-SYLOID complex, highlighting the potential of MSMs in enabling the transformation of SEDDS into stable oral dosage forms [126]. A similar application was reported for zafirlukast, where MSMs were used to enhance bioavailability through SMEDDS [130]. In this approach, Neusilin® US2 was employed to solidify zafirlukast-based SMEDDS, leading to the successful development of a tablet formulation with a significantly improved dissolution profile compared to the commercially available zafirlukast formulation. Pharmacokinetic studies further revealed that the MSM-SMEDDS system resulted in a notable increase in the maximum plasma concentration (Cmax) and area under the curve (AUC) values under both fed and fasted conditions, demonstrating enhanced drug absorption and bioavailability [130]. Overall, MSMs have emerged as highly versatile excipients in tablet formulations, offering multiple functional benefits beyond API loading. Their incorporation enhances powder flowability, dissolution, permeability, and content uniformity, while also addressing key formulation challenges such as tablet sticking and poor compressibility. Furthermore, their integration into advanced delivery systems such as liquisolid compacts and SEDDS highlights their potential in improving drug bioavailability. Despite these advantages, considerations such as particle size, surface morphology, and excipient interactions must be carefully evaluated to optimise MSM-based formulations. Future research should continue to explore MSMs as a strategy for overcoming formulation challenges and enhancing the bioavailability of poorly soluble drugs.

4.3.4. Enhancement for dissolution and permeability

Oral drug delivery remains the most widely preferred route for pharmaceutical administration due to its ease of use, high patient compliance, and cost-effectiveness. However, effective drug absorption via the gastrointestinal (GI) tract is contingent on the drug's ability to dissolve rapidly, as dissolution is a key determinant of bioavailability and the onset of therapeutic action. The rate and extent of drug absorption are significantly influenced by its solubility under physiological conditions. Unfortunately, many drugs exhibit poor aqueous solubility, posing a substantial challenge in pharmaceutical formulation. This solubility limitation not only affects numerous commercially available drugs but also hinders the clinical translation of promising drug candidates in development. Consequently, there is a pressing need for innovative formulation strategies to enhance drug solubility and dissolution, thereby improving therapeutic efficacy and patient outcomes [131-134].

Mesoporous silica have emerged as a promising class of excipients for addressing solubility-related challenges in oral drug delivery. Classified as "generally recognised as safe" (GRAS), silica is biodegradable and chemically versatile, allowing for surface modifications that optimise drug loading and release kinetics. The highly tenable pore size, morphology, and surface chemistry of MSMs facilitate strong drug-carrier interactions, which play a crucial role in preventing drug crystallisation and enhancing dissolution kinetics. A significant advantage of these materials lies in their ability to accommodate drug molecules in an amorphous state within their porous framework. Since amorphous forms of drugs typically exhibit superior dissolution rates compared to their crystalline counterparts, MSMs effectively promote faster and more complete drug dissolution. Additionally, these porous carriers provide a controlled release profile by dispersing the drug molecules within their internal structure, further preventing recrystallisation and improving oral bioavailability. This multifaceted functionality underscores the potential of mesoporous silica as an advanced platform for formulating poorly water-soluble drugs, thereby expanding the therapeutic possibilities for challenging pharmaceutical compounds [135-137]. The following section will explore the specific applications of MSMs in enhancing drug dissolution and solubility, with a summary of key carrier materials provided in Figure 7.

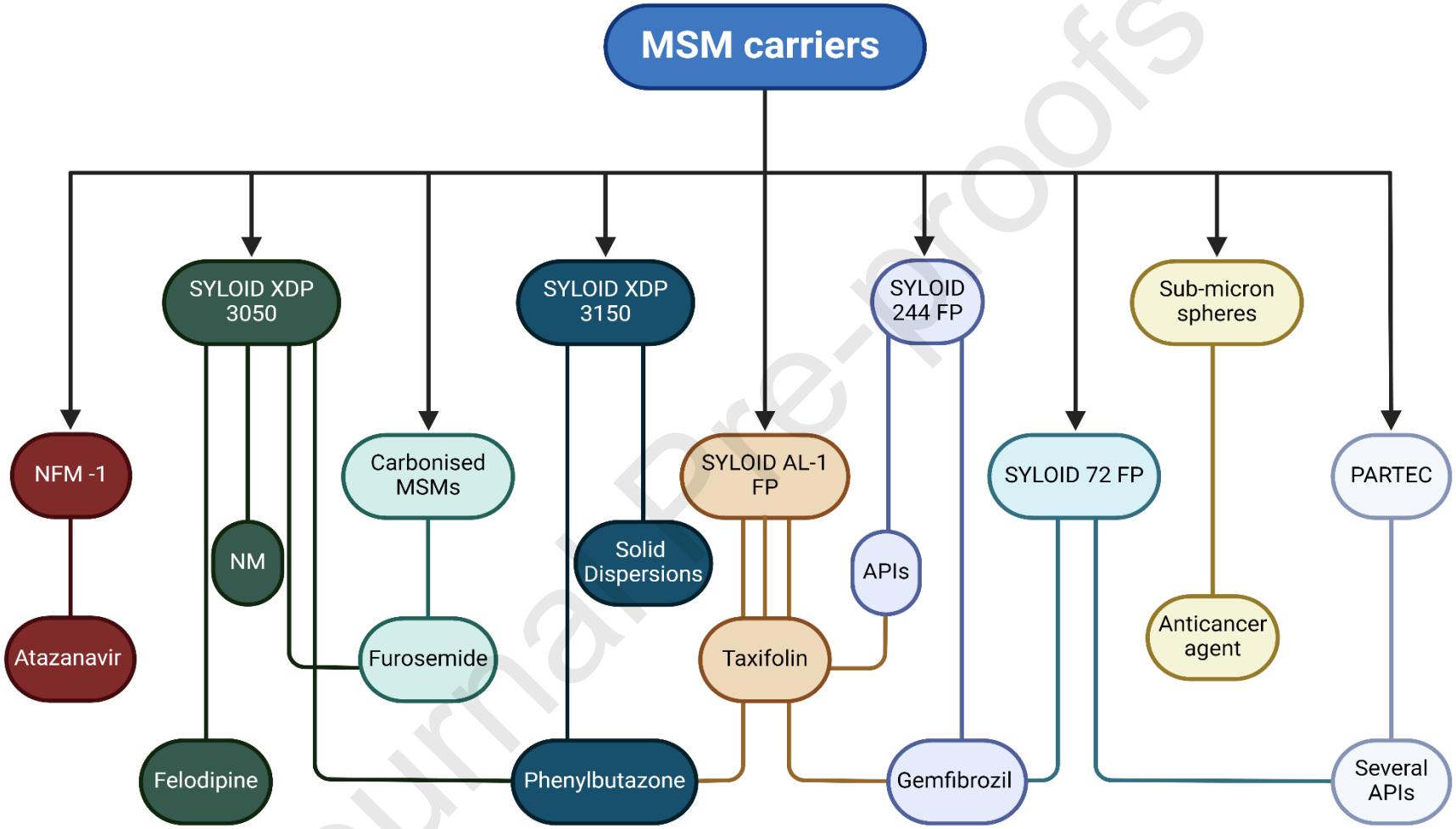


Fig. 7. The used MSM carriers for the purpose of enhancing dissolution and solubility of APIs, corresponding to the drug they incorporate. NM refers to Neratinib maleate.

The application of mesoporous silica in drug delivery has been widely investigated due to their ability to enhance the dissolution, solubility, and bioavailability of poorly water-soluble APIs. One such example is the utilisation of MSMs to improve the release and gastrointestinal (GI) residence of taxifolin, a plant-derived flavonoid frequently employed as a food additive. A study focusing on the development of a gastroadhesive drug delivery system incorporated chitosan and hydroxypropyl methylcellulose (HPMC) to enhance taxifolin retention in the GI tract and sustain its release [138]. In this work, SYLOID® Al-1 FP, a commercially available mesoporous silica, was selected as the primary carrier due to several advantageous properties. First, SYLOID® Al-1 FP is known to stabilise drugs in their amorphous state, thereby improving their solubility and preventing recrystallisation. Additionally, its high surface area facilitates the effective distribution of drug molecules within the porous structure, ensuring enhanced dissolution. The incorporation of chitosan, a positively charged polymer, contributed to the mucoadhesive properties of the formulation, particularly due to its ability to undergo protonation in acidic environments. The addition of HPMC, on the other hand, served a dual purpose: not only did it function as a viscosity enhancer, but it also exhibited controlled release properties and further reinforced mucoadhesion through interactions between its hydroxyl groups and the glycoproteins of mucins. This optimised gastroadhesive system demonstrated effective adherence to porcine stomach tissue for up to five hours, while ensuring a prolonged release profile under acidic conditions for a period of eight hours [138].

Beyond gastroadhesive applications, MSMs have been extensively employed to enhance both solubility and permeability, as demonstrated in a study by Kaukonen et al., where thermally carbonised MSMs were used to improve the in vivo permeation of furosemide [139]. The drug-loaded MSMs exhibited superior dissolution and permeability across Caco-2 cell monolayers at various pH levels, without compromising the integrity of the cells. Notably, the enhancement in drug permeation was more pronounced at higher pH values, which is likely attributed to drug ionisation effects. The findings indicated that furosemide, when incorporated within MSMs, exhibited a five-fold increase in drug flux and a four-fold increase in permeability compared to the unmodified drug

In a 2019 study, researchers further investigated the use of MSMs to enhance the delivery of poorly water-soluble drugs, focusing particularly on the impact of silica overloading on the release properties and thermal stability of MSM-drug formulations [140]. This work employed SYLOID® XDP 3050, a commercially available mesoporous silica, to load both felodipine and furosemide beyond their theoretical monolayer surface coverage. The inclusion of hydroxypropyl methylcellulose acetate succinate (HPMCAS) aimed to assess its role in amorphisation and release modification. Interestingly, while HPMCAS did not significantly enhance drug amorphisation, it exerted a notable influence on drug release kinetics, resulting in a slower dissolution profile for both drugs. The highest dissolution efficiencies achieved were 96.4% and 96.2% for felodipine and furosemide, respectively. Furthermore, scanning electron microscopy (SEM) analysis revealed that HPMCAS coating slightly altered the morphology of the silica particles, likely due to partial surface coverage

Similarly, MSMs have been utilised to enhance the dissolution of gemfibrozil, where researchers employed various grades of SYLOID® in conjunction with a microwave-assisted drug loading method [141]. The study demonstrated that the drug was successfully incorporated into the mesoporous carrier in an amorphous state, thereby improving its solubility. The results also highlighted the impact of pore size and volume on drug release. After 30 minutes, the percentage of drug released was 15.4% from pure gemfibrozil, compared to 40.9%, 42.8%, and 55.9% from SYLOID® AL-1 FP, SYLOID® 244 FP, and SYLOID® 72 FP, respectively. The superior dissolution observed with SYLOID® 72 FP was attributed to its large pore volume and diameter, findings that align with previous studies on MSM-based drug delivery systems.

In 2016, Brigo et al. explored the use of mesoporous silica sub-micron spheres to improve the dissolution of 7-phenyl-3H-pyrrolo [3,2-f]quinolin-9(6H)-one, an anticancer agent with inherently low solubility [142]. The study reported a 50% drug loading efficiency and identified a correlation between drug concentration and dissolution medium composition. Notably, immediate drug release was observed upon immersion in simulated body fluids, with drug concentration levels in the early dissolution phase reaching 2.5 times higher than those observed with the pure drug. Moreover, the study demonstrated that silica modification could either enhance dissolution (as observed with ibuprofen) or reduce drug loading (as seen with the anticancer agent), highlighting the complexity of MSM-drug interactions.

Further studies have examined the influence of pore size on drug amorphisation, dissolution, and release kinetics. In 2021, Šoltys et al. investigated four different MSM grades, including SYLOID® 72 FP and PARTECK® SLC 500, to assess their effects on drug stabilisation [143]. Their findings indicated that pore size plays a crucial role in both crystallisation and dissolution rates. Specifically, MSMs with small pore sizes (< 2.5 nm) were more prone to drug recrystallisation post-loading, while also demonstrating slower initial dissolution rates, despite maintaining an amorphous drug state within the porous matrix.

In another study, SYLOID® was evaluated for its potential in enhancing the dissolution of phenylbutazone, a poorly soluble anti-inflammatory drug [144]. The study found that different SYLOID® grades exhibited varying release profiles, with SYLOID® XDP 3050 achieving the highest dissolution rate (99.6% after 30 minutes), compared to SYLOID® XDP 3150 (78.3%) and SYLOID® AL-1 FP (86%). In contrast, unmodified phenylbutazone exhibited a markedly lower dissolution rate of 43.8%. The results suggested that, while drug amorphisation was a key factor in dissolution enhancement, pore diameter also played a significant role in promoting efficient drug release.

The method of drug loading and the specific grade of MSM used also significantly influence the dissolution profile. Tahir et al. compared SYLOID® 244 FP and SYLOID® AL-1 FP for the loading of artemether via various techniques, including physical mixing, co-grinding, solvent evaporation, and solid dispersion [145]. In their investigation, the researchers employed two distinct grades of SYLOID, namely SYLOID® 244 FP and SYLOID® AL-1 FP, to load artemether using a range of methodologies, including physical mixing, co-grinding, solvent evaporation, and solid dispersion. Their findings indicated that SYLOID® 244 FP facilitated a greater drug release compared to SYLOID® AL-1 FP, a phenomenon primarily attributed to its larger pore volume and diameter. Additionally, the smaller particle size of SYLOID® 244 FP, relative to SYLOID® AL-1 FP, provided an enhanced access pathway to the porous matrix, thereby improving the dispersion of confined drug molecules and promoting dissolution. Furthermore, the solvent evaporation method exhibited the most pronounced enhancement in drug release, which was ascribed to the increased pore confinement and surface adsorption. The use of organic solvents facilitated stronger interactions between the solvent molecules and the silanol groups present on the mesoporous silica, thereby enabling the rapid desorption of the drug from the silica surface. [146].

The enhancement of drug dissolution and bioavailability through MSMs is well-documented, with research consistently demonstrating that pore structure plays a fundamental role in these processes. Xia et al. studied MSM-based carriers for in vivo dissolution enhancement of atazanavir, concluding that pore size relative to API molecular size was more critical than pore connectivity [147]. Their findings demonstrated that the ratio of pore size to the molecular dimensions of the API plays a more critical role in drug release than the connectivity of the pores, whether they are two-dimensional (2D) or three-dimensional (3D). Notably, the mesoporous silica carrier NFM-1 exhibited a sustained drug release over an eight-hour period, with a remarkable solubility enhancement effect—up to 71-fold higher than that of the unloaded drug. This significant improvement can be attributed to the specific structural characteristics of the porous matrix, wherein the confined drug molecules are prevented from

undergoing recrystallisation due to the restrictive dimensions and shape of the carrier's pores, which were measured to be smaller than 15 nm in diameter.

An additional example of the application of mesoporous silica materials (MSMs) in improving drug bioavailability is reflected in the work conducted by Mahajan and Ravi, who explored the use of SYLOID-based amorphous solid dispersions to enhance the oral bioavailability of neratinib maleate [148]. The formulation of solid dispersions is a well-established strategy for increasing the oral bioavailability of poorly water-soluble drugs, primarily through mechanisms such as particle size reduction and enhanced wettability. Traditional methods for producing solid dispersions include melting and solvent evaporation techniques, and recent advancements have incorporated surfactants to improve both stability and solubility. Furthermore, innovative approaches have been introduced to mitigate the limitations of conventional processing techniques [149]. In this study, SYLOID XDP 3050 was selected as the mesoporous silica carrier due to its superior drug-loading capacity (15.7%) and exceptional flow properties. In vitro dissolution studies revealed that the optimised neratinib maleate-MSM-solid dispersions exhibited a substantially higher dissolution rate and extent compared to the unprocessed drug across multiple pH conditions (pH 3.0, pH 4.5, and pH 6.8). Additionally, oral pharmacokinetic studies (conducted at a dosage of 10 mg/kg) demonstrated significantly enhanced plasma exposure of the neratinib maleate-MSM-solid dispersions in comparison to the pure drug, with an observed 73% increase in relative oral bioavailability [148].

Another notable application of MSMs in solid dispersions is their use in the formulation of an amorphous solid dispersion-based DDS for silymarin [150]. Silymarin, an extract derived from the seeds of milk thistle (*Silybum marianum* L. Gaertner), is particularly rich in flavonoids and flavonolignans and is widely utilised as a herbal extract in therapeutic applications. [151]. This study focused on employing SYLOID XDP 3150 as the mesoporous silica candidate for the preparation of solid dispersions, which were fabricated using a solvent evaporation method with the incorporation of Tween as a surfactant. The results indicated that dispersions prepared using SYLOID demonstrated superior stability compared to formulations based on Avicel. This difference was primarily attributed to the unique properties of SYLOID, particularly its smaller pore size, which facilitated the confinement of API molecules within the porous structure. This structural feature effectively restricted molecular mobility, preventing API precipitation on the surface, as observed in Avicel-based formulations. Additionally, drug release from SYLOID-based formulations was significantly enhanced, a phenomenon ascribed to the increased specific surface area of the carrier, which played a crucial role in promoting dissolution [150].

Taken together, these studies illustrate the significant potential of mesoporous silica materials (MSMs) in improving the dissolution, permeability, and bioavailability of poorly soluble drugs. The research emphasises the importance of pore size, volume, and structural characteristics in dictating the release kinetics and solubility enhancement of active pharmaceutical ingredients (APIs). It is evident that the relationship between the pore size of the carrier and the molecular dimensions of the API plays a more critical role in drug release than the connectivity of the pores themselves. For instance, sustained release profiles observed with carriers like NFM-1 are attributed to the pore structure, which restricts recrystallisation and enhances solubility. Furthermore, the application of SYLOID-based carriers in solid dispersions has led to notable improvements in drug dissolution and oral bioavailability, particularly in the cases of Neratinib maleate and silymarin. The results underscore the importance of selecting the appropriate MSM grade and loading method, with solvent evaporation techniques showing superior release profiles due to higher pore confinement. Collectively, these studies reinforce the versatility of MSMs as drug carriers capable of addressing solubility and stability challenges in pharmaceutical formulations. Future investigations should focus on optimising pore characteristics and surface modifications to enhance drug loading efficiency and control release dynamics.

4.3.5. Antimicrobial applications

Certain elements and materials possess advantageous antimicrobial properties, with silver being particularly favoured due to its low toxicity and broad-spectrum antimicrobial activity Consequently, extensive research has focused on developing silver-based platforms to combat multidrug resistance. One such approach involves the design of hybrid antimicrobial mesoporous microspheres incorporating silver phosphate and pectin [152]. In this system, porous silica microspheres were loaded with levofloxacin and tested against *Escherichia coli* and *Staphylococcus aureus*, demonstrating a strong bactericidal effect. This enhanced efficacy is attributed to the synergistic action of silver ions and levofloxacin. Additionally, pectin was incorporated to reduce particle aggregation, improve biocompatibility, and prevent the formation of salt residues during microsphere synthesis. Such hybrid systems offer a promising strategy for overcoming bacterial resistance while ensuring stability and safety in biomedical applications.

4.3.6. Targeting

Despite advancements in drug delivery systems, several promising therapies encounter significant challenges, including toxicity and drug resistance. The development of improved delivery materials has enabled more precise targeting of specific organs and tissues while minimising damage to healthy cells, thereby enhancing therapeutic efficacy [153]. This targeted approach is particularly crucial in addressing conditions such as cancer, where selective drug accumulation can improve treatment outcomes. The following sections will explore the application of MSMs as DDSs for organ-specific and cancer-targeted therapy. Various MSM-based carriers designed for targeted delivery applications are illustrated in Figure 8, highlighting their potential to optimise drug bioavailability and reduce systemic side effects.

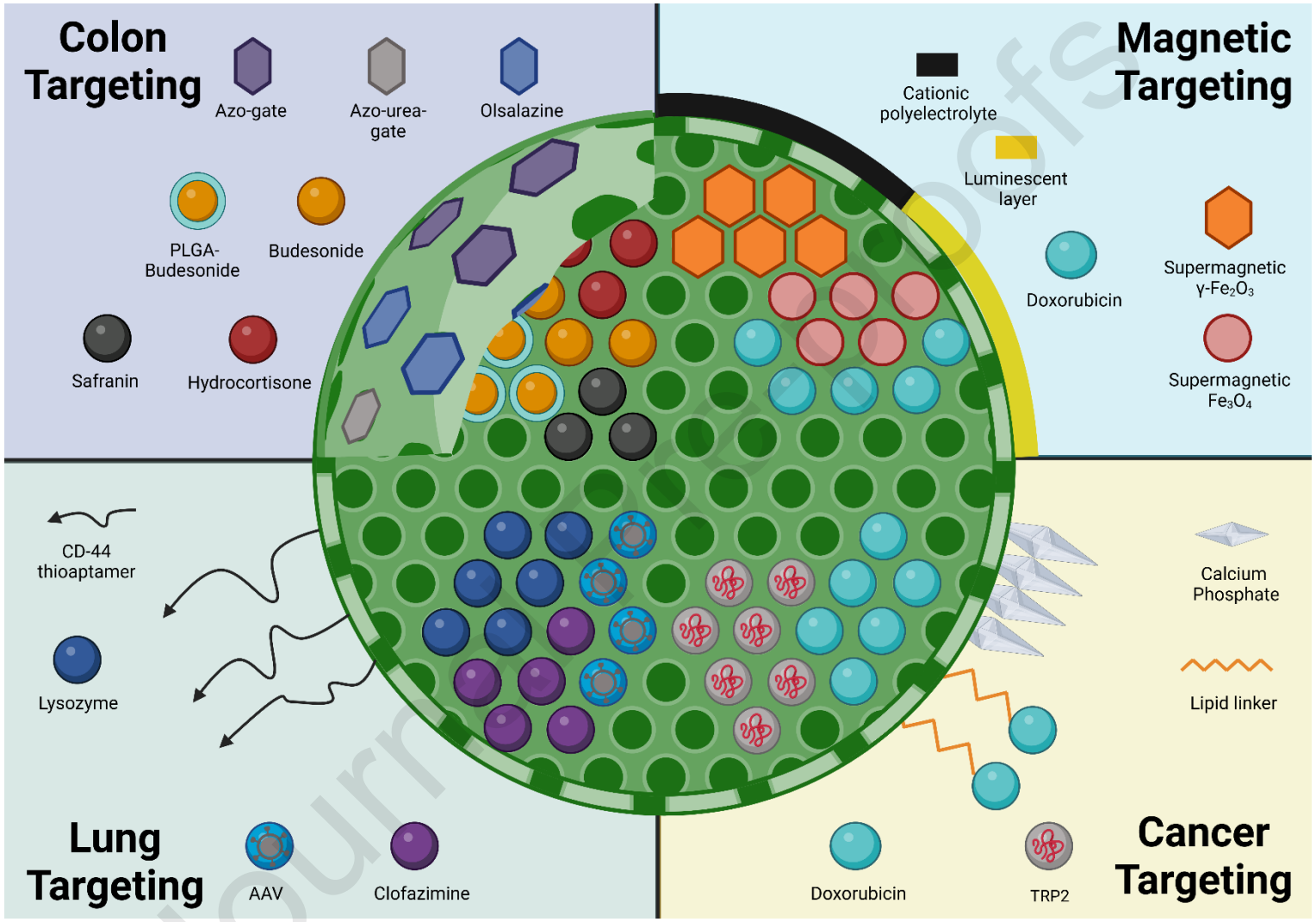


Fig. 8. The different targeting applications of MSMs identifying the approach and the used drug. PLGA refers to poly lactic-co-glycolic acid, AAV to adeno-associated virus, and TRP2 to tyrosinase related protein 2.

4.3.6.1. Magnetic-based targeting

In 2008, Ruiz-Hernández reported the development of hexagonal porous-structured magnetic MSMs [154]. These MSMs successfully incorporated varying amounts of superparamagnetic γ-Fe_2O_3 nanoparticles while preserving their mesoporous structure, with a maximum loading of 11% w/w. This achievement demonstrated the potential for magnetic MSMs in targeted drug delivery applications.

Another example involves mesoporous silica-coated Fe_3O_4 microparticles functionalised with a cationic polyelectrolyte for thrombosis treatment and controlled drug release [155]. The polyelectrolyte coating served multiple functions: it regulated pH-responsive drug release, improved colloidal stability, enhanced dispersibility, and increased drug loading efficiency via electrostatic interactions. Aspirin was used as the model drug, and the system exhibited promising anti-inflammatory effects and clot lysis activity, confirming the suitability of MSMs for vascular applications.

In 2022, Fuentes et al. investigated the cytotoxicity of MCM-41 loaded with carvacrol and thymol against the hepatocarcinoma cell line (HepG2) [156]. The study found that functionalised MSMs exhibited greater cytotoxicity than the free bioactive compounds, primarily due to oxidative stress mechanisms. The overexpression of ROS was linked to direct interactions between the particle surface and cell membranes. This was attributed to alterations in surface charge and hydrophobicity, which facilitated stronger cell-particle interactions. Such findings highlight the potential of MSMs in cancer therapy through targeted cytotoxic effects.

A further notable example is the work of Gu et al., who developed dual magnetic and luminescent porous silicon microparticles for drug delivery [157]. The fabrication process involved the porosification of silicon wafers via etching, followed by post-processing techniques to introduce luminescence and magnetic properties. Borate activation was employed to induce photoluminescence, while ultrasonication and filtration removed residual fragments. Superparamagnetic Fe_3O_4 nanoparticles were incorporated into the porous matrix, granting magnetic responsiveness. Doxorubicin (DOX) was loaded at a concentration of 9.8% w/w, and the system demonstrated effective in vitro drug release under magnetic guidance. This research underscores the versatility of MSMs in site-specific drug delivery, particularly for cancer treatment.

4.3.6.2. Colon-based delivery targeting

MSMs have been explored for their potential in colon-targeted drug delivery systems, particularly for the treatment of inflammatory bowel diseases (IBD). A notable example is the incorporation of budesonide into MSMs, capped with an azo derivative, for the treatment of colitis in rats [158]. The system utilised MCM-41 as the carrier, with the azo-gate serving to release the drug cargo specifically in the colon. This azo-gate is cleaved by azoreductase enzymes, which are present in the colon microbiota, thereby enabling targeted drug release. The formulation was compared to a commercial drug, demonstrating superior efficiency. The use of silica microparticles enhanced the targeted delivery of the drug to the colon, resulting in reduced side effects. This system highlighted the potential of MSMs for IBD treatment, as it allows for controlled drug release at the site of inflammation.

Another significant approach for colon-targeted drug delivery was proposed by Leonard et al. (2020) [159], who developed a multistage porous silica microparticle-based system loaded with budesonide and poly lactic-co-glycolic acid (PLGA) nanoparticles (NPs). In this system, silica microparticles served as the first stage of the delivery system, with the PLGA NPs loaded into the pores of the microparticles. The porous structure of the silica microparticles enabled effective targeting of the inflamed mucosal tissues, while the PLGA NPs facilitated the delivery

of the drug cargo into epithelial cells. This formulation exhibited a pH-controlled release, with 20% of budesonide released at acidic pH levels, mimicking the conditions found in the stomach, while the remaining drug was released in a prolonged manner, accumulating in the inflamed areas of the colon. This approach provided a controlled release profile and showed potential for enhancing drug delivery to the colon.

In a further development of MSM-based drug delivery, Teruel et al. (2018) reported the use of smart gated-targeted magnetic-based MSMs for the delivery of safranin or hydrocortisone [160]. The system incorporated surface functionalisation with an azo derivative bearing a urea moiety as gatekeepers, and Fe_3O_4 oleate as the magnetic NPs. The magnetic properties of the carrier allowed for controlled release in pH levels above 7.4, with the highest release observed in the colon. This release could be attributed to the reduction of the azo bond by sodium dithionite, which mimics the azoreductase enzymes in the colon. Additionally, the inclusion of magnetic NPs increased the efficiency of hydrocortisone in an in vivo-induced colitis model when a magnetic belt was applied, highlighting the potential of this system for enhanced drug delivery and localisation at the site of inflammation.

Further advancements in MSMs for colon targeting include the use of an olsalazine derivative for the capping of MSMs loaded with hydrocortisone for IBD treatment [161]. The concept relied on the hydrolysis of the olsalazine derivative, which releases 5-aminosalicylic acid and triggers pore opening, thereby facilitating the release of the loaded drug. The carrier exhibited no release in acidic or neutral environments, but when sodium dithionite, a reducing agent that simulates the function of azoreductase enzymes, was applied, the drug was released. This system resulted in pathological improvement in rats with chronic colonic inflammation, demonstrating the therapeutic potential of MSMs in colon-targeted drug delivery for IBD treatment.

4.3.6.3. Lung-based delivery targeting

The application of MSMs has been widely explored for targeted drug delivery to the lungs. A significant example is the use of functionalised MSMs loaded with CD44-targeting thioaptamers, aimed at targeting macrophages in Mycobacterium tuberculosis (M. tuberculosis)-related infections in mice [162]. Thioaptamers, known for their ease of production, robustness, stability, and high affinity to proteins due to their thiophosphate ester bonds, were incorporated into the design [163]. The novel platform demonstrated that discoidal-shaped particles were significantly more efficient at causing toxicity to infected cells compared to spherical particles. This increased efficacy could be attributed to the discoidal shape's concentration in the lungs, likely due to the organ's hemodynamics, which favour the deposition of such shapes. Moreover, the negatively charged thioaptamers enhanced the uptake by macrophages, thereby facilitating more effective drug delivery. This study highlighted the potential of MSMs for targeted pulmonary drug delivery in the treatment of bacterial infections [162].

Further advancements in lung-targeted delivery using MSMs were described in a study by Campos Pacheco et al. in 2024 [164]. This approach involved the development of dual micro-nano carriers designed for targeted delivery to both extracellular and intracellular bacteria. MSMs were loaded with clofazimine, a drug known for its effectiveness against multidrug-resistant tuberculosis. The MSMs enabled rapid dissolution of the drug in lung fluid, increasing the concentration of clofazimine to target the extracellular bacteria, including biofilms of M. tuberculosis. Once dissolved into smaller, nano-sized carriers within the lung fluid, the MSMs were designed to target intracellular bacteria by facilitating the delivery of clofazimine into macrophages. This dual approach aimed to enhance the therapeutic effect by addressing both forms of bacterial infection, underscoring the versatility and potential of MSMs for targeted pulmonary therapy.

MSMs have also been explored in the context of organ failure caused by ischemic reperfusion injury (IRI), specifically in gene delivery applications. In this instance, adeno-associated virus (AAV)-loaded porous silicon microparticles were utilised to prevent IRI in porcine vasculature tissues [165]. The choice of AAV was based on its unique ability to escape the endosome following cellular uptake, thus enabling efficient gene delivery. The incorporation of AAV into MSMs allowed for enhanced gene expression in porcine venous tissue, with the virus being released from the carrier and transported to the nucleus, where it could exert its effects. This innovative strategy demonstrated the potential of MSMs in gene therapy for organ regeneration, presenting a promising approach to address the challenges of ischemic injury.

In addition, MSMs have been investigated for their role in pulmonary drug delivery via dry powder formulations. One such development utilised disordered MSMs as carriers for lysozyme, a model antimicrobial protein abundant in the airways [166]. The MSMs were designed with an optimal lung deposition size of 2.43 ± 0.13 μm, ensuring effective pulmonary delivery. The formulation achieved a high lysozyme loading capacity of 0.35 mg/mg in phosphate-buffered saline, significantly outperforming water-based loading. Aerodynamic tests showed that the fine particle fraction, representing particles smaller than 5 μm, was 70.32%, indicating excellent deposition in the lungs. Moreover, the formulation demonstrated sustained lysozyme release in simulated lung fluid, maintaining enzymatic activity between 71–91% and achieving almost complete dissolution (93%) within 24 hours. Importantly, the MSMs were nontoxic to lung epithelial cells, suggesting that this system could be a viable option for delivering proteins with retained bioactivity, providing a promising strategy for pulmonary protein delivery.

4.3.6.4. Cancer-based delivery targeting

The use of MSMs as carriers in cancer therapy has garnered significant attention in recent years. One notable example is the work by Zhu et al. (2018), where they developed silica microparticle vesicles aimed at inducing immunotherapy for melanoma treatment [167]. In this approach, mesoporous silica vesicles were loaded with a peptide derived from B16 melanoma, specifically tyrosinase-related protein 2 (TRP2), and two toll-like receptor (TLR) agonists: monophosphoryl lipid A and CpG oligonucleotide. These vesicles were then loaded into dendritic cells to enhance immune responses. The study demonstrated that using mesoporous silica as a platform provided excellent biocompatibility and significantly enhanced the durability of the immune response. Furthermore, the combination of TLR agonists with the TRP2 peptide elicited a stronger antigen-specific immune response against B16 tumour cells. This study highlighted the potential of MSMs in cancer immunotherapy, offering a promising strategy for inducing long-lasting anti-tumour immune responses.

The modification of MSMs for cancer applications can take several forms, depending on the desired therapeutic outcome. In 2016, Prokopowicz et al. explored the use of calcium-modified bioactive MSMs to deliver DOX [168]. The calcium modification was specifically designed to enhance the interaction between MSMs and bone tissues, as the modified particles formed hydroxyapatites on their surface, which is a key component of bone tissue. DOX is known for its severe side effects, particularly cardiotoxicity, which limits its use in chemotherapy, especially in treating childhood bone tumours. By incorporating DOX into calcium-modified MSMs, the side effects could be mitigated, enabling more targeted drug delivery. The study found that the release of DOX from the MSMs could be controlled by adjusting the concentration of calcium diethoxide, the precursor used in the modification process. Increased calcium content in the formulation led to a higher release rate of DOX, likely because the DOX molecules were situated closer to the surface of the particles, where they experienced weaker interactions with the silanol groups on the silica surface. This approach demonstrated the potential of MSMs in targeting bone-related cancers while reducing the systemic toxicity of chemotherapeutic drugs.

Another study by Wu et al. focused on the oxidation-triggered release of DOX from lipid-based linker-functionalised MSMs [169]. In this system, the drug was covalently attached to the MSMs carrier via a Si-C bond, and the release of DOX was triggered by the oxidation and subsequent dissolution of the silicon matrix. The release kinetics of DOX varied depending on how the drug was attached to the carrier. For particles where DOX was physically adsorbed onto the silica surface, an initial burst release occurred within 2 hours, followed by complete release within 24 hours. When both covalent and physical adsorption methods were employed, the release rate was slower, characterised by a reduced burst release followed by a more gradual release over 24 hours. Exclusively covalent attachment (via methanol washing) led to a sustained release profile, with drug release extending over five days. However, in all cases, the total amount of released DOX was lower than the initial loading due to chemical degradation of the drug, as doxorubicin is known to be moderately unstable in aqueous solutions at physiological pH levels. This study provided valuable insights into the potential for controlled and triggered drug release using MSMs, which could be beneficial in managing the timing and dosage of chemotherapy drugs in cancer treatment.

In summary, MSMs demonstrate strong potential as effective drug delivery systems for various diseases, including cancer, IBD, and pulmonary infections. Their ability to be functionalised with a wide range of therapeutic agents—such as TLR agonists, peptides, and chemotherapeutic drugs like DOX—enables precise drug release, enhancing therapeutic outcomes while reducing adverse effects. Further functional modifications, including calcium incorporation for bone targeting or oxidation-triggered release, support the delivery of drugs to specific sites. These systems also offer excellent biocompatibility, structural stability, and adaptability, making them well-suited for advanced medical applications. As research progresses, MSMs continue to gain attention as promising carriers for controlled and targeted therapy, with the potential to significantly improve patient outcomes and reshape conventional treatment approaches. The carriers highlighted in this review are summarised in the table below, along with their morphological features and reported academic applications.

Table 1. The uses of MSM-based carriers and their morphological properties (particle size, surface area, and pore size).

MSM Carrier		Uses	Particle Size (μm)	Surface area (m^2/g)	Pore Size (nm)	Reference
SYLOID Family	ED3	Controlling arthropods	5.3 - 6.3	-	-	[94]
	ED5		8.4 - 10.2	-	-	
	XDP 3050	Octreotide and BSA delivery, stearic acid functionalised carrier, S-SEDDSs tablets, enhancing dissolution (furosemide, felodipine, phenylbutazone, and neratinib maleate)	41.38 - 48.10	340.44	15.49	[18, 105, 126, 140, 144, 148]
	XDP 3150	Enhancing dissolution of phenylbutazone and silymarin	182	320	22.9	[144, 150]
	Al-1 FP	Enhancing dissolution of (taxifolin, gemfibrozil, phenylbutazone, and artemether)	6.5 - 8.1	683	3.2	[138, 141, 144, 145]
	72 FP	Enhancing drug amorphosiation and the dissolution of gemfibrozil.	4.5 - 5.8	405	10	[141, 143]
	244 FP	Sublingual tablets of zolmitriptan, enhancing ketoprofen tablet properties, liquisolid-based compacts, S-SEDDSs tablets, and enhancing dissolution of (gemfibrozil and artemether)	2.5 - 3.7	395	16	[118, 120, 123, 126, 141, 145]

MCM-41		Fortifying yoghurt with folic acid, octyl methoxycinnamate loading for sunscreen protection, and targeting applications (budesonide for colon targeting, carvacrol and thymol for magnetic targeting)	0.9	-	2-3	[90, 100, 156, 158]
Neusilin®		Tablets (MSM-based composites, liquisolid-based compacts, and solidifying zafirlukast-based SMEDDS)	106	342	12.3	[119, 123, 130]
Aeroperl®		Tablets (MSM-based composites, preventing sticking to compression punch, and liquisolid-based tablets)	20 - 60	300	30	[119, 120, 125]
Aerosil®		Enhancing ketoprofen tablet properties and liquisolid-based tablets	2.47 - 4.51	-	-	[120, 125]
Spheres	Sub-micro	Efficient separation of histidine-tagged proteins	0.16	170	3.5	[107]
	Silica sub-micro	Improve solubility of an anti-cancer agent: 7-phenyl-3H-pyrrolo [3,2-f] quinolin-9 (6H)-one	1	1011	2.5	[142]
	micro	Silver phosphate and pectin microspheres loaded with levofloxacin	1.4 - 1.5	43	16.57	[152]
Thermal	Oxidised	Improving indomethacin dissolution and permeability	53 - 75	223	11.2	[122]

	Carbonised	Improve the in vivo permeation of furosemide	-	-	-	[139]
	Thermohydro	For the in vivo delivery of lys-GHRP6 (a ghrelin antagonist)	38 - 53	401 - 444	11.8 - 15.6	[109]
Organised porous	NFM-1	In vivo dissolution enhancement of atazanavir	10.16	793	26	[147]
	AMS-6		9.44	874	43	
	STA-11		9.85	874	79	
Functionalised MSMs	Chitosan	Enhance the stability and photoprotective efficacy of octyl methoxycinnamate	2.24 - 4.96	88.38	15.21	[99]
	Poly (acrylic acid)	pH triggered release of indigo carmine	106.94	197 - 400	1.85 - 20.7	[113]
	Fe_3O_4	For thrombosis treatment and controlled drug release	468.4	50.63	3.8	[155]
	Smart gated	For the delivery of safranin/hydrocortisone	-	1097	2.66	[160]
	Calcium bioactive	Doxorubicin delivery	100 - 200	350	3-4	[168]

	Lipid linker	Oxidation-triggered release of doxorubicin	30 - 50	260	17 - 23	[169]

Despite the prominent role of silica-based carriers in drug delivery systems, alternative non-silica microparticle platforms remarkably present valuable benefits and distinct functionalities. These alternative systems exhibit unique properties that may enhance targeted delivery, controlled release, and compatibility with various therapeutic agents. In the following sections, we provide a concise overview of these non-silica microparticles, elucidating their potential contributions and roles within advanced therapeutic applications. The following sections aim to broaden the perspective on available drug delivery carriers beyond conventional silica-based materials.

5. Alternative Non-Silica-Based Porous Microparticle Platforms

Although MSMs are extensively employed as drug delivery carriers, the literature documents the use of various porous microparticles, including porous microspheres [170] and large porous microparticles for the effective delivery of loaded drugs into the lungs [171]. The following sections provide an overview of these alternative porous microparticle systems as drug delivery carriers, as illustrated in Figure 9.

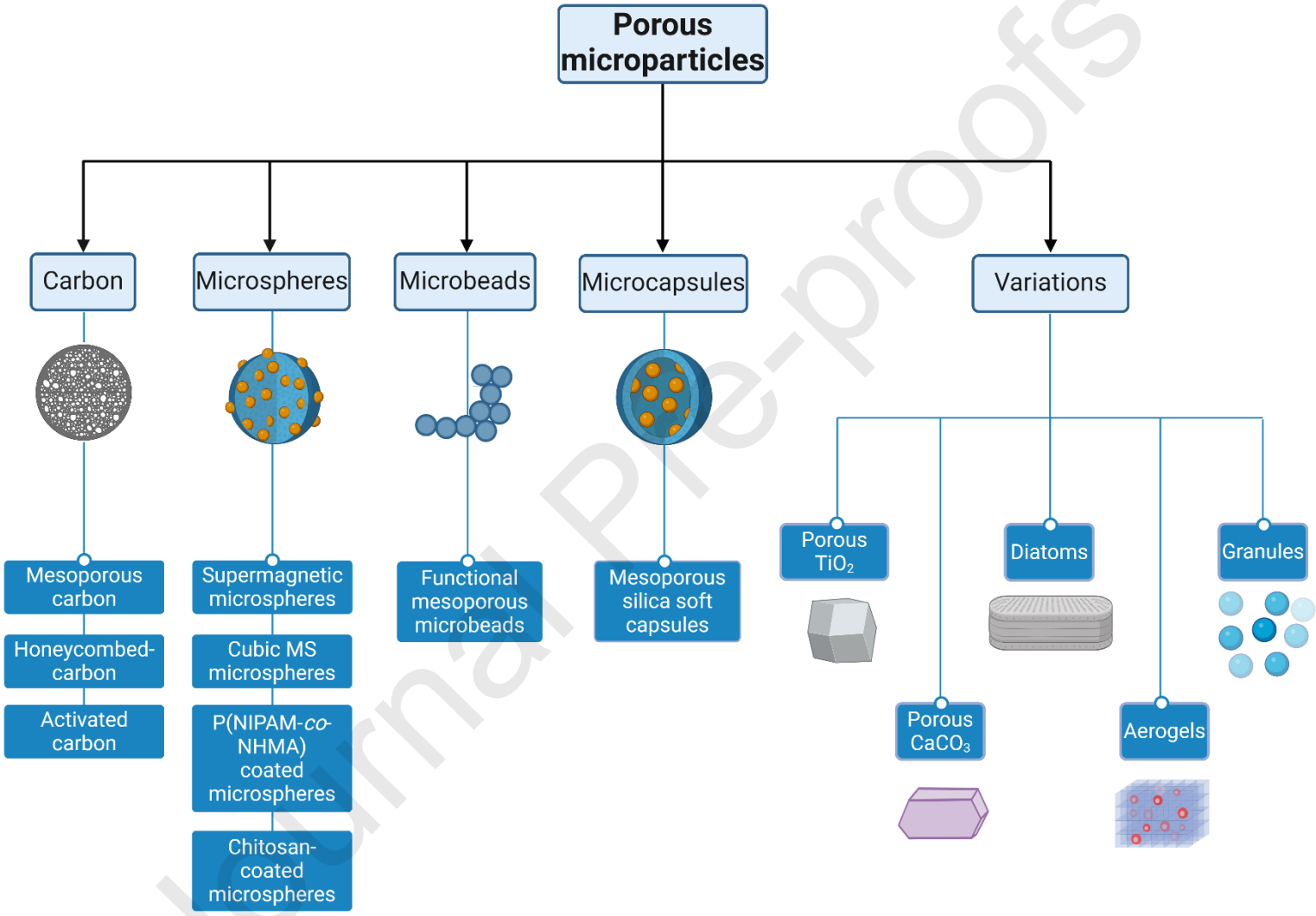


Fig. 9. The different types of non-silica porous microparticles.

5.1. Carbon-based microparticles

While MSMs have been widely reported for various applications, alternative porous materials, such as carbon-based particles, present promising candidates for drug delivery. Carbon particles are particularly valued for their exceptional chemical and frictional stability, which can be tailored to meet diverse biomedical requirements [172]. Additionally, mesoporous carbon materials offer a large surface area, adjustable pore sizes, and modifiable surfaces, making them suitable for targeted drug delivery. Their biocompatibility and unique optical properties further enable advanced drug delivery systems, alongside real-time diagnostic and therapeutic approaches [173]. Several studies have demonstrated the potential of carbon-based porous materials, such as mesoporous carbon microparticles. These have been successfully utilised as a sensing platform for thrombin detection [174]. with the development of a thrombin aptasensor that offers high selectivity and a low detection limit of 0.25 nM, providing an effective method for detecting thrombin in blood serum and buffered systems.

In 2013, Zhang et al. reported the utilisation of modified mesoporous carbon microparticles to enhance the bioavailability of carvedilol [175]. Their method involved surface modification of the carriers through carboxylation to improve the carrier's properties. The results demonstrated an increase in the dissolution rate and solubility of carvedilol while maintaining it in an amorphous state. Furthermore, the carboxylated microparticles exhibited a higher loading capacity compared to the unmodified particles, which can be attributed to their larger surface area and increased pore volume.

The application of MSM-based carriers extends beyond drug delivery to the determination of chemical organic compounds. Yao et al. (2020) developed a novel variation of MSMs in the form of uniform honeycombed carbon nanotube-based microparticles for electrochemical detection of methyl parathion [176]. Methyl parathion, an organophosphate pesticide used in agriculture, is known for its harmful side effects. The researchers employed a droplet microfluidic technique to fabricate these microparticles, mixing porous carbon nanotubes with silicon dioxide. The honeycombed structure was achieved by etching the microparticles with hydrofluoric acid. This approach enabled the development of an efficient platform for the sensitive electrochemical detection of methyl parathion, demonstrating the versatility of MSM-based carriers in applications beyond drug delivery, particularly for environmental and analytical purposes.

In 2017, Miriyala et al. investigated activated carbon particles as amorphous carriers for the delivery of paracetamol and ibuprofen [177]. Their findings demonstrated that the activated porous carbon microparticles exhibited minimal cytotoxicity against Caco-2 cells at concentrations not exceeding 1 mg/ml. The two active pharmaceutical ingredients (APIs) displayed differing characteristics post-loading; paracetamol remained fully amorphous, while ibuprofen showed 19% crystallinity. Despite this, both APIs exhibited complete in vitro release within 10 minutes, highlighting the potential of activated carbon microparticles as effective, low-toxicity carriers for controlled drug delivery.

5.2. Microspheres

Microspheres, a form of porous microparticles, are free-flowing particles ranging from 1 μm to 1000 μm. These carriers are highly effective for sustained or controlled drug release profiles [178]. In 2012, Teng et al. reported the development of supermagnetic capped mesoporous silica microspheres as a targeted drug delivery system with a controlled release mechanism [179]. his system employed a stimuli-responsive release strategy, using EDTA and sodium citrate as stimulating agents and amino-terminated iron oxide nanoparticles (NPs) as capping materials. The microparticles were loaded with a model drug and functionalised with 3-

Glycidoxypropyltrimethoxysilane (GLYMO) to facilitate interaction with the iron oxide NPs for pore capping. Upon interaction with the triggering agent, the NPs were removed, and the drug cargo was released. This novel approach exhibited low cytotoxicity, biocompatibility, and efficient endocytosis of the anticancer agent, paclitaxel, across various cell lines.

In 2011, Hu et al. synthesised novel cubic mesoporous silica microspheres for indomethacin delivery [180]. They designed a controllable pore-sized carrier using temperature variation, with the Santa Barbara 16 (SBA-16) carrier exhibiting a 3D-cubic arrangement of interconnected mesopores. The study showed that the varying pore sizes enhanced the dissolution profile, with indomethacin release increasing from 64% after 1 hour to 90% when loaded into the carrier with approximately 9 nm pores, demonstrating significant improvement in the drug release rate.

Additionally, Liu et al. explored the application of magnetic mesoporous silica microspheres coated with a thermo-sensitive polymer shell (P(NIPAM-co-NHMA)) for controlled drug release [181]. This temperature-sensitive carrier was loaded with Zn(II) phthalocyanine tetrasulfonic acid, a photodynamic therapy drug, and the system demonstrated temperature-dependent drug release, highlighting its potential in thermally triggered therapeutic applications.

Furthermore, hollow mesoporous silica microspheres were developed for controlled drug delivery in pancreatic cancer therapy [182]. These microspheres were coated with chitosan, providing pH-sensitive gatekeeper functionality to protect the loaded drug in acidic environments typical of cancerous tissues. The drug, N6L, a pro-apoptotic NCL antagonist, was released in a pH-dependent manner, resulting in significant anticancer activity and inhibiting tumour growth by 60%, demonstrating the promising potential of these carriers for targeted cancer therapy.

5.3. Microbeads, microcapsules, and microparticles variations

In addition to microspheres, microbeads present another promising option for drug delivery systems (DDS). Microbeads are spherical particles with diameters ranging from 0.5 μm to 1000 μm, capable of encapsulating drug molecules within polymeric matrices and facilitating the slow release of the drugs over a prolonged period in a controlled manner [183]. These properties make microbeads attractive candidates for sustained release drug delivery applications. A notable example of functional microbeads for controlled release is the work of Restani et al. in 2010. They developed mesoporous microbeads using poly(1,3-glycerol dimethacrylate) (PGDMA), a biocompatible polymer derived from glycerol dimethacrylate, which is often used as a crosslinker in polyethylenimine (PEI)-based gene carriers [184]. The microbeads, loaded with S-ibuprofen, exhibited high drug-loading capacity due to strong hydrogen bond interactions between ibuprofen and the carbonyl and hydroxyl groups of PGDMA. The microbeads demonstrated different morphologies depending on the stabiliser used during their formation; without a stabiliser, the particles aggregated, while stabilisers led to spherical shapes. Furthermore, the microbeads released over 95% of their contents within eight hours, highlighting their potential as DDS candidates for oral delivery applications [184].

Another interesting variation of mesoporous silica-based carriers is the development of mesoporous silica soft microcapsules. These microcapsules have a silica-based shell, with a thickness not exceeding 1 μm, and possess ordered hexagonal mesopores approximately 6 nm in diameter. Their structural characteristics make them highly functionalisable and offer superior mechanical stability compared to traditional polymer-based microcapsules [185]. In addition, these microcapsules exhibit remarkable elastic behaviour, with the ability to increase their size two-fold after absorbing large amounts of dyes and solvents, without losing their morphology. This ability to expand while maintaining structure makes these soft microcapsules excellent candidates for drug loading and controlled delivery.

In 2017, Zhuang et al. reported the development of amino-functionalised mesoporous titanium dioxide microparticles designed to immobilise adenosine deaminase, an enzyme important for therapeutic applications [186]. These mesoporous titanium dioxide carriers were synthesised to possess large pores and high crystallinity, with hydroxyl groups enhancing the efficiency of adenosine deaminase encapsulation. The particles were further functionalised with glutaraldehyde (GLU), which acted as a cross-linker to form stable enzyme–carrier interactions, inhibiting enzyme leaching and ensuring sustained activity. The use of the GLU linker significantly improved enzyme stability in polar environments, demonstrating the potential of these carriers for enzyme delivery and biotechnological applications.

Functionalisation of porous microparticles also enables their application in various fields. For instance, Presisig et al. developed mucoadhesive porous microparticles for local drug delivery within the gastrointestinal tract [187]. They utilised porous calcium carbonate (CaCO3) particles and coated them with chitosan to impart mucoadhesive properties, ensuring that the drug-loaded particles adhere to the mucosal lining for prolonged release. Additionally, fumed silica nanoparticles were employed to improve the dispersibility of the particles, ensuring better distribution throughout the intestinal mucosa. The drug-loaded particles were subsequently encapsulated within a capsule, representing a viable approach for localised drug delivery to the gastrointestinal system.

Diatoms, a unique type of porous material derived from photosynthetic algae, also show significant potential as drug delivery carriers. These materials have highly ordered 3D porous structures and have been reported as carriers for the delivery of drugs such as prednisone and mesalamine [188]. iatom-based carriers have demonstrated enhanced permeation properties across Caco-2 cells and improved absorption of prednisone, making them excellent candidates for BCS Class III drugs [189]. In addition, diatoms are non-cytotoxic and exhibit high potential for targeted cancer therapy, adding further value to their use in drug delivery applications.

Further variations in mesoporous silica-based materials have been explored, such as the development of antioxidant nanosystems. One approach involved the functionalisation of mesoporous silica aerogels with tetraazamacrocyclic copper(II) complexes, which possess neuroprotective properties [190]. he copper(II) complex mimics the enzyme superoxide dismutase, dismutating ROS-generated superoxide anions. The mesoporous aerogels provided a stabilising environment for the copper(II) complexes, ensuring their stability and preventing premature degradation. This approach demonstrated the potential for using mesoporous silica aerogels in neuroprotective drug delivery systems, especially for diseases related to oxidative stress.

Moreover, silica-polydimethylsiloxane (PDMS)-based mesoporous granules have been reported as carriers for controlled delivery of DOX hydrochloride [191]. These granules exhibit a controlled, slow release of DOX, with an initial burst release followed by zero-order kinetics, which ensures a prolonged, constant release. Additionally, after soaking in simulated body fluid (SBF), the surface of the granules self-forms a layer of carbonated hydroxyapatite. This mineralised layer enhances the granules' ability to target bone tumours, making them promising candidates for cancer treatment, particularly for bone-related cancers.

In summary, porous microparticles, including microbeads, microcapsules, diatoms, and silica-based granules, represent a broad range of innovative carriers for drug delivery systems. These materials offer various advantages, such as controlled and sustained release profiles, biocompatibility, and the ability to functionalise for specific therapeutic applications. The continued development and optimisation of these porous materials have the potential to revolutionise drug delivery, enabling more effective and targeted therapies for a wide array of medical conditions.

Conclusion

Mesoporous silica microparticles (MSMs) offer significant advantages in drug delivery systems, particularly for localised drug release and reduced systemic distribution. Their larger size ensures safe encapsulation of toxic compounds, making them ideal for sustained, targeted therapies while minimising cellular toxicity often associated with nanoparticles (NPs). MSMs improve the solubility, stability, and bioavailability of poorly soluble drugs, addressing a critical challenge in pharmaceutical development. They are versatile in various applications, including tablet formulations and the loading of large molecules like proteins. When combined with antimicrobial agents, MSMs hold promise in overcoming multi-drug resistance. Furthermore, MSMs can be functionalised with aptamers or loaded with magnetic nanoparticles, enabling targeted drug delivery to specific organs or tissues, such as the lungs, colon, and cancer cells. Their ability to be tailored for specific therapeutic needs makes MSMs highly adaptable and effective. As research progresses, MSMs are positioned to play a crucial role in clinical applications, advancing biomedical technologies and drug delivery systems. Their versatility and efficiency in targeted therapies mark them as a promising tool for the future of medical treatments and the improvement of patient outcomes.

CRediT authorship contribution statement:

Conceptualisation, M.A.A.T., M.M., H.E.Z, and S.A.T.; Literature survey, M.A.A.T.; Figure preparation, M.A.A.T., H.E.Z, and S.A.T.; Project administration, M.A.A.T., M.M. and L.S.A; Supervision, M.M. and L.S.A.; Writing—original draft, M.A.A.T., M.M., H.E.Z, and S.A.T; Writing—review and editing, M.M. and L.S.A.

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Highlights

- MSNs applications and limitations related to size, charge, and shape.
- MSMs offer enhanced drug delivery with controlled release and bioavailability.
- Surface modifications enable MSMs to target organs and cancerous tissues.
- MSMs improve solubility and stability of therapeutic compounds.

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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