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Sugar-Smart Nano Boosters: Mesoporous Silica Nanoparticles for Dual-Action Therapy in Obesity-Linked Diabetes

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Abstract
The rising global burden of obesity and type 2 diabetes mellitus (T2DM) increasingly manifesting as the comorbid condition 'diabesity' demands integrated therapeutic strategies that address their shared and complex pathophysiology. Conventional glucose-centric approaches to T2DM management often neglect the pivotal role of excess adiposity in disease progression. This review underscores the promise of mesoporous silica nanoparticles (MSNs) as next-generation nanocarriers for dual-action therapies, capable of co-delivering anti-obesity and antidiabetic agents. MSNs possess a highly tunable structure, including adjustable pore sizes, large surface areas, and modifiable surfaces, facilitating the efficient encapsulation and controlled release of multiple therapeutics. Their versatility allows for synergistic modulation of interconnected metabolic pathways implicated in obesity and T2DM. Functionalization with targeting ligands enables tissue-specific delivery particularly to adipose tissue and pancreatic β-cells while minimizing systemic exposure and off-target effects. Moreover, MSNs can be engineered for stimuli-responsive release, activated by metabolic cues such as hyperglycaemia or local acidosis, enabling temporally and spatially controlled drug administration. Preclinical evidence, encompassing *In vitro* assays and *in vivo* models, supports the therapeutic potential of MSNs in enhancing lipid metabolism and improving glycaemic control. For instance, delivery of microRNA-33 antagomirs via MSNs has been shown to reverse lipid dysregulation in murine models. Separately, MSN-based insulin carriers have demonstrated sustained glucose reduction and pancreatic tissue preservation. These findings highlight the potential of MSNs to revolutionise diabesity management by enhancing therapeutic efficacy, reducing dosing complexity, and improving patient compliance through multifaceted, targeted interventions.

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Introduction

Obesity and type 2 diabetes mellitus (T2DM) are two chronic diseases with a growing global prevalence and intricate connections in their epidemiology and pathogenesis, representing a significant public health challenge. The close relationship between these two conditions has even led to the term 'diabesity', highlighting that the majority of individuals with diabetes are overweight or obese (Leitner *et al*., 2017) [28]. Obesity is a condition characterised by the excessive accumulation of adipose tissue, recognized as a major driver in the development of T2DM (Leitner *et al*., 2017; Malone and Hansen, 2019; Kawai *et al*., 2021) [28, 39, 26]

Epidemiological studies conducted over several years consistently show that individuals with obesity are at a significantly higher risk of developing type 2 diabetes (T2DM). On the other hand, people who already have T2DM are more likely to experience obesity compared to the general population. Even individuals with a body mass index (BMI) within the higher end of the "normal" range are at an increased risk of developing T2DM (Leitner *et al*., 2017) [28]. This two-way relationship underscores the importance of understanding the underlying mechanisms and implementing integrated therapeutic approaches.

A complex interplay of genetic predisposition and environmental factors underpins the pathogenesis of obesity and T2DM. Obesity triggers a cascade of metabolic and biochemical changes, most notably the development of insulin resistance, a condition where the body's cells become less responsive to the effects of insulin. This insulin resistance is a central feature in the development of T2DM. It is fuelled by various factors associated with increased adiposity, including adipose tissue inflammation, the altered secretion of adipocyte-derived cytokines, increased lipid accumulation leading to lipotoxicity, and mitochondrial dysfunction (Unger, 2002; Greenberg and McDaniel, 2002; Montgomery and Turner, 2015; Kawai *et al*., 2021) [60, 19, 26, 41]. In addition to metabolic and inflammatory pathways, a study by Shen *et al.* (2013) [54] reviews that gut microbiota alterations cause a link between obesity and insulin resistance. Dysbiosis, often seen in obese individuals, can promote increased intestinal permeability and the release of endotoxins into systemic circulation, exacerbating inflammation and metabolic dysfunction.

Historically, the management of T2DM has often adopted a primarily glucose-centric approach, focusing on lowering glycated haemoglobin (HbA1c) levels and addressing diabetes-related complications. While glycaemic control remains crucial, this approach frequently emphasizes the significant impact of obesity on the disease trajectory and associated comorbidity (Leitner *et al*., 2017) [28]. Evidence increasingly demonstrates that weight loss in individuals with obesity and T2DM can lead to improvements in a range of obesity-related conditions and, in some instances, even induce remission of diabetes (Lean *et al*., 2018) [27]. This highlights the limitations of solely targeting blood glucose without addressing excess adiposity.

Given the interconnected nature of obesity and type 2 diabetes mellitus (T2DM), developing and implementing integrated therapeutic platforms that simultaneously target both conditions is crucial. Fortunately, the growing availability of pharmacological agents with dual benefits, such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), is simplifying the therapeutic landscape by addressing both weight management and glycemic control (Matyjaszek-Matuszek *et al*., 2018; Zhang *et al*., 2018) [40, 64]. Combination therapies, such as empagliflozin and liraglutide, have shown notable effectiveness in improving blood glucose levels, body weight, blood pressure, and insulin sensitivity in overweight or obese individuals with T2DM (Lin *et al*., 2022). Alongside pharmacotherapy, lifestyle interventions, including dietary modification and increased physical activity, remain foundational for preventing and managing these interrelated conditions (Franz *et al*., 2017) [12].

Most recently, mesoporous silica nanoparticles (MSNs) have garnered attention as promising carriers for dual-action therapy, offering the capacity to co-deliver anti-obesity and antidiabetic agents with high precision, controlled release, and minimal systemic toxicity. Their tunable pore size, large surface area, and excellent biocompatibility position MSNs as ideal candidates for integrated treatment strategies aimed at improving metabolic outcomes and enhancing patient adherence in managing obesity-associated diabetes. Hence, this review explores the potential of mesoporous silica nanoparticles as a dual-action therapeutic platform for the integrated treatment of obesity-linked type 2 diabetes.

Mesoporous Silica Nanoparticles (MSNS)

Mesoporous Silica Nanoparticles (MSNs) are nanostructured materials composed of silica with highly ordered pore structures ranging from 2 to 50 nanometers. Their large surface area, tunable pore size, and surface functionalization capacity make them ideal for targeted drug delivery and therapeutic applications.MSNs have garnered significant attention in the biomedical field for their potential for designing versatile multifunctional nanosystems, enabling them to carry drugs that overcome various diseases (Mamaeva *et al*., 2013; Gupta *et al*., 2017; Vallet-Regí *et al*., 2018; Nayak and Garg, 2018) [20, 61, 42]. They are considered key innovation precedents in material sciences and have become remarkable nanoplatforms, attracting researchers for various biomedical applications, including cancer imaging and therapy (Freitas *et al*., 2017; Cao *et al*., 2022) [13,5].

The primary interest in MSNs for drug delivery stems from the scale of their interaction with living systems, given their size similarity to cells (Vallet-Regí *et al*., 2018) [61]. Their advantageous features include well-ordered internal mesopores (typically ca. 2–6 nm) with large pore volume (0.6–1 cm^3/g) and surface area (700–1000 m^2/g), tunable size (50–200 nm) and shape, robustness, and ease of surface modification, making them ideal platforms for designing multifunctional nanosystems (Vallet-Regí *et al*., 2018; Tang *et al*., 2012) [58, 61]. MSNs can improve the therapeutic efficiency of drugs, introduce new drug delivery strategies, and provide advantages that traditional drugs lack (Cao *et al*., 2022) [5]. They are being immensely used for targeted or controlled drug delivery in various diseases, including cancer, as they have the potential to become useful therapeutic and diagnostic (theranostic) tools (Freitas *et al*., 2017) [13].

MSNs have shown remarkable results in animal experiments, and the US FDA has even approved the first silica material, C dots, for clinical research, indicating the great promise of porous silica (Cao *et al*., 2022) [5]. Scientists have conducted extensive research to develop MSNs and apply them as drug delivery systems or in therapeutic strategies for a wide range of medical applications (Cao *et al*., 2022) [5].

Properties of Mesoporous Silica Nanoparticles (MSNs)

MSNs possess several key physicochemical properties that contribute to their effectiveness as drug delivery vehicles. These properties include the following:

1. Pore Size

MSNs consist of a honeycomb-like porous structure with a uniform pore size that enables the encapsulation of large amounts of drug cargoes. They have a very narrow pore size distribution, with a tunable pore diameter typically between 2 and 6 nm (Vallet-Regí *et al*., 2018; Tang *et al*., 2012) [61, 58]. This tunable pore size behaves as a size selector for the

loading of biologically active molecules within the mesoporous cavities (Vallet-Regí *et al*., 2018) [61]. The pore diameter also regulates the release rate of the loaded drug, acting as a limiting factor that governs molecule diffusion processes to the physiological environment (Vallet-Regí *et al*., 2018) [61]. There are different types of MSNs with varied sizes. The most widely used type, called MCM-41 (Mobil Composition of Matter No.41), possesses a pore diameter ranging from 1.5 to 8 nm. While SBA-15 (Santa Barbara Amorphous-15) has larger pores ranging from 6 to 30 nm (Nayak and Garg, 2018) [42]. The choice of pore size is crucial as it influences drug loading and release kinetics (Figure 1).

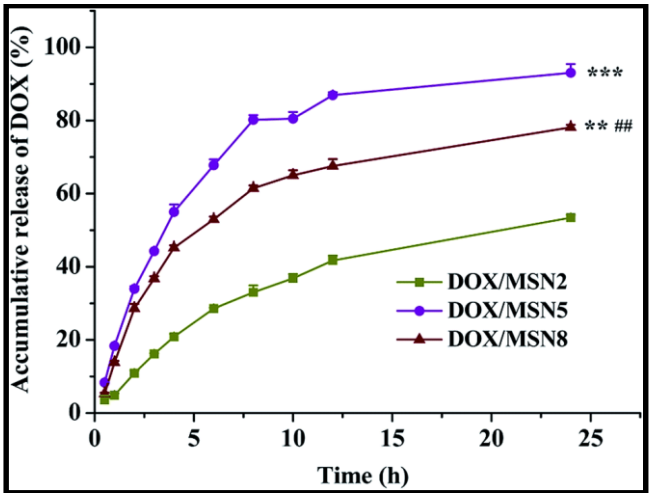

Fig 1: *In vitro* drug release of DOX/MSN in 0.2 mol L−1 PBS. Indicated values were mean ± SD (n = 3). **P < 0.01, ***P < 0.001 vs. DOX/MSN2, P < 0.01 vs. DOX/MSN5. MSN2, MSN5, and MSN8 have mean pore sizes approximately 2, 5, and 8 respectively (Li *et al*., 2018).

2. Surface Area

MSNs possess a large specific surface area, typically ranging from 700 to 1000 m²/g (Vallet-Regí *et al*., 2018) [61]. This high surface area is one of the key features that yields a high drug-loading capacity for both hydrophilic and hydrophobic drugs (Cao *et al*., 2022) [5]. The surface area determines the molecule loading capacity of these nanoplatforms because the higher the contact surface, the greater the number of guest molecules incorporated (Vallet-Regí *et al*., 2018) [61] as shown in Figure 2. MSNs can have a surface area greater than 900 m²/g. The large surface area, coupled with the mesoporous structure, promotes functionalization of the inner and outer surfaces of the MSN with different types of moieties (Choi *et al*., 2022).

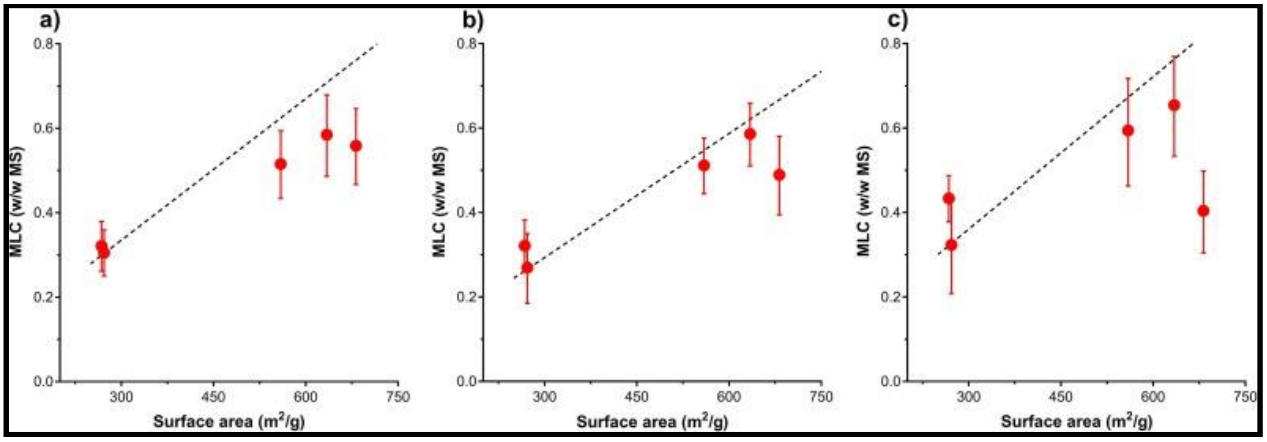

Fig 2: Monomolecular Loading capacity (MLC) plotted as a function of Mesoporous silica surface area for three model drugs a) CCX, b) CIN, and c) PAR in five grades (Bavnhøj *et al*., 2019) [3].

3. Functionalization

The active surface of MSNs is rich in silanol groups, making them easily modified with various organic and inorganic moieties, allowing for different coatings and targeting strategies to be applied (Cao *et al*., 2022) [5]. This easy surface functionalization is a crucial advantage that enables the attachment of targeting ligands (such as antibodies, peptides, or folic acid) to enhance uptake by specific cells or tissues (Slowing *et al*., 2008; Tang *et al*., 2012) [56, 58]. Functionalization can also involve the incorporation of gatekeepers (e.g., polymers, cyclodextrins, or other nanoparticles) at the pore entrances to prevent premature drug release and allow for stimuli-responsive controlled drug delivery in response to environmental stimuli like pH, glucose levels, or oxidative stress (Tang *et al*., 2012) [58], factors that are often dysregulated in obesity-linked T2DM (Figure 3). For instance, glucose-sensitive gates using phenylboronic acid moieties have been explored to enable insulin release in response to elevated glucose levels, mimicking pancreatic β-cell function (Giret *et al*., 2018; Nayak and Garg, 2018; Cao *et al*., 2022) [42, 17, 5].

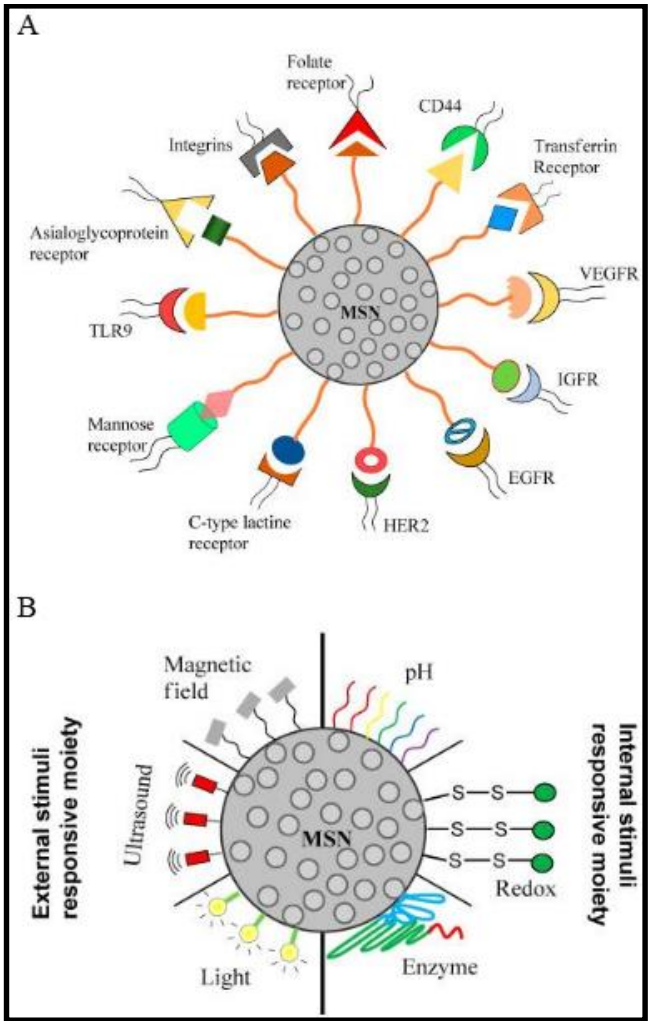

Fig 3: Schematic illustration showing (A) wide variety of agents for functionalization of MSNs, (B) Most relevant stimuli responsive gatekeepers to decorate MSN for controlled cargo release in the cancer site (Barui and Cauda 2020) [2].

4. Biocompatibility and Drug-Carrying Potential

The biocompatibility and biosafety of MSNs are critical for their clinical translation (Cao *et al*., 2022; Farjadian *et al*., 2019) [11, 5]. Biocompatible particles such as MSNs do not assemble in the human body, and they have been reported not to cause severe biological effects during longer-term treatment compared with viral vectors (Choi *et al*., 2022). Studies have shown that the cytotoxicity of MSNs is mainly related to their surface silanol groups, which may non-specifically bind to specific proteins on the cell membrane and cause cell lysis and necrosis (Slowing *et al*., 2009; Lin and Haynes, 2010) [57, 35]. However, the surface properties of MSNs can be modified to improve their biocompatibility. For example, using polyethylene glycol (PEG) for functional modification can reduce the capture of MSNs by the liver, spleen, and lungs, prolonging their circulation time (He *et al*., 2011; Breznan *et al*., 2018) [4]. Roggers *et al.* (2014) [51] showed that Lipid bilayer-coated MSNs have significantly better blood compatibility. *In vivo* studies in mice have indicated that the lethal dose of 110 nm MSNs can be higher than 1,000 mg/kg, and repeated dose toxicity studies showed no deaths within 14 days of intravenous administration of repeated MSN doses up to 80 mg/kg (Liu *et al*., 2011) [36].

Due to their biocompatibility, mesoporous silica nanoparticles hold significant promise for treating diseases beyond cancer, including obesity-linked T2DM (Esmaeili and Mousavi, 2017; Nayak and Garg, 2018) [10, 42]. This means that MSNs have excellent drug-carrying potential and the possibility of targeted and controlled drug delivery. The high drug loading capacity due to the large pore volume and surface engineering properties of MSNs makes them suitable carriers for antidiabetic drugs or gene therapies, improving insulin sensitivity or reducing blood glucose levels (Nayak and Garg, 2018) [42]. MSNs can be loaded with various anti-diabetic drugs, including insulin, glucagon-like peptide-1 (GLP-1) analogues (like liraglutide), dipeptidyl peptidase-4 (DPP-4) inhibitors (like 16-Hydroxycleroda-3,13-Dine-16,15-Olide), and other agents that improve glucose homeostasis and insulin sensitivity (Yoncheva *et al*., 2014; Esmaeili and Mousavi, 2017; Huang *et al*., 2017; Shirsath and Goswami, 2021) [10, 22, 55].

The possibility of surface functionalization allows for the incorporation of targeting ligands that could target adipose tissue or pancreatic beta cells, further enhancing the therapeutic efficacy and reducing systemic side effects (Cao *et al*., 2022) [5]. Stimuli-responsive release mechanisms can also be engineered to release the drug in response to specific metabolic conditions associated with diabetes, such as elevated glucose levels (Vallet-Regí *et al*., 2018; Cao *et al*., 2022) [61, 5]. For instance, glucose-responsive MSN-based systems have been developed to control the release of insulin in response to changes in glucose levels (Zhao *et al*., 2009; Palanikumar *et al*., 2017) [65, 47].

Dual-Action Therapy Design

As with many intertwined disease conditions, the conventional treatment strategies of obesity-linked diabetes, which involved separate administration of anti-obesity and antidiabetic medications, have often resulted in poor therapeutic outcomes, adverse drug reactions, and reduced patient adherence due to complex dosing regimens.In response to these challenges, nanocarrier-based drug delivery systems have gained attention for their potential to co-deliver multiple therapeutic agents with improved pharmacokinetics, biodistribution, and synergistic efficacy (Liu *et al*., 2020) [37]. Mesoporous silica nanoparticles (MSNs) have emerged as promising nanocarriers for drug delivery owing to their unique properties, including uniform and tunable pore size, high surface area, biocompatibility, and ease of surface functionalization (Nayaka *et al*., 2018; Sabio *et al*., 2019) [42, 52]. These characteristics make them well-suited for hosting, protecting, and transporting therapeutic agents to targeted sites, potentially enhancing treatment efficacy while minimizing adverse effects (Freitas *et al*., 2017; Nayaka *et al*., 2018) [13].

Design of MSNs for Co-delivery

The structural versatility of MSNs facilitates the co-delivery of multiple therapeutic agents, which is particularly advantageous in addressing complex, multifactorial conditions such as obesity and type 2 diabetes mellitus (T2DM) (Freitas *et al*., 2017) [13]. Due to their high drug-loading capacity, MSNs can accommodate anti-obesity and antidiabetic agents within a single nanocarrier (Nayaka *et al*., 2018) [42]. This strategy may promote synergistic effects by simultaneously targeting different molecular and physiological pathways implicated in these interrelated diseases (Freitas *et al*., 2017) [13].

Surface Functionalization for Targeted Delivery and Enhanced Loading

To increase drug-loading efficiency and achieve site-specific delivery, the surfaces of MSNs can be engineered with diverse functional groups and targeting ligands (Liao *et al.*, 2017; Paiva *et al.*, 2017) [32, 46]. Surface functionalization enables the selective accumulation of nanoparticles in tissues or cells relevant to obesity and diabetes, such as adipose tissue or pancreatic beta cells, thereby enhancing therapeutic concentration at the target site while reducing off-target effects (Goel *et al.*, 2014) [18]. For example, conjugation with antibodies or peptides that recognize receptors overexpressed in these tissues can improve cellular uptake and therapeutic precision (Yoo *et al.*, 2019) [62]. Additionally, surface modifications can regulate the drug release profile, with gatekeeping molecules or polymers at pore entrances as safeguards against premature release. These tailored designs ensure that therapeutic agents are released only upon reaching specific physiological environments (Freitas *et al.*, 2017) [13].

Release Mechanisms and Triggers

Therapeutic release from MSNs can be mediated through several mechanisms, including passive diffusion and stimuli-responsive strategies (Nayaka *et al.*, 2018) [42].

1) **Passive Drug Release Mechanisms:** This basic approach primarily relies on diffusion or biodegradation of the nanoparticle matrix. Drug molecules gradually diffuse from the MSN pores into the surrounding medium in this mechanism. Release kinetics depend on factors such as pore size, drug concentration, and surface characteristics (Nayaka *et al.*, 2018) [42]. This mechanism is governed by the physicochemical properties of the drug and the polymer (e.g., hydrophilicity, molecular weight, degradation rate). Hydrolytic degradation of polymers such as PLGA and PCL enables sustained release over days or weeks. For example, in the PLGA-based dual drug system reported by Kamble *et al*. (2021) [24], drug release occurred through both diffusion and erosion of the polymer matrix.
2) **Stimuli-Responsive ReleaseMechanisms:** More advanced MSN systems are engineered to respond to internal or external stimuli that are either inherent to pathological environments or applied externally (Qu *et al.*, 2020; Li *et al.*, 2020).

a. **Internal Triggers:** These include changes in pH, enzyme activity, redox conditions, or reactive oxygen species (ROS), all of which are hallmarks of diseased tissues (Freitas *et al.*, 2017) [13]. For instance, the acidic microenvironment of tumors or inflamed tissues can activate pH-sensitive gatekeepers, leading to localized drug release (Qu *et al.*, 2020). Similarly, MSNs modified with ROS-responsive linkers can trigger release in oxidative stress-rich environments (Li *et al.*, 2020).

b. **External Triggers:** External stimuli such as light, heat, ultrasound, or magnetic fields can also be exploited to activate drug release in specifically designed MSN systems (Nayaka *et al.*, 2018) [42]. For example, MSNs integrated with photothermal materials can release their cargo upon exposure to near-infrared light (Cheng *et al.*, 2015) [6].

Applications in Obesity and Type 2 Diabetes

Although there are limited sources that explicitly describe a single MSN platform co-delivering both anti-obesity and antidiabetic agents, studies have underscored the utility of MSNs in treating T2DM. Geng *et al.* developed N-EDMSNs/pFGF21/Lira complexes based on MSNs for T2DM treatment, demonstrating the potential of these systems for delivering agents such as fibroblast growth factor 21 (FGF21) and possibly liraglutide. Their use of embedded dual MSN types (EDMSNs) highlights the capability of MSNs to enhance therapeutic efficacy in T2DM (Geng *et al.*, 2021) [16].

Given the well-established interplay between obesity and T2DM (Leitner *et al.*, 2017) [28], it is feasible to envision MSN-based systems for dual-drug delivery targeting both conditions. For instance, a rationally designed MSN platform could:

1. Encapsulate an anti-obesity drug such as liraglutide (a GLP-1 receptor agonist known to support weight loss and glycemic control) (Pi-Sunyer *et al.*, 2015; Pratley *et al.*, 2018) [48, 49], along with an antidiabetic agent like metformin or an SGLT2 inhibitor such as empagliflozin (which also supports modest weight reduction) (Zhang *et al.*, 2018; Neeland *et al.*, 2016) [45, 64].
2. Be functionalized with targeting ligands to enhance uptake by adipose tissues and pancreatic beta cells.
3. Include pH-responsive gatekeepers to release the drugs specifically in mildly acidic, inflammation-prone microenvironments.

***In vitro* and *In vivo* Evaluation**

Mesoporous silica nanoparticles (MSNs) have been extensively evaluated both *In vitro* and *in vivo* for their potential in biomedical applications, including those related to glucose regulation, fat metabolism, and insulin sensitivity.

***In vitro* Evaluations**

Fat Metabolism

A study by Tao *et al*. (2020) [59] demonstrated that mesoporous silica nanoparticles (MSNs) can serve as effective carriers for the delivery of microRNA-33 (miR-33) antagomirs to ameliorate lipid metabolic disorders. While the *In vitro* aspects are not detailed extensively in the provided excerpts, the broader context of their work suggests that initial *In vitro* studies likely evaluated the efficacy of MSN-mediated antagomir delivery to target cells and their impact on lipid metabolism-related pathways at a cellular level. Another study investigated the impact of silica nanoparticles (a broader category including MSNs) on hepatic lipid metabolism *In vitro* using human hepatic L-02 cells (Duan *et al*., 2018) [8]. This research indicated that silica nanoparticles could trigger hepatic lipid metabolism disorders in these cells. The study suggests a direct interaction between silica-based nanoparticles and cellular lipid processing mechanisms, highlighting potential concerns or areas for further investigation when using MSNs for therapeutic purposes related to metabolic health.

Glucose Regulation and Insulin Sensitivity

Salarkia *et al*. (2023) [53] conducted silico docking studies to explore the interactions of polymeric MSNs with insulin and the insulin receptor (IR). These in silico analyses, while not strictly *In vitro* cellular assays, provide valuable insights into the potential molecular interactions. The docking results revealed strong interactions between specific MSN compounds (Zn-grafted, Co-grafted, and Al-grafted MSNs)

and insulin and the IR, characterised by hydrogen bond formation and high binding energy. Notably, Co-grafted MSN exhibited the highest docking scores for insulin and IR, suggesting a strong affinity and potential to influence insulin signalling pathways at a molecular level. This in silico work supports using modified MSNs to interact with key components of glucose regulation and insulin action.

In vivo Evaluations

Fat Metabolism

Furthermore, in their *in vivo* experiments, Tao *et al*. (2020) [59] reported significant improvements in lipid metabolic profiles in mice treated with the MSN-antagomir complexes, reinforcing the therapeutic promise of this nanosystem.They cited findings by Karunakaran *et al*. (2015) [25], which indicated that therapeutic inhibition of miR-33 did not exacerbate obesity, insulin resistance, or hepatic lipid accumulation, thereby supporting the therapeutic potential of miR-33 modulation.This provides a context for the therapeutic target being delivered by MSNs in the study by Tao *et al*.(2020) [59]. The research by El-kadya *et al*. (2021) [9] evaluated MSNs as delivery vehicles for novel hybrid steroids in managing metabolic syndrome in mice. While the specific outcomes related to fat metabolism are not detailed in the provided excerpts, the study's focus on metabolic syndrome implies an investigation into parameters such as lipid profiles and adiposity, suggesting that the MSN-mediated delivery aimed to modulate these aspects *in vivo*. Similarly, Li *et al*. (2018) found that intravenous administration of MSNs affected hepatic metabolism in mice, with alterations suggesting a reduction in mitochondrial energy metabolism. Additionally, Mahmoud *et al*. (2018) [38] in an *in vivo* study in rats showed that MSNs induced dose-dependent damage in the liver, potentially impacting lipid metabolism. These *in vivo* studies highlight the potential of MSNs to interact with and influence lipid metabolism in animal models, sometimes with unintended effects on liver function.

Glucose Regulation and Insulin Sensitivity

Baek *et al*. (2022) [1] conducted an *in vivo* study where engineered mesoporous silica reduced long-term blood glucose (HbA1c) and improved metabolic parameters in prediabetics. This human study suggests a direct positive impact of certain engineered MSNs on glucose homeostasis, which could involve improved insulin sensitivity or enhanced glucose uptake mechanisms. Salarkia *et al*. (2023) [53] performed *in vivo* tests in type 1 diabetic rats treated with various MSN samples, including pure MSN and metal-grafted MSN/PEG/Insulin nanocomposites. Their findings demonstrated that the MSN family, including the nanocomposites, significantly reduced blood glucose levels compared to the diabetic control group. The researchers also reported that the synthesised nanocomposites were safe, non-toxic, and showed high efficiency in oral insulin delivery, potentially bypassing the need for injections. They even observed self-repairing of the pancreas in the treated rats, suggesting a broader positive impact beyond glucose lowering. Huang *et al*. (2017) [22] investigated the encapsulation of a natural dipeptidyl peptidase-4 (DPP-4) inhibitor in MSNs, demonstrating potentiated hypoglycemia in diabetic mice. DPP-4 inhibitors enhance insulin secretion and reduce glucagon release, thus improving glucose control. The use of MSNs as a delivery system enhanced the efficacy of this inhibitor *in vivo*. Zhao *et al*. (2016) [65] developed glucose-responsive MSN-based systems for double-drug release and real-time glucose monitoring, as well as for controlled release of insulin and cyclic AMP, respectively, *in vivo*. These studies highlight the potential of MSNs to create 'smart' delivery systems that can respond to physiological glucose levels, offering a more controlled and targeted approach to managing blood glucose and potentially improving insulin sensitivity.

Both *In vitro* and *in vivo* studies suggest that MSNs offer promising avenues for addressing glucose regulation and potentially influencing fat metabolism and insulin sensitivity. Engineered MSNs have demonstrated the ability to lower blood glucose levels in prediabetic and diabetic animal models, and their use as delivery vehicles for insulin and other glucose-regulating agents has shown significant potential. Research into fat metabolism indicates complex interactions of silica nanoparticles with hepatic lipid pathways, necessitating careful consideration of their impact on liver health. The biocompatibility and biodistribution profiles of MSNs are critical factors being actively investigated to ensure the safe and effective translation of these nanocarriers for therapeutic applications in metabolic disorders.

Safety and Biodegradability

Due to their potential as nanocarriers, understanding the safety of MSNs is crucial. MSNs are generally considered biocompatible, and some studies suggest they are safer than non-porous silica nanoparticles (Li *et al*., 2015; Farjadian *et al*., 2019; Djayati *et al*., 2023) [7, 11]. Their porous structure may reduce the contact area with cell membranes, potentially leading to reduced toxicity compared to colloidal or Stöber silica nanoparticles.

Short-Term Safety Profile

Properties such as surface chemistry, shape, and size are the factors that influence the short-term safety of MSNs (Djayati *et al*., 2023) [7].

- **Surface Chemistry:** Studies have indicated that the cytotoxicity of MSNs is mainly related to their surface silanol groups, which can non-specifically bind to proteins on the cell membrane, potentially causing cell lysis and necrosis (Li *et al*., 2015; Lin and Haynes, 2010) [35]. However, mesoporous silica has shown a lower haemolytic effect compared to non-porous silica, possibly due to a lower density of silanol groups (Lin and Haynes, 2010) [35]. Surface modification with polyethylene glycol (PEG) has been shown to reduce the capture of MSNs by the liver, spleen, and lungs, thereby prolonging their circulation time and potentially improving biocompatibility (He *et al*., 2011; Li *et al*., 2015).
- **Shape:** The shape of MSNs can affect their biodistribution and clearance. For instance, Li *et al*. (2015) found that spherical nanoparticles showed rapid excretion via faeces, while rod-shaped counterparts had slower degradation, especially in intestinal fluid. Spherical nanoparticles, however, induced renal tubular necrosis and haemorrhage in some cases after oral administration, which might be due to degradation products. In contrast, no significant kidney abnormalities were detected after intravenous administration (Li *et al*., 2015).

- **Size:** The biodistribution and excretion of MSNs are majorly influenced by their size. Larger particle sizes (80-360 nm) tend to accumulate more in the liver and spleen following intravenous administration (He *et al*., 2011). Smaller-sized MSNs might undergo slower degradation as they can escape degradation by the liver and spleen. Particles with a diameter exceeding 200 nm can be readily entrapped in the liver, spleen, and lung capillaries, while those below 200 nm can be eliminated via tumour vasculature and escape hepatic and splenic filtration (Djayati *et al*., 2023) [7]. Particles above 150 nm tend to be trapped in the liver and spleen, and those below 5 nm can be filtered out through the renal system (Djayati *et al*., 2023) [7]. These findings thus reveal that the larger-sized MSNs are safer.

Long-Term Safety Profile

Long-term safety evaluations involve assessing the effects of repeated exposure to MSNs. Liu *et al*. (2011) [36] showed in a mouse model that the lethal dose of 110 nm MSNs was higher than 1,000 mg/kg. Repeated dose toxicity studies showed no deaths within 14 days of intravenous administration of repeated MSN doses of 20, 40, and 80 mg/kg, suggesting good biocompatibility (Liu *et al*., 2011; Li *et al*., 2015) [36]. However, it's important to note that repeated doses might lead to different toxicity profiles compared to single doses (Li *et al*., 2015). Long-term studies involving intraperitoneal injection of fluorescent MSNs at 1 mg/mouse/day twice per week for 2 months showed no apparent changes in histopathological examination of body tissues or haematological parameters compared to controls.

Metabolic By-products and Excretion Pathways

The primary metabolic by-product of MSNs is silicic acid, which is generally considered non-toxic at physiological concentrations (Martin, 2007; Farjadian*et al*., 2019; Djayati *et al*., 2023) [7, 11]. Silica nanoparticles undergo degradation to silicic acid through hydration, hydrolysis, and ion-exchange processes. The degradation rate depends on the properties of the MSNs, such as pore size, morphology, and surface chemistry (Djayati *et al*., 2023) [7]. Generally, silica nanoparticles without functionalization are degraded via fast hydrolysis into water-soluble silicic acid in the body (Li *et al*., 2015).

The excretion of MSNs and their degradation products primarily occurs via urine and faeces (He *et al*., 2011;Li *et al*., 2015). Following oral administration, excretion via urine and faeces tends to be higher compared to other routes (Fu *et al*., 2013). Smaller MSNs (around 5-6 nm) might experience fast clearance by the kidneys (Djayati *et al*., 2023) [7]. Biodegradation and clearance can be managed by controlling particle size, pore size, morphology, and surface chemistry during synthesis (Djayati *et al*., 2023) [7]. PEGylation can also influence excretion pathways and circulation time (He *et al*., 2011).

Clinical studies have shown that silica-based nanoparticles possess an acceptable safety profile and can significantly enhance the bioavailability of various drugs, including simvastatin, ibuprofen, and fenofibrate (Djayati *et al*., 2023) [7]. These findings suggest the potential of silica-based nanomedicines in improving therapeutic outcomes with minimal side effects.

Technological and Clinical Challenges

Drug Stability

A major challenge in the use of mesoporous silica nanoparticles (MSNs) is maintaining drug stability until delivery at the target site. Despite their high loading capacity and controlled release potential, preventing premature drug leakage remains critical (El-kady *et al*., 2021; Iranshahy *et al*., 2023) [9, 23]. To address this, environment-responsive MSNs are being developed to release drugs only under specific conditions, such as pH changes (Iranshahy *et al*., 2023) [23].

Drug loading methods significantly affect release profiles. For instance, curcumin-loaded MSNs prepared via the solid-state method release the drug more slowly than those loaded using the incipient wetness technique, due to the lower adsorbed amount and crystalline form of curcumin (Iranshahy *et al*., 2023) [23]. Additionally, the purity of MSNs and any functionalization agents used during synthesis (e.g., CTAB) can influence drug efficacy and stability, potentially interfering with cytotoxicity assays (Iranshahy *et al*., 2023) [23]. Therefore, rigorous purification is essential. El-kady *et al*. (2021) [9] also note that drug composition affects loading efficiency and release kinetics. This variability complicates efforts to achieve predictable delivery patterns across different therapeutic agents.

Limitations in Personalised Treatment

Although MSNs show promise in targeted therapy, several factors limit their application in personalised medicine. A key barrier is the incomplete understanding of the *in vivo* behaviour of functionalized MSNs. While surface modifications aim to improve targeting and reduce side effects, more pharmacokinetic and pharmacodynamic studies in humans are needed to translate preclinical successes into clinical settings (Iranshahy *et al*., 2023) [23].

Patient-specific factors, such as physiological differences and disease heterogeneity, also complicate personalised treatment. The effectiveness of targeting ligands like folic acid depends on biomarker expression, which varies among individuals and disease stages (Iranshahy*et al*., 2023) [23].

Moreover, the route of MSN administration influences biodistribution and drug release, requiring tailored approaches for different diseases and patients (Iranshahy *et al*., 2023) [23]. In gene therapy applications, such as delivery of miR-33 antagomirs, MSNs show promise but still face challenges with efficient and sustained *in vivo* delivery (Tao *et al*., 2020) [59].

Conclusion

Mesoporous silica nanoparticles (MSNs) represent a highly versatile and promising nanoplatform for tackling multifaceted conditions such as obesity-linked type 2 diabetes mellitus (T2DM). Their tunable physicochemical properties which include high surface area, adjustable pore size, and modifiable surfaces facilitate the co-delivery of multiple therapeutic agents with spatial and temporal control, offering potential for synergistic effects and enhanced treatment adherence. Functionalization strategies further enable tissue-specific targeting, while stimuli-responsive systems can be engineered to respond to metabolic cues, minimising off-target effects and maximising therapeutic efficacy.

Despite these advantages, several challenges must be addressed to enable clinical translation. Chief among them

are the limited understanding of long-term *in vivo* behaviour, potential toxicity, and variability in patient-specific responses. Refining drug-loading strategies to prevent premature release and improve stability remains a critical area of focus. Additionally, the heterogeneity of obesity and T2DM underscores the need for patient-tailored approaches. Future studies should prioritise comprehensive pharmacokinetic and pharmacodynamic evaluations and the development of dual-action MSN-based therapies that simultaneously address both metabolic dysregulation and inflammation. These efforts will be instrumental in advancing MSNs toward clinical application in precision medicine.

Conflicts of Interest

All authors declare no conflict of interest associated with this research article**.**

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