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Drug loading methods and kinetic release models using of mesoporous silica nanoparticles as a drug delivery system: A review

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ABSTRACT

Oral drug administration remains one of the most convenient routes due to its Simplicity, high patient compliance, and cost-effectiveness. However, many medicinal products available on the market exhibit poor water solubility, which adversely affects the dissolution rate of drugs in biological fluids. Drug loading is a promising strategy to produce highly stable amorphous drugs with improved dissolution rates, solubility, and bioavailability. Mesoporous silica nanoparticles (MSNs) are particularly advantageous due to their tunable surface area, pore size, and pore volume, making them suitable to load various molecules such as drugs, genes, and proteins. The use of mathematical models is crucial for predicting and analyzing the release profile of active molecules and diffusion patterns within delivery systems. This enables the design and development of new systems with more desirable release patterns. This review provides an overview of MSNs and drug loading methods, discusses the mechanisms of drug release and release kinetic models using mesoporous carriers, and highlights critical considerations in designing MSNs, such as particle stability and cytotoxicity.

1. Introduction

Drug delivery systems (DDS) aim to transport drugs from the initial administration site to the targeted site of infection or disease (Huang et al., 2021). Oral drug administration is still the most convenient route as it is easiest to take, has high patient compliance, and is cost-effective. Furthermore, some estimates suggest that oral formulations comprise 90 % of manufacturing drugs and about 50 % of the drug delivery market (Laracuente et al., 2020). Despite these advantages, oral drug delivery poses a significant challenge before it gets the therapeutic purpose. These difficulties are primarily induced by the biological barriers along the way of traveling drug molecules inside the body. These barriers include the degradation environment of acidic fluids in the stomach, enzymatic degradation, low absorption capacity, and low permeability of active molecules through the intestinal wall (Ahadian et al., 2020). In addition, most medicinal products available in markets are poorly soluble in water, which affects the dissolution rate of drugs inside the biological fluids (Sreeharsha et al., 2022). As a result, oral bioavailability is much lower than other administration routes. The use of conventional drug delivery systems could be accompanied by adverse effects, as higher doses of drugs are required to elevate the bioavailability. Furthermore, these systems usually exhibit unspecified bio-distribution and lack controllability of drug release characteristics (Laffleur and Keckeis, 2020). Novel DDS should be able to protect the drug from the harsh environment, increase the absorption of the drug into the circular systems, and promote controlled release to specific target sites (Lou et al., 2023). Nanotechnology enables to the production of novel pharmaceuticals by precisely targeting diseased areas, minimizing the toxicity of active molecules, and lowering healthcare costs. A large number of nanocarriers with different properties have been synthesized and applied to drug delivery, such as liposomes (Fan et al., 2021), micelles (Movassaghian et al., 2015), polymers, quantum dots (Ye et al., 2014), metal oxide nanoparticles, metal-organic frameworks (MOFs) (Fard et al., 2024), Zeolites (Servatan et al., 2020) and mesoporous silica nanoparticles (Albayati et al., 2019; Ali et al., 2024). Inorganic nanoparticles have gained significant attention in developing innovative drug delivery systems due to their large uptake capacity, high selectivity, good biocompatibility, and high stability compared to organic nanoparticles (Paul and Sharma, 2020). Among various inorganic nanomaterials, mesoporous silica nanoparticles (MSNs) have attracted attention due to their tunable surface area, pore size, and pore volume (Ali et al., 2023; Mahdi et al., 2023). Their unique porous

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structure with low-density solids, high silanol groups, tunable surface activity, and controllable selectivity makes them a popular choice in different science sectors (Fig. 1) (Djayanti et al., 2023; Tella et al., 2022). Due to MSNs tunable characteristics, it is easy to load different kinds of molecules such as drugs, genes, and proteins. Besides that, it can be modified easily with functional groups to increase the loading capacity and enhance the release rate (Kazemzadeh et al., 2022). MSNs offer many outstanding advantages over other inorganic materials, for instance, good biocompatibility, biodegradability, and high chemical, thermal, mechanical, and biological stability (Hoang Thi et al., 2019). Subsequently, MSNs have emerged as good candidates for biomedical and drug delivery applications in recent years. Several literature reviews have investigated the effectiveness of drug loading methods by MSNs to produce stable amorphous drugs with enhanced solubility and bioavailability (Khalbas et al., 2024; Seljak et al., 2020; Trzeciak et al., 2021) . Furthermore, previous studies have extensively investigated the release kinetic models, with a primary focus on organic matrices such as polymers (Jahromi et al., 2020; Fu and Kao, 2010) . Therefore, the purpose of this review is to expand the knowledge of previously published work by providing new insight into drug loading techniques related to MSNs, with a particular emphasis on the principles of kinetic release models using inorganic matrices. This review explores the different types of MSNs, investigates the principles and control parameters for synthesizing mesoporous silica, and comprehensively examines various techniques for drug encapsulation into MSNs. It also discusses and examines mass transfer mechanisms in controlled release systems involving both porous and non-porous materials. Additionally, the application of release kinetic models for drug-loaded mesoporous silica carriers is discussed. Finally, key considerations for designing ideal MSNs, such as particle stability and cytotoxicity, are also highlighted.

2. Types of mesoporous silica nanoparticles

Based on the International Union of Pure and Applied Chemistry (IUPAC), porous nanoparticles can be classified as microporous (mean pore size <2 nm), mesoporous (2–50 nm), or macroporous (>50 nm) (Baumgartner and Planinšek, 2021). The novel type of mesoporous silica, MCM-41 was first synthesized by a scientist at mobile research in 1992. It has a hexagonal arrangement with tunable pore sizes (1.5–10 nm) (Chen et al., 1993). Due to the ability to generate a wide range of pore sizes, MCM-41 has gained significant prominence in drug delivery applications.(Vallet-Regi et al., 2001) examined for the first time the applications of mesoporous silica in the drug delivery of ibuprofen. MCM-41 belongs to the M41S family along with other types such as MCM-48 (Khader et al., 2024) with (3D) cubic system and Ia3d space group symmetry; and MCM-50 with lamellar structure without space-group symmetry (Fig. 2) (Costa et al., 2021). SBA-n (Santa Barbara Amorphous) is another family of MSNs that has attracted researchers due to their large pore sizes (4.6–30 nm), thick pore walls, and high hydrothermal stability compared with other types of MSNs. A wide variety of SBA-n material have been synthesized such as SBA-1 (Pm3n, cubic), SBA-15 (P6mm, hexagonal), and SBA-16 (Im3m, cubic) (Chaudhary and Sharma, 2017). The first periodic mesoporous materials (PMO) were synthesized by (Inagaki et al., 1999) . It involves the hybrid system of organic fragments and inorganic oxide at the molecular level by a covalently bonded network. These materials exhibit a highly ordered structure with well-defined external morphologies reflecting the symmetries of the pore arrangement structure, whose ordering is greater than that of conventional mesoporous materials. Dendritic mesoporous silica nanoparticles (DMSNs) are a new generation of mesoporous material with unique open three-dimensional dendritic superstructures and pore diameters ranging from 4–15 nm. These particles have attracted rapidly growing attention since the 2010s because of the possibility of synthesizing them with fewer reaction parameters compared to conventional MSNs. Furthermore, DMSNs exhibit a fast degradation rate due to their large pore sizes and low cross-linking silica frameworks (Albayati et al., 2024). Table 1 highlights some types of MSNs and their characteristic properties.

3. Generalized fabrication of MSNs

The origins of nano-scale silica date back to the Stöber method in 1968, when monosized spherical silica nanoparticles were synthesized by sol-gel techniques. MSNs are generally synthesized via a combination of sol-gel process and self-assembled surfactants under hydrothermal treatment (Lei et al., 2020). The reaction can take place under acidic, basic, or neutral conditions. The main critical steps in MSN formation are hydrolysis and condensation of the silica precursors. The hydrolysis step involves the reaction between alkoxysilane groups and water to produce the reactive silanol species Si-OH. These reactive molecules undergo a condensation reaction to form siloxane bonds (Si–O–Si) (Tella et al., 2022). During these reactions, the surfactant molecules can self-assemble into micelles at a concentration higher than the critical micelle concentration (CMC). As a result, the condensed silica precursors interact with surfactant micelles through hydrogen bonding and electrostatic interactions to form the organic-inorganic (i.e., surfactant-silicate) composite. The organic surfactant molecules can be removed via calcination or extraction with solvents to form the pore network and subsequently MSNs (Fig. 3) (Asefa and Tao, 2012a; Huang et al., 2020).

$$\text{Hydrolysis} :\equiv Si - OR + H_2O \rightleftharpoons \equiv Si - OH + ROH$$

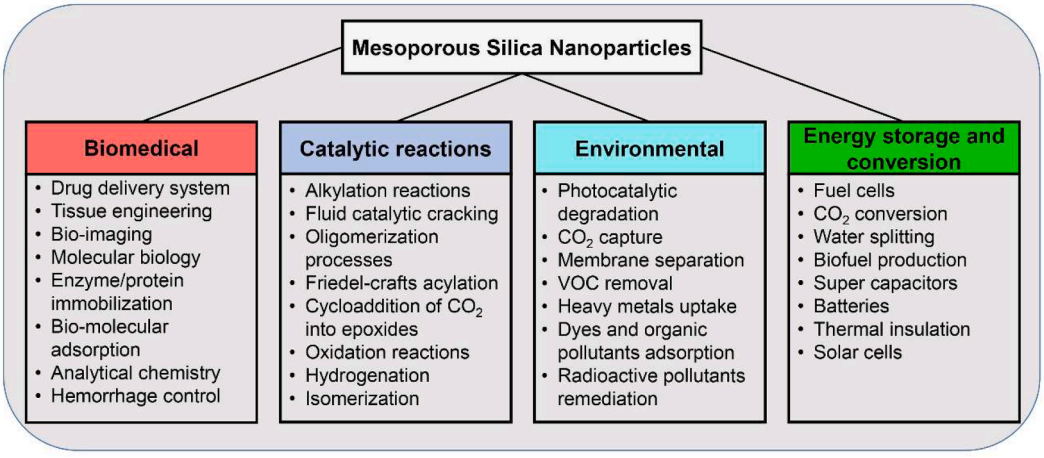

Fig. 1. Versatile applications of mesoporous silica nanoparticles.

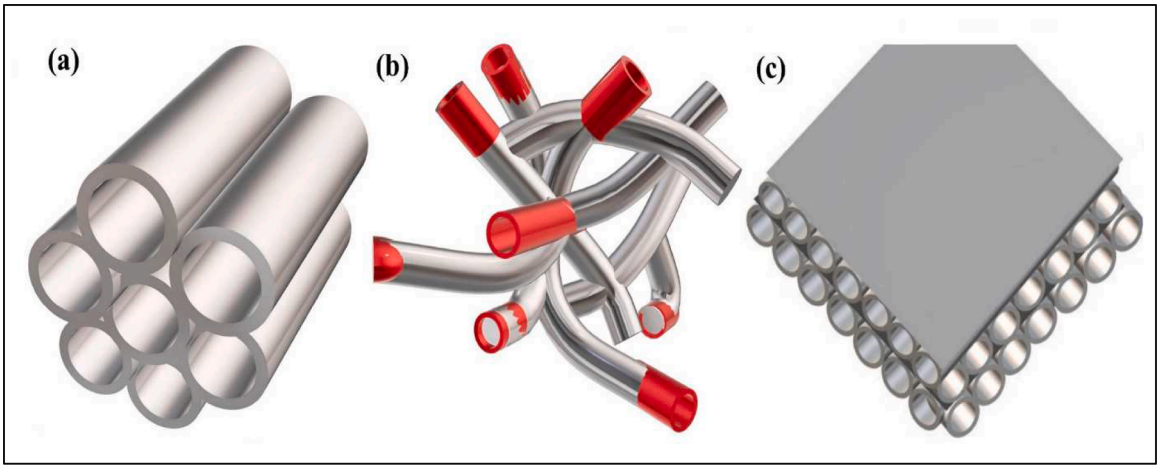

Fig. 2. Schematic representation of the structure of MCM-41 (a), MCM-48 (b), and MCM-50 (c) mesoporous materials of the M41S family. Reprinted with permission from (Costa and Paranhos, 2020). Copyright 2020, Elsevier.

Table 1
List of different types of mesoporous silica nanoparticles (MSNs) and their characteristic properties.

MSN Type	Pore Symmetry	Surface area (m^2/g)	Pore Size (nm)	Pore Volume (cm^3/g)	Reference
MCM-41	P6mm	1082	2.53	0.97	(Costa et al., 2021)
MCM-48	Ia3d	1014	2.62	0.94	(Costa et al., 2021)
SBA-1	Pm3n	1470	2.4	0.84	(Zapilko and Anwander, 2006)
SBA-2	P63/mmc	850–1010	2.5–2.6	0.58–0.69	(Zapilko and Anwander, 2006)
SBA-15	P6mm	900	8.5	1.88	(Albayati and Doyle, 2015)
FDU-12	Fm3m	654–716	10.2	0.60–0.68	(Seljak et al., 2020)
TUD-1	Disordered	400 – 1000	4 – 18	0.5 – 1.7	(McCarthy et al., 2016)
COK-12	P6mm	429–547	5.8–9.4	0.45–0.88	(Seljak et al., 2020)
FSM-16	Disordered	~1000	1.5–3.2	~0.65	(Khalbas et al., 2024)
KIT-5	Fm3m	447–740	6.1–9.8	0.21–0.75	(Tsoncheva et al., 2009)
KIT-6	Ia3d	359–780	5.3–8.1	0.26–0.85	(Tsoncheva et al., 2009)
MCF	Foam	590	22.6	2.12	(Khalbas et al., 2024)
HMSNs	Hollow	590	22.6	2.12	(Xu et al., 2017)
PMO-1	P6mm	750	3.1	n.a	(Inagaki et al., 1999)
PMO-2	P63/mmc	1170	2.7	n.a	(Inagaki et al., 1999)

$$\text{Condensation}: \equiv Si - OH + OH - Si \equiv \rightleftharpoons \equiv Si - O - Si \equiv + H_2O$$

$$\equiv Si - OH + RO - Si \equiv \rightleftharpoons \equiv Si - O - Si \equiv + ROH$$

3.1. Synthesis parameters of MSNs

The characteristics of the particles produced during the synthesis can be vary according to the silica precursor and the type of surfactants. Hydrolysis and condensation are highly dependent on the type of silica precursor and the pH of the reaction medium. In addition, the generated pores vary in size and length according to the size and concentration of the micelles. Therefore, these synthesis parameters highly affect the physicochemical, surface, and structural properties of produced MSNs (Wu et al., 2013). Accordingly, manipulating the synthesis conditions enables us to control the characteristics of the produced MSNs.

3.1.1. Silica precursors

Two different sources of silica can be used in the production of MSNs. a) Synthetic silica precursors such as tetraethyl orthosilicate (TEOS), tetramethyl orthosilicate (TMOS), and tetramethylsilane (TMS). b) Natural silica sources such as those derived from silicon-rich biomass ash (e.g. rice Husk and sugarcane bagasse) (Porrang et al., 2022). The choice of silica precursors can affect the rate of hydrolysis and condensation of silica, the arrangement of silica around the micelles, and the formation of mesopores. The silica density and equilibrium concentration during hydrothermal treatment can also affect the order of the mesoporous structure. By using natural silica sources, the method of silica extraction significantly impacts the purity and structure of the resulting MSNs. Furthermore, the presence of minerals may alter the particle size and surface area of produced MSNs (Okada et al., 2010; Porrang et al., 2022).

3.1.2. Surfactant type

Surfactants are considered the main critical component in the synthesis procedure, as they contribute to modifying and generating the pores and crystalline structures. Surfactants have both hydrophilic and hydrophobic parts. When a surfactant reaches a desired concentration in solution, the existence of hydrophilic groups induces the molecules to self-assemble into aggregates that take various shapes and promote the formation of morphology-defined nanocrystals (Song et al., 2021). In addition, the length of the hydrophobic organic chain significantly influences the morphology and structure. Based on the functional group of surfactants and the surface charge of silica precursor, a suitable surfactant template can be selected to tailor and control the nanostructure of synthesized products (Li et al., 2021). Depending on the dissociation of surfactant molecules in aqueous media, there are three types of surfactants: a) Cationic surfactants, which are nitrogenous compounds such as amine salts and quaternary ammonium salts (e.g. CTAB and CTAC). b) Anionic surfactants of alkaline metals (Na+, *K*+) or a quaternary ammonium ions (e.g. sodium dodecylbenzene sulphonate. c) Nonionic surfactants with a non-dissociable hydrophilic part, such as triblock polymers (P123 and F127) (Pal and Bhaumik, 2013).

3.1.3. Co-surfactants

These materials include solvents such as butanol, ethanol, and

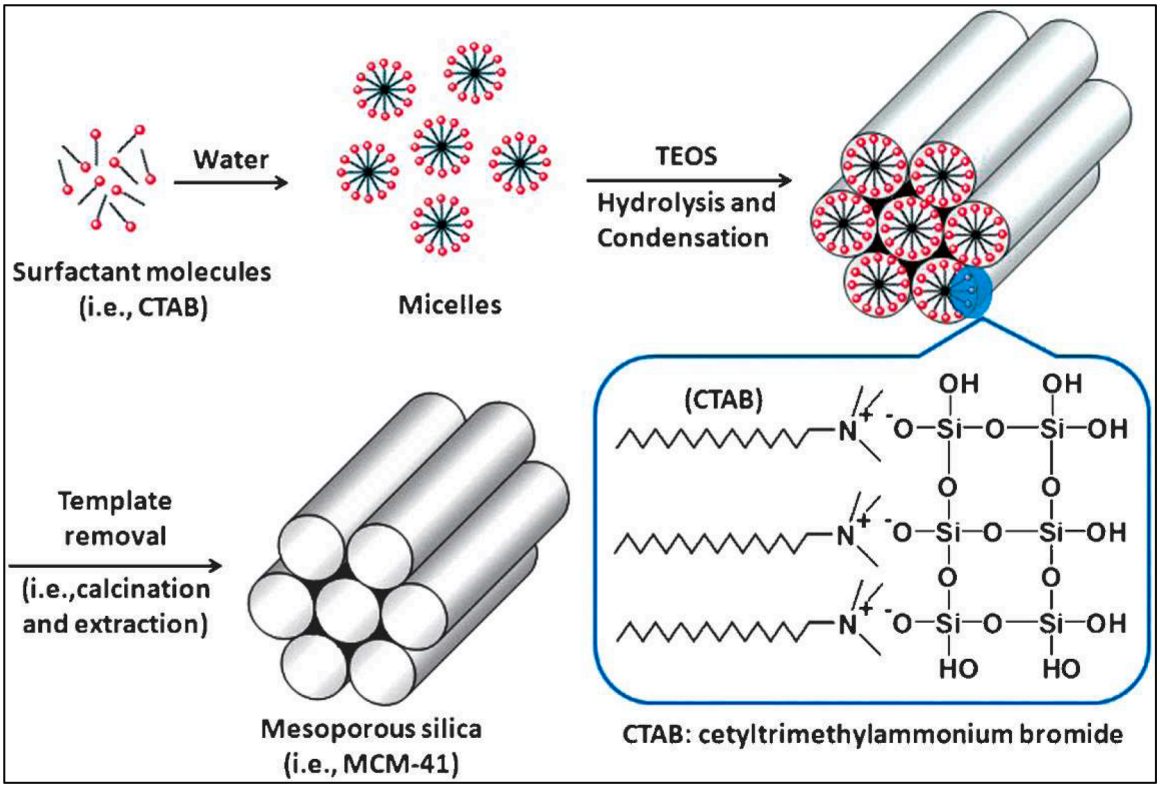

Fig. 3. Scheme of the formation mechanism of mesoporous silica nanoparticles (e.g. MCM-41). Reproduced with permission from (Yang et al., 2012). Copyright 2012, Royal Society of Chemistry.

propanol or co-template such as copolymers and ionic liquids. The purpose of using a co-solvent is usually to increase the solubility of the surfactant to prevent the agglomeration of particles, manipulate the critical micelle concentration, and tune the pore architectures within the MSNs (Q.L. Wu et al., 2012). However, using large volumes of the co-solvent may lead to diluting the reaction medium and reducing the condensation reactions of silica (Porrang et al., 2022). Co-template is usually used to control the morphology and particle size of MSNs. Subsequently, a wide range of mesostructured silica with different symmetries can be synthesized by changing the type and concentration of the co-template (Huang et al., 2020).

3.1. 4 pH

pH is one of the important parameter that can affect the rate of hydrolysis and condensation of silica. Below the isoelectric point of silica (IEP = 2.0), the positively charged silica and the charge density increased. The silica condensation rate increases up to pH=7.5. In this range, Si-O− species increased and led to self-assembly with surfactant molecules through electrostatic and hydrogen bonding forces. At pH>7, silicate molecules with high negative charges can only interact with cationic surfactants by strong electrostatic forces. pH-changing process can be used to shift the pH range of the reactant silanol groups by adding alcohols, amines, and inorganic salts. In general, pH plays an essential role in the size tuning of the produced nanoparticles (Porrang et al., 2022; Wu et al., 2013).

3.1.5. Temperature

The structure and morphological properties of the produced MSNs are highly dependent on the silica condensation rate and the interaction behavior of the surfactant molecules, which are highly sensitive to temperature and time. Therefore, the concentration and nature of silanol groups, in addition to the degree of microporosity, can be modified by changing the temperature during synthesis steps. Generally, two steps are performed with respect to temperature during the synthesis procedure, : ripening and aging temperature (Brodie-Linder et al., 2008). The influence of the ripening temperature (28, 40, or 55 °C) on the physicochemical characteristics of SBA-15 was investigated by (Benamor et al., 2012). The results showed that the size and shape of the hybrid micelles are temperature-dependent, being slightly elongated at low temperatures and larger like-thread at high temperatures. Furthermore, increasing the ripening temperature increases the hydrophobicity of the PEO units of triblock p123; consequently, the microporous volume decreases, the pore size increases, and the siliceous region becomes thinner. (Sousa and Sousa, 2006), evaluated the effects of aging temperature (60 °C, 80 °C, 100 °C and130 °C) on structural properties of mesoporous silica. It was concluded that higher temperatures during the aging process resulted in larger pore sizes and thinner silica walls.

3.2. Functionalization methods

The hydrophilic surface nature, with abundant Si-OH groups of MSNs, is a key factor that allows for the tuning of the material by introducing of functional groups on both the exterior as well as interior porous surfaces (Kankala et al., 2020). The functional groups play a significant role in drug delivery by regulating the release of drugs based on particulate stimuli or physiological conditions and overcoming biological barriers. The loading of drugs into MSNs can also be enhanced by increasing the adsorption capacity through the generation of strong bonds. Furthermore, the biocompatibility and biodegradability of MSNs are highly dependent on the surface functional groups (Natarajan and Selvaraj, 2014). Generally, there are two types of modification strategies:1) Post-grafting synthesis, 2) One-pot synthesis (co-condensation). The post-grafting method involves a direct reaction between organosilane and silica surface after the free template -mesostructured silica is obtained. Indirect reactions between organic groups and silica surfaces can be done by covalent bonding or molecular recognition (Vinu et al., 2005). This method can preserve the structure of pores and channels with a simple and effective procedure. However, there is an issue with

obtaining a uniform distribution of functional groups throughout MSNs (Asefa and Tao, 2012a). Co-condensation method involves the direct reaction between alkoxysilane such as TEOS and functional groups with the presence of surfactant. This method exhibits a highly uniform distribution of functional groups with only one step. However, the template must be removed carefully to avoid the destruction of functional groups (Chircov et al., 2020). The advantages and disadvantages of the two methods are summarized in Table 2.

4. Drug loading

Drug loading is a promising strategy to produce highly stable amorphous drugs with improved dissolution rate, solubility, and bioavailability. The ideal loading process should be able to load large amounts of drugs, minimize drug deposition on the external surface, maximize pore filling, and release the drug to the targeted sites in the desired pattern. The drug can be encapsulated into MSNs in an amorphous form by two mechanisms: a) the adsorption of drugs to the inner/outer surface of MSNs through drug-carrier interactions such as hydrogen bonding, van der waals interactions, electrostatic binding, or covalent bonding. b) The nanoconfinement effect is due to the smaller pore size of MSNs compared to critical crystalline nuclei (Budiman and Aulifa, 2022; Trzeciak et al., 2021). The amount of drug loaded mainly depends on the characteristics of the carrier such as surface area, pore size, pore volume, and surface functional groups. In addition, the physicochemical properties of the solution such as solubility, pH, and the affinity between the solvent, drug, and carrier. The choice of loading method also affects the loading capacity, drug distribution inside the carrier, degree of crystallinity, and amount of drug released (Juère and Kleitz, 2018; Xu et al., 2013). The following equations represent the content and effectiveness of drug loading:

$$\text{loading efficiency \%} = \frac{\text{mass of drug in MSNs}}{\text{initial mass of drug}} \times 100\%$$

$$\text{Drug loading content \%} = \frac{\text{mass of drug in MSNs}}{\text{mass of MSNs}} \times 100\%$$

Table 2
Advantages and Disadvantages of the Two Commonly Adopted functionalization methods.

Method	Advantages	Disadvantages	Reference
Post-grafting (step-wise) synthesis	1. it enables the introduction of functional groups to as-made mesoporous silica without causing the mesostructure and mesoporosity of the material to degrade or alter. 2. suitable organosilanes,a wide range of organic functionalized silica can be synthesized selectively with different physical and chemical properties.	1. The conditions and reagents employed during the grafting of the organosilanes onto the mesoporous silica, such as pH, temperature, reaction time, and the solvent used, can also affect the density of the grafted organic groups in the final material. 2. low control over the final location of the precursor groups (non-homogeneous functionalization) and the ligand spatial arrangement of metallic complex or organic molecules.	(Asefa and Tao, 2012a; Costa et al., 2021; Pal and Bhaumik, 2013)
co-condensation (one-pot) synthesis	1. uniform distribution of the functional groups within the structure and less time consuming method. 2. avoid pore blockage in case of using bulky and high molecular weight functional groups. 3. it is very efficient in immobilizing enormous amounts of functional groups onto the mesoporous silica surface.	1. functional molecules may be co-condensed and cross-linked with the silica precursors, affecting hydrolysis and condensation rates and subsequently the structural features of resultant MSNs. 2. the possibility of destroying the functional groups during template removal. Only the extractive method should be used due to the high temperatures of the calcination method.	(Da'na, 2017; Rath et al., 2014)

4.1. Drug loading methods

API loading into porous carriers is most commonly achieved by solvent-based methods and solvent-free approaches. The solvent-based methods generally involve immersing silica particles in a solution, where the adsorption of drug molecules takes place. Then, the organic solvent is separated from the solution through filtration, evaporation, or drying, resulting in the loaded material (Khalbas et al., 2024). Solvent methods are the ideal choice for heat-sensitive materials and when precise loading amounts and highly stable amorphous drugs are needed. The major challenges of these methods are the use of large amounts of organic solvents and the need for an extra drying step to remove the solvents. In addition, the yield is often quite low, and the scale-up process can be challenging (Genina et al., 2018). Compared with solvent methods, solvent-free methods are less time-consuming and can achieve a high degree of drug loading. Moreover, the saturation state of a solution containing drug and MSNs is easy to predict as it is directly influenced by the ratio between API and MSN. They are environmentally friendly techniques, as they do not require checking the residual solvent in drug products (Trzeciak et al., 2021). However, the stability of drug loaded by these methods should be continuously monitored, as the possibility of re-crystallization of drug is highly prevalent. Table 3 presents some literature studies concerning drug loading methods using MSNs.

4.1.1. Adsorption equilibrium

The adsorption mechanism mostly involves the transfer of drug molecules from the bulk solution to the active sites of MSNs, followed by the penetration of molecules into the internal structure of MSNs. The degree of attaching molecules to the inner pores and channels is determined by the nature of bonds created between the drug and the silica particles (Ghaedi, 2021; Maleki et al., 2020). The adsorption equilibrium method has been used extensively in drug delivery applications due to its simplicity, preservation of drug structure and bioactivity compared to covalent bonding, and its potential to create novel stimulus-responsive carriers (Mochalin et al., 2013). However, this method results in low drug loading levels, and the drug concentration must be kept below the saturation level to avoid the deposition on the external surface of the carrier. Therefore, the monolayer capacity of a carrier must be determined to avoid excessive loading and undesirable potential leakage of the adsorbed drug (Farzan et al., 2023). By using adsorption equilibrium, (Šoltys et al., 2019) explained that the type of solvent affects the drug loading efficiency. For example, valsartan loaded from dichloromethane (DCM) achieved a loading of 34.6 % by weight, which was significantly higher than the 14.4 % achieved when methanol was used, despite the drug concentration in DCM being much lower than that in methanol. The high solubility of a drug in a solvent does not necessarily translate to high loading efficiency. This is because the solvent may interact favorably with the drug molecules, which competes with the adsorption of the drug onto the carrier surface.

4.1.2. Solvent evaporation

This method is similar to the adsorption equilibrium method in which the drug is dissolved in a suitable solvent and brought into contact

Table 3
Some studies related to drug loading methods using mesoporous silica nanoparticles.

Loading method	MSN type	Active drug	Loading (wt.%)	Ref
Incipient wetness impregnation	MCM-41	Kaempferol	25	(Trendafilova et al., 2021)
	Mg-MCM-41		30	
Incipient wetness impregnation	SBA-15	Mirtazapine	33.33	(Musallam et al., 2022)
Solvent evaporation	SBA-15	Quercetin	41.8	(Trendafilova et al., 2017)
	Zn- SBA-15		45.5	
Solvent evaporation	SBA-15	Carbamazepine	20	(Wu et al., 2012a)
Adsorption Equilibrium	MSNs	Carvedilol	7.9	(Han et al., 2019)
Adsorption Equilibrium	MCM-41	Mirtazapine	n.a	(Musallam et al., 2022)
	SBA-15			
One pot drug loading and synthesis	MSNs	Doxorubicin	n.a	(Jiang et al., 2018)
One pot drug loading and synthesis	SBA-15	Ibuprofen	n.a	(Wan et al., 2016)
		Heparin		
Supercritical carbon dioxide method	MCM-41	Ibuprofen	15.1- 38.6	(Li-hong et al., 2013)
Liquid carbon dioxide (CO_2) method	NH_2-MCM-41 PO_3-MCM-41	Meropenem	25–31	(Raza et al., 2021)
Co-spray drying	SBA-15	Artemisinin	23.6–48.8	(Letchmanan et al., 2015)
Co-spray drying	MSNs	Fenofibrate	30	(Zhang et al., 2022)
Fluidized bed dryer	MSNs	Paracetamol	18.8	(Hacene et al., 2016)
Melt method	SBA-15	Indomethacin	45	(Shen et al., 2017)
		Iitraconazole	45	
Fluid bed hot-melt impregnation	MSNs	Ibuprofen	30–50	(Mužík et al., 2020)
Microwave-assisted loading	SBA-15	Fenofibrate	n.a	(Waters et al., 2013)
	Syloid®			
Microwave-assisted loading	Syloid AL-1	Gemfibrozil	n.a	(Hussain et al., 2017)
	Syloid 244			
	Syloid 72			
Milling-assisted loading	SBA-15	Ibuprofen	37	(Malfait et al., 2019)
Milling-assisted loading	Syloid®XDP3050	Mangiferin	n.a	(Baán et al., 2019)

with silica nanoparticles to reach adsorption equilibrium (Fig. 4). However, the solvent separation step is different. The solvent is allowed to evaporate gradually by a hot plate or rotary evaporator. This gradual removal of the solvent produces a moderate driving force by increasing the drug concentration, which may enhance the mass transfer of the drug between MSNs and the external solution and improve the uptake of the drug into MSNs (He et al., 2017). The evaporation method provides more loading capacity than adsorption equilibrium. However, recrystallization of the drug on the surface of the carrier may occur at an excessive drug concentration. Furthermore, the recovery of large quantities of evaporated organic solvents may lead to elevated operational costs in the case of large-scale production (Šoltys et al., 2021). Ritonavir (RTV) was loaded into MSNs using the solvent evaporation (Budiman and Aulifa, 2022) . Amorphization of RTV was successfully achieved. The loading process improved the physical stability of the amorphous RTV after storage in the presence of humidity. This is due to the strong interaction between RTV and the surface of MSNs, which inhibited the crystallization of RTV. In comparison with the simple adsorption impregnation method, (Deng et al., 2021) showed that the loading percentage of water-insoluble paclitaxel (PTX) into dendritic mesoporous silica was only ~1.33 wt%. This is likely because the silica substrate lacks sufficient affinity to sequester the hydrophobic

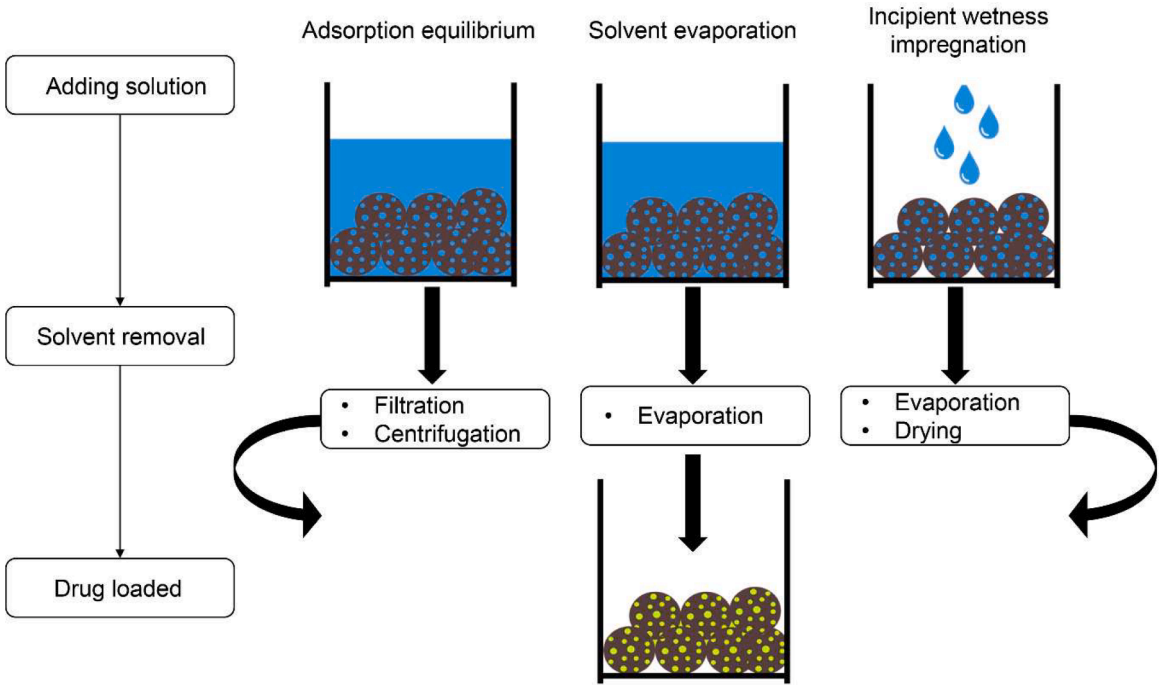

Fig. 4. Illustration of the process steps for the solvent immersion loading methods. Reprinted with permission from (Khalbas et al., 2024). Copyright 2024, Elsevier.

drug molecules from the outer organic solvent into the mesopores. Therefore, by applying the vacuum-rotary evaporation technique, a higher loading capacity with uniformly distributed drugs was achieved.

4.1.3. Incipient wetness impregnation

Incipient Wetness Impregnation (IWI) involves the addition of a minimum amount of concentrated drug solution just enough to fill the pore volume of the carrier. During the addition of solution, the drug distribution inside the carrier pores is driven by capillary forces. The pore characteristics and the concentration of the drug directly affect the amount of drug loading (Ebrahimi et al., 2017). Besides the loading of different molecules, the IWI method has been widely used in the preparation of metal support catalysts. This eliminates the need to use large amounts of solvent and the need for a filtration step. However, catalysts made by this method may not always produce high-dispersion particles due to the absence of favorable interaction between the precursor and support matrix. Furthermore, the drying of the solvent may lead to movement of the molecules from the pores to the external surface of the carrier, causing the accumulation of particles (Mehrabadi et al., 2017). Itraconazole and ibuprofen were loaded into SBA-15 using different methods (Mellaerts et al., 2008) . No signals that can be ascribed to the drug phase transition were observed using IWI or solvent evaporation, which evidenced the molecularly dispersed state. The IWI entailed a stronger reduction in the micropore volume and a smaller reduction in the mesopore volume in comparison with the solvent method. In addition, the IWI method favors the positioning of itraconazole molecules in the micropores, whereas the solvent method favors their positioning on mesopore walls. To study the effect of the drug loading method on loading efficiency, (Musallam et al., 2022) studied mirtazapine (MRT) loading into SBA-15 using incipient wetness, solvent evaporation, and solvent impregnation methods. The optimization results indicated that higher drug efficiency was achieved by the incipient wetness method. This may be due to the high initial concentration of the MRT solution that efficiently drives the molecules to enter the micropores and deposit along pore walls, preventing the migration of molecules to the external surface during solvent evaporation.

4.1.4. One pot drug loading and synthesis

This method is an alternative to post-synthesis drug loading methods that involves the self-assembly of drug molecules together with a silica precursor in one pot to form a drug-silica composite (Stewart et al., 2018). The encapsulation of the ibuprofen drug in the channels of mesoporous silica can be accomplished by a one-step, drug self-templating technique. Ibuprofen can be used as a model drug and template simultaneously. The formation of the mesostructure is controlled by using a co-template of aminopropyltriethoxysilane (APTES). The negatively charged carboxylic group of ibuprofen electrostatically interacts with the positively charged amine group of APTES. Then, the condensation of silica occurs in specific sites of alkoxysilane, resulting in the formation of the silicate framework (Qu et al., 2006). (Jiang et al., 2018), utilized the one-pot green method to load doxorubicin (DOX) in silica particles using biocompatible Tween 80 as a template. DOX molecules are first loaded within the Tween 80 micelles, followed by the condensation of silica precursors around the micelles to form DOX-loaded mesoporous silica. The results showed that in the presence of DOX, the resulting nanoparticles exhibited a larger particle size with a wide particle size distribution. This can be attributed to the amount of drug loaded that enlarges the micelles and possibly reduces the stability of the silica nuclei. Evaporation-induced self-assembly (EISA) is another strategy for loading drugs with both hydrophilic and hydrophobic nature. (Wan et al., 2016), used EISA to load heparin and ibuprofen into mesoporous silica by using P123 as a template in a one-pot co-self-assembly method. The in-situ of heparin by EISA method, increased the amount of drug in mesoporous silica four times higher than that impregnated with SBA-15. Besides that, the amount of ibuprofen increased by 166 % compared with that when the impregnation method was used. This method can be used to load drugs and control the pore characteristic at the same time without the use of a toxic solvent. However, due to the low temperature used in the synthesis, the produced MSNs often have a low-ordered structure. Furthermore, the amount of drug loaded strongly affects the properties of the resulting MSNs.

4.1.5. Fluidized bed dryer

Fluidized bed dryers are widely used in industrial applications for drying, coating, and granulation. They provide sufficient contact area between the solid carrier, drug solution, and gas with a high degree of mixing. This enhances the heat and mass transfer rates between the loaded material and drying gas. All of these factors shorten the drying time without affecting the structure of the produced formulation, such as in the case of heat-sensitive materials (Mortier et al., 2011). In this method, impregnation and drying occur simultaneously without the need for repetitive cycles of spraying and drying. This process involves three consecutive steps: 1) the drug solution in a suitable solvent is sprayed onto a porous carrier in a fluidized state, 2) the solution containing the active drug penetrates the porous carrier by capillary force, and 3) the carrier loaded with the drug, is dried while it moves around the bed (Fig. 5). This method offers uniform distribution of the drug within MSNs by providing uniform blending conditions with narrow-sized particles. It is a single-step method and easy to scale up for large-scale production. The spray rate, fluidization gas inlet temperature, and gas flow rate ultimately control the impregnation process (Grigorov et al., 2013; Omar et al., 2019). However, the sieving of particles to a suitable size is necessary to avoid attrition caused by friction and the possibility of clogging the nozzles. In addition, poor working conditions may lead to particle agglomeration, decrease in the quantity of drug/carrier, and the accumulation of drugs onto the external surface of the carrier rather than the pore network (Hacene et al., 2016).

4.1.6. Co-spray drying

Spray drying is a technique used to produce pharmaceutical formulations by converting solutions or suspensions into fine powders. It consists of four basic steps: atomization of the drug solution containing porous particles, mixing of the solution with drying gas, solvent evaporation, and separation of the dried solid from gas (Fig. 6). Atomization converts the liquid into fine droplets by a nozzle, which increases the surface area/volume ratio by reducing the size distribution and thus promotes the rapid drying of particles. This makes it effective in producing highly amorphous solid dispersions (Paudel et al., 2013) . To examine the stabilization of the amorphous state of ibuprofen (IBU) with SBA-15, (Shen et al., 2010) compared drug loading via co-spray drying and the impregnation method. X-ray diffraction peaks showed a fully amorphous state of ibuprofen and excellent homogenous particle size distribution of IBU in the mesoporous matrix. At a ratio of IBU/SBA-15 (50:50, w/w), IBU crystals were formed using the impregnation process, whereas only spray drying produced IBU without any trace of crystalline peaks observed. The drug loading of MSNs results from two consecutive steps of pore filling: 1) the physisorption of IBU in the initial stages of mixing with nanoparticles prior to the atomization process, and 2) the diffusion of IBU molecules into the pores driven by the force generated from solvent evaporation during the drying stage (Ruffel et al., 2020). Another comparison between spray drying and physical mixing was conducted by (Letchmanan et al., 2015) for loading artemisinin (ART) drugs in SBA-15. The results showed that the physical state of ART changed from a crystalline state to an amorphous state after co-spray drying with SBA-15. In addition, the physical mixing of ART/SBA-15 still revealed a completely crystalline form. The reason for successful amorphization is due to the nano-confinement effect of SBA-15, besides the favorable rapid evaporation of the solvent. The encapsulation of ART inside the nano-sized pore channels of SBA-15 through capillary condensation prevents the nucleation and formation of long-range

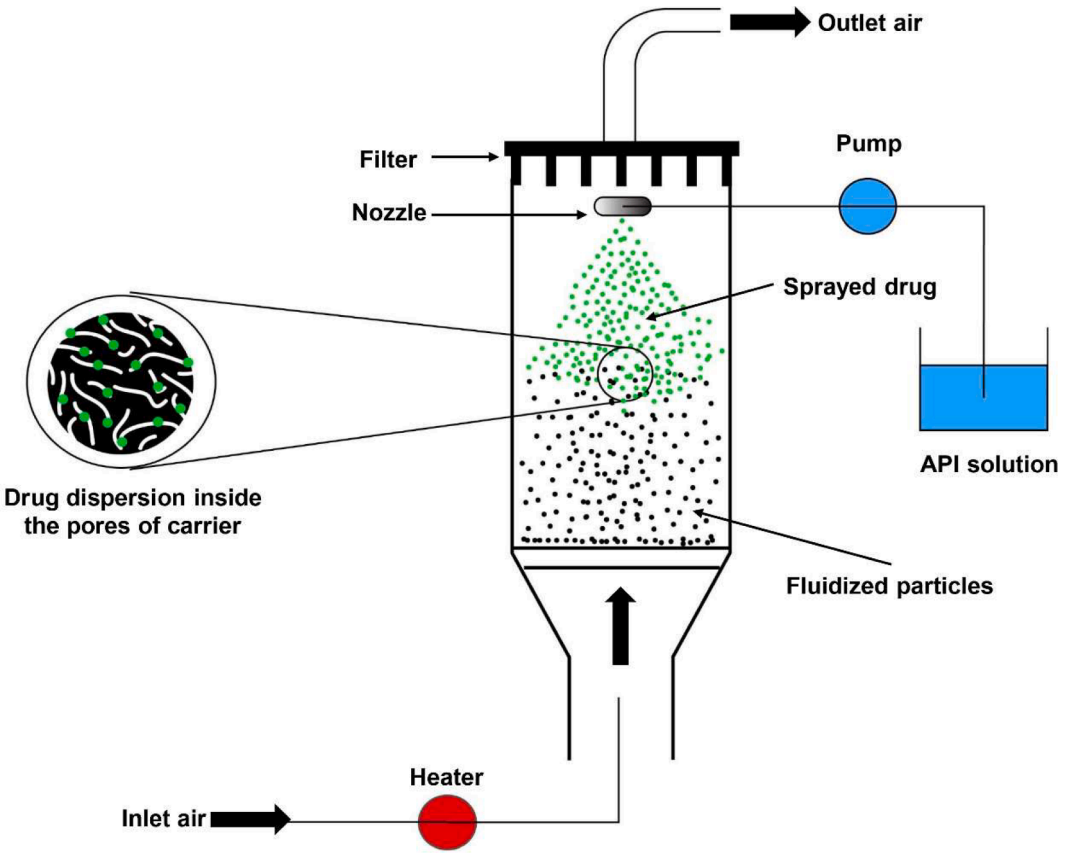

Fig. 5. Experimental setup of the fluidized bed dryer.

ordered crystalline structures.

4.1.7. *Supercritical carbon dioxide technology ($scCO_2$)*

Supercritical solution impregnation involves the dissolution of drugs in supercritical fluids, in which the drug diffuses into the pores of the carrier matrix not only by diffusion but also via precipitation from the critical solution during the depressurizing steps. Supercritical fluids have unique properties, such as a density close to that of a liquid, viscosity similar to that of gases, and higher diffusivity (Bouledjouidja et al., 2016; González et al., 2023). Among various fluids, CO2 is cost-effective, nontoxic, and non-flammable. It can be easily removed from the particles by the depressurizing step without leaving any residual solvents. The low surface tension of CO2 enhances the impregnation process with a low working temperature, which prevents the drug from decomposing (Raza et al., 2021). ScCO2 is an alternative method to solvent immersion for loading poorly soluble drugs. The inclusion of fenofibrate on mesoporous silica was evaluated by ScCO2 compared to the IWI method (Bouledjouidja et al., 2016). The results indicated that supercritical impregnation has a higher loading (>485 mg drug/g silica) compared to that in the witness impregnation (300 mg drug/g silica). They also reported that the degree of crystallinity can be reduced to a comparable value with the IWI by using slow depressurization conditions. Likewise, ibuprofen was loaded into MCM41 using solvent immersion and $ScCO_2$ (Li-hong et al., 2013). The drug loading content was higher in supercritical immersion (34.7 %) compared with solvent immersion (15.1 %). This may be due to the following: a) the viscosity of $ScCO_2$ is much lower than that of liquid, which enhances the diffusion rate of the drug; b) the volume of pore channels of MCM41 is increased after the pressurizing step, which also increases the diffusion rate; c) the use of CO_2 as a solvent eliminates the drying and filtration steps, which prevent the migration of the drug to the external surface of the carrier; and d) during decompression, the pressure in the pores is slightly higher than that of the surface, leading to drug migration from the surface to the internal pores. Although $ScCO_2$ is a green and effective method for encapsulating drugs, the addition of co-solvents is sometimes necessary to achieve impregnation due to the low solubility of some drugs (e.g., mangiferin) in CO_2 (García-Casas et al., 2018). The experimental setup of supercritical immersion loading is presented in Fig. 7.

4.1.8. *Melt method*

The method involves heating a mixture of API and MSNs to a temperature above the melting point of the drug, after which the molten drug moves into the porous structure by strong capillary force, where quench cooling is applied to obtaine the powdered form. When the pore size is small, approximately not exceeding ten times the equivalent molecular diameter of the drug, the drug can be confined in an amorphous state for a long period of time (Zůza et al., 2019). Poorly soluble drugs, ibuprofen and fenofibrate , were loaded into SBA-15 by melting methods (Shen et al., 2017). The results revealed that the molten drugs were quickly adsorbed into the pores of SBA-15. After cooling to room temperature, the powder was obtained in an amorphous state as the drug molecules were confined within the mesoporous channels without sufficient space for crystal formation and growth. Due to the high viscosity of some molten drugs and the complex pore networks of the carrier, the distribution of the drug may occur randomly in the structure and selectively deposited on the external surface of the carrier. (Mellaerts et al., 2008), confirmed that itraconazole failed to disperse into SBA-15, and that the drug aggregated outside the carrier. In contrast, ibuprofen was uniformly distributed inside the pores due to its low viscosity. The melting process can be used on a large scale by adopting a fluidized bed, in which the contact time can be significantly reduced and the overall output can be increased. By using this technique, ibuprofen was successfully loaded into mesoporous silica microparticles with loading contents of 30 % and 40% w/w. Controlling

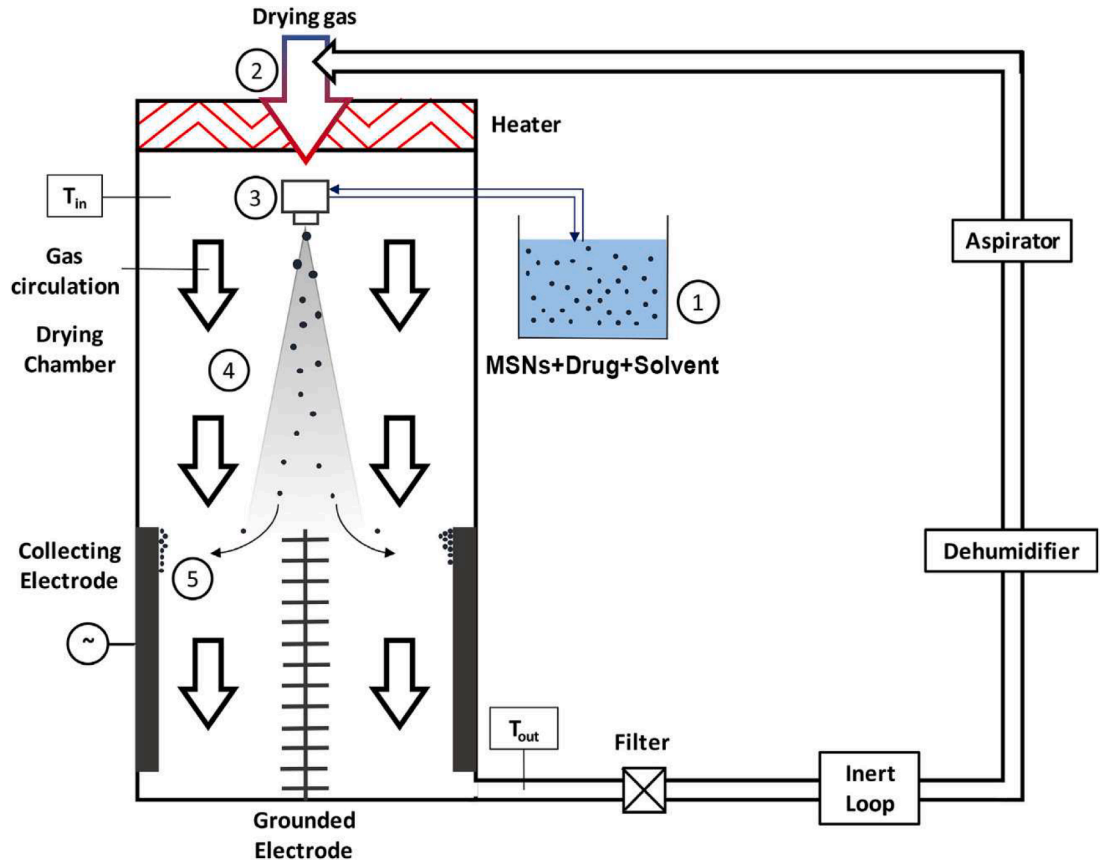

Fig. 6. Flowsheet of the nano spray-drying process. Adapted with permission from (Ruffel et al., 2020). Copyright 2020, Elsevier.

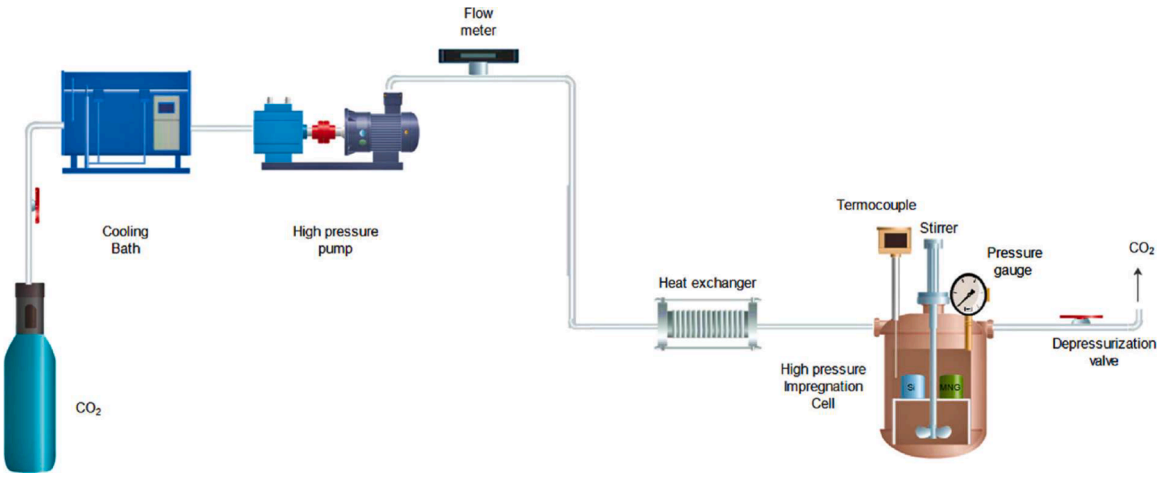

Fig. 7. Experimental setup of supercritical immersion loading. Reproduced with permission from (García-Casas et al., 2018). Copyright 2018, Elsevier.

time and temperature, besides the hierarchical porosity of the carrier, all contributed to promoting the amorphous state of API up to 50 % loading content (Mužík et al., 2020) . Hot melt extrusion (HME) is another type of large-scale melting method (Genina et al., 2018). This method is based on the solid materials transfer through a heated barrel, equipped with single or twin screws, in which the solid material melts and mixes in the barrel and exits as a semi-solid strand (extrudates) through the die and solidifies instantly. HME can produce a high dispersion of the drug in an amorphous state. However, due to the friction between silica particles and extruder parts, polymers should be added to the carrier to avoid extruder blockage. Sometimes, the presence of a polymer may be problematic if the interaction forces between the polymer and drugs are much higher than those with silica particles, leading to low drug loading.

4.1.9. Milling-assisted loading

Dry-milling amorphization is another strategy for increasing the bioavailability of poorly soluble drugs. This method applies mechanical energy to a drug-silica mixture that affects the particle size and surface area properties. The mechano-chemical activation leads to the disordering of the crystalline structure of drugs, resulting in amorphization (Szafraniec et al., 2017). Milling methods allow a relatively high degree of filling with an elevated loading capacity of (35 to 40 wt%). However, the conversion of the loaded drug into a crystalline phase may initiate

due to thermodynamic alternation. Besides, agglomeration of particles may occur due to the increased free energy of micronized particles with high surface energy. The degree of loading may be influenced by several parameters such as time, energy intensity, and surface chemistry of the nanoparticles (Malfait et al., 2019; Moutamenni et al., 2023). The stability of amorphous drugs can be increased by using excipients such as polymers. A poorly water-soluble compound, mangiferin, was processed with ball milling using MSNs. (Baán et al., 2019), concluded that the amorphization of mangiferin was achieved after 20 min of processing in a planetary mono mill with a milling speed of 600 rpm. By applying low energy, mangiferin crystals are still present, whereas with high-energy milling, complete dispersion of mangiferin in the silica pores is achieved. The preparation of ternary systems using mesoporous silica-API-polymer systems can improve the amorphization of the API and also the stability of the amorphous form in the formulation. A higher amorphization rate was confirmed, even with low milling settings (11.5 ± 0.5 % crystalline compound content) compared to the binary formulation (30.5 ± 1 % crystalline compound content).

4.1.10. Microwave-assisted loading

The microwave-assisted technique has been extensively utilized for the synthesis of various types of materials, including metallic nanomaterials, mesoporous silica, and metal-organic frameworks. Microwaves produce an intense electromagnetic field that generates dynamic dipole moments in molecules. These molecules are polarized and begin to oscillate and generate heat. Therefore, microwave heating offers advantages such as a uniform temperature distribution inside the material, rapid volumetric heating, low consumption of time, and the possibility of obtaining materials with diverse properties (Díaz De Greñu et al., 2020; Purcar et al., 2021). The microwave technique can be used to load drugs into MSNs by controlling the temperature of the sample and avoiding unwanted drug degradation. Tailored microwave heating is used to incorporate fenofibrate into mesoporous silica. A significant enhancement in the release profile of fenofibrate was observed (Waters et al., 2013). In another study by (Hussain et al., 2017), gemfibrozil was loaded into three different types of nonordered mesoporous silica (Syloid AL-1, Syloid 72, and Syloid 244). The results showed that the decrease in the melting peak intensity of gemfibrozil was more prominent than that of the physical mixing method. A large payload of drug molecules, high pore filling, and a complete amorphous state of gemfibrozil were achieved by Syl-244. This was attributed to the large pore volume and diameter of Syl-244, confirming that the pore volume has an influence on the drug loading and amorphous state when the microwave loading method is used.

5. Drug release

The term drug delivery generally refers to the transfer of active pharmaceutical substances from the route of administration to a biological system at a particular organ or tissue (Ahmady et al., 2022). An ideal drug delivery system should maintain the drug concentration within the therapeutic window with maximum therapeutic efficiency and minimum toxicity (Hassan and Zhang, 2019). The carrier system must satisfy several considerations before use for controlled release, such as: 1) high biocompatibility, 2) high drug loading capacity, 3) zero premature drug release, 4) site-specific release to the cell or tissue, and 5) proper controlled release to achieve the desired level of drug (Xu et al., 2012). Poorly water-soluble drugs have several adverse effects such as rate-limiting release, low absorption, and insufficient bioavailability. One key solution to overcome these issues is to load the drug on a high surface area inorganic carrier with multifunctional properties. MSNs are one of the promising nanomaterials due to their unique features such as a large surface area, easily modified pore size and volume, being chemically inert, and easier chemical functionalization of their surface (Xu et al., 2013; Zhang et al., 2010).

5.1. Factors influencing the drug release from MSNs

There are several factors influencing the drug release from MSNs. First, due to the release rate from MSNs is mainly driven by the diffusion process, the pore size is a major factor affecting the release process. (Zhu et al., 2014) examined the effect of MSNs with different pore sizes (16.0, 6.9, and 3.7 nm), referred to as FMS-15, FMS-18, and FMS-20 respectively, on the drug loading and release of celecoxib (CEL). They showed that the release rate increased with increasing pore size, in which FMS-15 exhibited a higher release rate. This can be attributed to the lower diffusion resistances encountered by larger pore size and volume, which increases the possibility of escaping molecules from the pores and transferring them into the medium. To study the influence of pore architecture on drug release, (Limnell et al., 2011) selected two types of silica materials, ordered MCM41 and non-ordered silica gel Syloid244 to investigate the dissolution behavior of indomethacin (IMC). The results showed that the ordered structure does not influence the drug release. The release of IMC was further increased using non-ordered Syloid244 due to its larger pore size, smaller particle size, and wide pore volume compared to MCM41. Besides pore characteristics, surface functionalization is another factor used to improve the controlled release of drugs by producing particular interactions between the functional groups on the surface of MSNs and the adsorbed molecules. In the loading procedure, a strong interaction is required to promote the adsorption process, whereas, at the release step, strong repulsion forces are favorable for rapidly releasing the drug from the matrix (Maleki et al., 2017). For example, the encapsulation of pentamidine (PTM) into bare MSNs and carboxy propyl-functionalized MSNs (MSN—COOH) influences both the drug loading capacity and release. A higher release rate of PTM was achieved from bare MSNs, reaching 90 % compared to MSN—COOH (60 %). These values are due to the contribution of carboxyl groups stabilizing the molecules in the inner pores of MSNs by hydrophobic interactions. As a result, the drug was retained for an expanded period inside the mesopores and released more slowly than that from the bare MSNs (Peretti et al., 2018). Functionalization of the pore surface with gating molecules has been widely used to produce stimuli-responsive mesoporous systems. This can be accomplished by surface coating, internal pore modification, or molecular pore gating. When the gating molecules cover the pores, they interact with macromolecular structures known as linkers attached to the surface of the particles. These linkers are highly responsive to specific stimuli (e.g., redox and pH), resulting in the removal of these linkers and the release of the drug (Fig. 8) (Murugan and Krishnan, 2018). (Chen et al., 2014), developed a stimuli-responsive carrier based on l-cysteine derivatives gold nanoparticles (AuNPs) with Cu^{2+} as a bridging ion. AuNPs serve as removable caps for stabilizing the release of the drug from amino-modified MSNs. Both pH and ATP concentration can trigger the opening of caps to release drugs. In the case of pH responsiveness, the rapid release of the drug from capped MSNs was occurred at a pH below 5, whereas an ATP stimulus can trigger elevated levels of adenosine triphosphate (ATP) (concentration > 4 mM). Therefore, MSNs are promising host matrices for stimuli-responsive controlled release.

5.2. Drug release mechanisms

Identifying the release mechanism is crucial to ensure that drug carriers provide sustained or controlled release of a drug, thereby achieving a system in which the drug level in the blood remains within the therapeutic window, between the minimum effective concentration and the minimum toxic concentration (Lee and Yeo, 2015). According to the mechanism by which a drug escapes from a carrier, drug release mechanisms can be classified into four categories: diffusion, dissolution, erosion, and ion exchange.

5.2.1. Diffusion controlled release systems

Diffusion describes the movement of matter from a region of higher

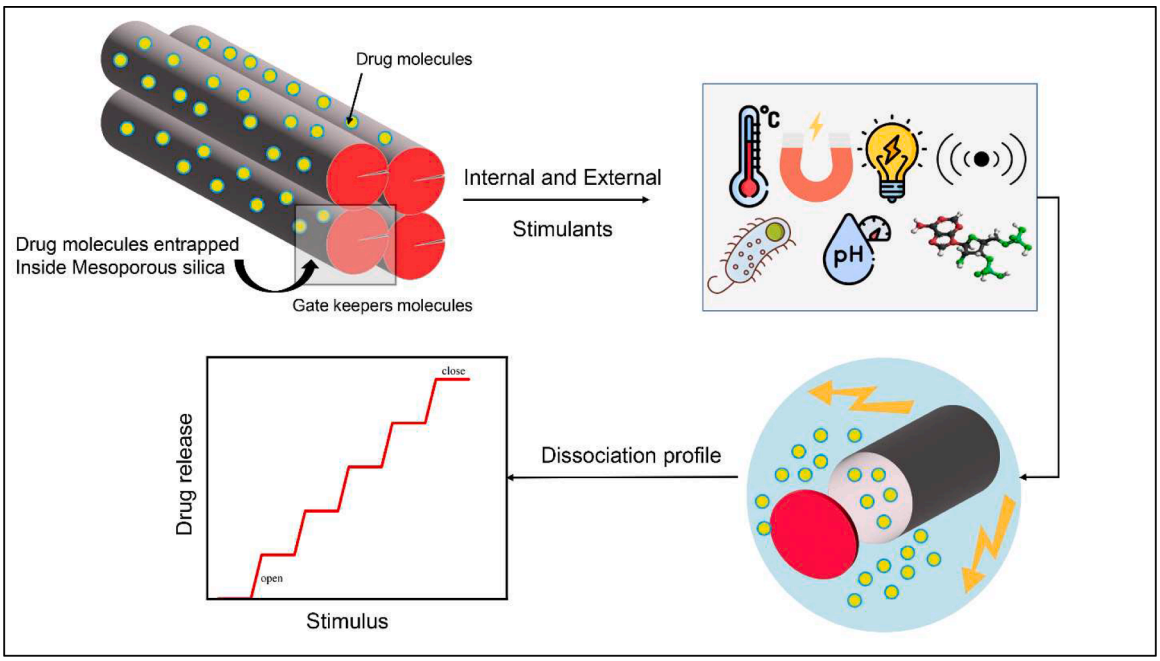

Fig. 8. Illustration of the controlled release of stimuli-responsive materials under different triggering conditions. Reproduced with permission from (Khalbas et al., 2024). Copyright 2024, Elsevier.

concentration to a lower concentration. The driving force for this movement is the Brownian motion, leading to the homogeneous distribution of small particles, molecules, atoms, and ions within the bulk of the fluid (Farzan et al., 2023). Diffusional mass transport is almost always involved in the control of drug release from a dosage form. In various cases, drug diffusion is the predominant step; in others, it "only" plays a major role, e.g., in combination with dissolution, ion exchange, or polymer degradation/matrix erosion. In certain cases, it even plays only a minor role (Siepmann and Siepmann, 2012). Under steady state conditions, Fick's first law of diffusion can be used to quantify diffusional mass transport:

$$F = -D_e \frac{dC}{dX}$$

where D_e is the effective diffusion coefficient, F is the rate of transfer per unit area of section (flux), and dC/dX is the concentration gradient. The effective diffusion coefficient for transport through the pores is estimated as follows:

$$D_e = \frac{D_m \varepsilon \delta}{\tau}$$

where τ and δ are dimensionless factors accounting for tortuosity (> 1) and constrictivity (≤ 1) of the pores, respectively, and ε is the effective porosity. The constrictivity is a function of the pore diameter and size of released molecules. Tortuosity is not a physical constant and depends first of all on other porous media characteristics, like porosity, pore diameter, channel shape, etc. (Coutelieris and Delgado, 2012). In a system of porous carriers coated with a polymeric membrane, the release of drug by diffusion is governed by the membrane thickness, porosity, and physicochemical characteristics of the drugs (partition coefficient, molecular size and diffusivity, protein binding and dosage) (Adepu and Ramakrishna, 2021) . The diffusion rate in this case can also be represented by Fick's first law by adding the partition coefficient (K):

$$F = -D\,K \frac{dC}{dh}$$

Where h is the membrane thickness. When the polymer membrane or matrix contains micropores, drug molecules are released through them by diffusion. In that case, the porosity (ε) and the tortuosity (τ) of the channels are incorporated into the equation:

$$F = -D_s\, K_s\, \varepsilon \frac{dC}{\tau\, dh}$$

In this case, diffusion occurs through the liquid in the micropores, the diffusion coefficient (Ds) and the partition coefficient (Ks) correspond with those for the liquid. For drugs soluble in the liquid filling the pores (for instance, water), K_s is 1 (Bermejo et al., 2020).

5.2.2. Dissolution controlled release systems

The dissolution process involves two steps, the initial detachment of drug molecules from the surface of the carrier to the adjacent liquid interface, followed by their diffusion into the bulk liquid phase. It is commonly believed that the first step is much faster than the second step. Therefore, at the steady state of the process, the concentration of the dissolving drug at the dissolution interface is equal or close to its solubility (Li and Jasti, 2006). By manipulation of Fick's first law, the rate of dissolution from the system can be represented by the Noyes–Whitney equation:

$$\frac{dM}{dt} = \frac{DA}{h}\,(C_s - C_b)$$

where dM/dt = dissolution rate, t = time, A = dissolution surface area, D = diffusion coefficient, h = thickness of the diffusion layer, C_s = solubility, C_b = concentration in the bulk solution.

Sustained-release products can be prepared by reducing the dissolution rate of the drug. This can be achieved by preparing a suitable salt, coating the drug with slowly dissolving materials, or incorporating the drug into the tablet with slowly dissolving carrier. In this case, the dissolution rate is highly dependent on the thickness of the coated polymer. For these systems, slow-dissolving materials such as cellulose, polymethacrylates, PEGs, and waxes are ideal (Bhansali et al., 2021; Kaur et al., 2018).

5.2.3. Ion exchange controlled release systems

Controlled release based on Ion exchange involves a water-insoluble matrix modified with ionic functional groups that are capable of

exchanging ions with those present in the bulk solution through contact. These systems feature drug molecules connected to ionic sites via electrostatic interactions. Once the formulation is immersed in solution, the drug molecules are swapped out with ions of the same charge, resulting in their release from the ion-exchange resin system (Trenfield and Basit, 2020). The release rate can be controlled by several factors, such as the charge type (cation or anion exchanger), the charge intensity, the degree of cross-linking, and the properties of ion exchange polymer or resin (e.g. particle size and porosity) (Guo et al., 2009). The drug, that is ionically bound within a resin core can be considered to be released in three stages: a) The counter-ion diffuses into the matrix. b) The counter-ion exchange with the bound drug at a rate determined by chemical equilibrium, and c) the free drug diffuses through the matrix for release at the resin/medium interface. Therefore, drug release is influenced by the resin's intrinsic properties and the external environment, such as Time, temperature, and pH (Lee et al., 2011a). The following equations serve as examples of the drug loading and release through the ion exchange mechanism:

$$Resin - SO_3^- Na^+ + Drug^+ \rightleftharpoons Resin - SO_3^- Drug^+ + Na^+$$

$$Resin - N^+(CH_3)_3 Cl^- + Drug^- \rightleftharpoons Resin - N^+(CH_3)_3 Drug^- + Cl^-$$

5.2.4. Erosion controlled release systems

Bioerodible matrix systems are sustained release systems in which the drug release is not primarily governed by diffusion or dissolution but rather by erosion/degradation of the matrix (Hillery and Park, 2016). Surface erosion occurs when polymers degrade starting at the matrix/scaffold surface, slowly reducing the size of the matrix/scaffold, from the exterior toward the interior, and occurs when the rate of erosion is greater than the rate of water penetration in the bulk polymer. Surface erosion is ideal for many drug delivery applications, as erosion kinetics and hence, drug release are controllable and reproducible. Moreover, a slow water permeation rate is ideal for drug delivery because water-vulnerable drugs are protected (Kamaly et al., 2016). Bulk erosion occurs when water penetrates the bulk of the polymer, resulting in homogeneous degradation of the entire matrix. The rate at which water permeates into the bulk is greater than the rate of erosion, and as a result, the polymers within the bulk of the matrix are likely to be hydrolyzed. Bulk erosion is less predictable than surface erosion and does not protect drugs from the environment, making it a substandard mechanism for controlled active ingredient delivery (Mattos et al., 2017).

5.3. Drug release kinetic models

The use of mathematical models is important for predicting the release rate of active molecules and diffusion patterns within delivery systems. This enables the design and development of new systems with more desired release patterns. Furthermore, the application of mathematical models can substantially reduce time and financial investments in drug delivery research and development (Kapoor et al., 2020). Table 5 summarizes the most important release kinetics models in porous and nonporous systems.

5.3.1. Zero-Order kinetic model

The release rate of zero-order systems describes the release of drugs at a constant rate throughout the lifetime of the formulation. It is independent of the concentration of drugs within the systems. At equilibrium, ideal zero-order systems release drugs at the same rate as those removed from the body. As a result, the overall cumulative dose within the body is reduced. Therefore, it enables uniform plasma concentrations, and precise dosage, minimizing adverse effects and reducing the risk of chronic toxicity. However, the production of devices with ideal zero order kinetics is still limited as it requires a large and expensive system with high cost, narrow range of time, and inconvenient use (Laracuente et al., 2020). Zero-order release kinetic is represented by the following equation:

$$Q_t = Q_0 + K_0 t$$

Where Q_t = The quantity of drug dissolved in time t, Q_0 = initial quantity of drug in the solution (usually referred to as zero), K_0 = zero order release constant estimated from linear relation of fraction of drug dissolved vs time.

5.3.2. First-Order kinetic model

The release rate of drugs with time is solely dependent on the amount of drug released in the system and can be expressed by the following equation:

$$\log Q_t = \log Q_0 - \frac{Kt}{2.303}$$

Where K is the first order constant obtained from the slope of the straight line produced from the plot of log% remaining cumulative release vs time. In this model, the release rate is proportional to the concentration gradient between the solid-liquid interface of the matrix and medium. The model can applied to the dissolution of pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices (Sawaftah et al., 2021).

5.3.3. Higuchi model

Between 1961 and 1963, Higuchi developed mathematical equations to describe the release rates of drugs from matrix systems for both low and high-soluble drugs. These mathematical equations represent a dispersed particle in a homogenous matrix introduced to a diffusing medium. For a system with a lipophilic and planar matrix, the following equation was proposed by Higuchi:

$$Q = \sqrt{D(2C - C_s)C_s t}$$

Where Q is the amount of drug released in time t per unit area, C is the initial concentration, Cs is the solubility of drug in the medium and D is the diffusion coefficient of drug.

This equation is valid throughout the dissolution process, except when the drug release reaches a saturation concentration in the medium. To expand the applicability of the model to another type of matrix, Higuchi proposed another equation to consider the role of porosity in the release and solubility of active substances (Bruschi, 2015):

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2C - \varepsilon C_s)C_s t}$$

Where ε is the porosity of the matrix, τ is the capillary tortuosity factor . This model assumes an insoluble matrix when in contact with a solution medium. The simplified form of the Higuchi equation which relates the concentration of released drug to the square root of time, can be written as:

$$Q = K_H \sqrt{t}$$

Where K_H is release Higuchi constant. The following assumption should be followed with the use of the Higuchi equation: a) Constant diffusivity of the drug. b) The initial drug concentration is much higher than the solubility of the drug. c) The thickness of the formulation is larger than the drug molecules.

5.3.4. Ritger–Peppas or Korsemeyer–Peppas model

This model was developed by Korsmeyer and his colleagues to describe both the Fickian and non-Feckian release of drugs from polymeric systems. This model is also known as the modified power-law model and represents an exponential relationship between the fraction of drug released and the time, when the release portion reaches 60 % as the following equation:

$$\frac{M_t}{M_\infty} = Kt^n$$

Where K is the release rate constant, which depends on the geometry and structural properties, M_t/M_∞ is the fraction of the drug released at time t and n is an exponent factor (describes the mechanism of release). Different release mechanisms are characterized using the n value (Table 4). The exponent factor should be estimated at $M_t/M_\infty < 0.6$ by plotting the log cumulative release vs log time. In Feckian diffusion, the rate of diffusion is higher than that of polymer relaxation and swelling. Therefore, the diffusivity of the drug affects the rate of release. In contrast, anomalous (non-Fickian) transport occurs due to polymer relaxation and swelling (Bhansali et al., 2021; Lakshani et al., 2023).

5.3.5. Hixson-Crowell model

This model describes the drug release from dosage forms including tablets, in which the surface area and diameter of the particles or tablets are change proportionally with time in the dissolution medium. This model assumes that the initial geometrical shape of the system is constant while the surface area of the dosage form gradually decreases. Therefore, the release behavior that follows this model is occurring due to dissolution only and not diffusion (Ofori-Kwakye et al., 2016). The following equation represents the model:

$$Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = K_H t$$

Where K_H is Hixson-Crowell's constant related to the surface area and volume. The validity of the model considers the following assumptions: a) The model is suitable for monodispersed spherical particles with identical properties such as size, surface, and volume characteristics. b) Dissolution takes place near the surface of the matrix and the effect of agitation of the medium on parts of the surface remains constant (Paarakh et al., 2018).

5.3.6. Baker-Lonsdale model

The Baker-Lonsdale model describes the drug release from a spherical matrix, in which the drug is initially dispersed throughout an inert diffusion matrix. It was developed from prior work by Higuchi on finely dispersed drug particles in an ointment base. In principle, the Baker-Lonsdale model is applied to spherical particles, through which transport occurs by dissolution of the permeating species in the polymer, and subsequent diffusion down a concentration gradient (Talevi and Ruiz, 2022). In essence, the release kinetics are estimated by solving Fick's laws with the appropriate boundary conditions and described as the following equation:

$$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] - \frac{M_t}{M_\infty} = Kt$$

This model is applied for linearization of the release data from formulations of microcapsules.

5.3.7. Weibull model

Weibull model is an empirical model that acts as a theoretical basis for almost all controlled release profiles in heterogeneous matrices. It represents a distribution function used to fit the time dependence of the normalized amount of molecules released.

$$\ln[-\ln(1 - Q_t)] = \ln(\propto) + \beta\ln(t)$$

Where ∝ is scale parameter, defines the time scale of the process and β= the curve shape of the dissolution profile (β > 1; sigmoidal curve β = 1; exponential curve β < 1; parabolic curve). Although the Weibull function often provides reasonable fits, it has no physical basis in the sense that it is not derived from the diffusion equation. For this reason, there is no obvious relationship between the Weibull fitting parameters and the physical parameters characterizing the system such as the diffusivity, the geometry of the system, or the structure of the matrix (Heredia et al., 2022; Ignacio et al., 2017).

5.3.8. Hofpenberg model

The drug release from the surface of eroding polymer with different geometrical shapes (slab, cylinder, and sphere) can occur in such a way that the surface area of the particles remains constant during the degradation process. Hofpenberg developed the following equation to describe this situation:

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{K_0 t}{C_0 a_0}\right]^n$$

Where k_0 is the erosion rate constant, a_0 is the initial radius for a sphere or cylinder or the half-thickness for a slab, and n is 1, 2, and 3, the value for a slab, cylinder, and sphere, respectively. This model assumes that the rate-limiting mechanism is matrix erosion. Furthermore, the internal and external diffusion resistances do not influence the eroding matrix (Kapoor et al., 2020).

Table 4
Release models based on the release exponent (n) values for different geometries of release systems.

Diffusion exponent (n)			
planar system	Cylindrical system	Spherical system	Transport mechanism
≤ 0.5	≤ 0.45	≤ 0.43	Fickian diffusion
0.5 < *n* < 1.0	0.45 < *n* < 0.89	0.43 < *n* < 1.0	Anomalous (non-Fickian)
1.0	0.89	0.85	Case-I transport
n > 1	*n* > 0.89	*n* > 0.85	Super case-II transport
1	1	1	Zero order release

Table 5
Summary of the most common mathematical models used in drug release kinetic studies.

Model	Mathematical equation	Applications
Zero order	$Q_t = Q_0 + K_0 t$ $\frac{M_t}{M_\infty} = K_0 t$	Osmotic pump systems, transdermal systems, matrix tablets with low solubility drugs and coated forms.
First order	$logQ_t = logQ_0 - \frac{Kt}{2.303}$ $\log(100 - Q) = log100 - Kt$	Matrix diffusion and dissolution-controlled systems, sustained-release systems.
Higuchi	$Q = K_H\sqrt{t}$ $\frac{M_t}{M_\infty} = K_H\sqrt{t}$	Matrix systems, transdermal patches, and topical gels.
Ritger−Peppas or Korsemeyer−Peppas Model	$\frac{M_t}{M_\infty} = Kt^n$	Drug release from several modified release dosage forms.
Hixson-Crowell	$Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = K_H t$ $\left(1 - \frac{M_t}{M_\infty}\right)^{\frac{1}{3}} = K_H t$	Erodible matrix formulations
Baker-Lonsdale	$\frac{3}{2}\left[1 - \left(1 - \frac{M_t}{M_\infty}\right)^{\frac{2}{3}}\right] - \frac{M_t}{M_\infty} = Kt$	Microcapsules, microspheres, and other spherical matrices
Weibull	$\ln[-\ln(1 - Q_t)] = \ln(\propto) + \beta\ln(t)$	Applicable for almost all systems but more useful in matrix-type systems
Hofpenberg	$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{K_0 t}{C_0 a_0}\right]^n$	Erodible matrix formulations, Biphasic systems

5.4. Drug release kinetics using MSNs

The interaction between the carrier and the drug may cause significant changes in the solubility, diffusivity, and release behavior of the drug. Conducting in vitro release studies helps to understand the release kinetics. Based on chemical and physical processes that control the release rate, the mechanisms can be classified into diffusion, dissolution, erosion, and precipitation/ degradation (Varga et al., 2015). To explore the kinetic release of vancomycin using MSNs, (Dolete et al., 2022) studied the effect of the loading method on release kinetics by using physical mixing (MSNs@Van_PM), solvent evaporation (MSNs@Van_SE), and vacuum-assisted loading (MSNs@Van_VA). Based on the Higuchi model, in MSNs@Van_PM and MSNs@Van_VA, vancomycin release is governed by Fickian diffusion. On the contrary, MSNs@Van_SE showed the best fit to the first-order kinetic model, indicating a mechanism based on dissolution. This can be attributed to the effect of rotary evaporation on molecule crystallization and that a large portion of vancomycin is found outside the pores, accelerating the dissolution of molecules from the surface into the bulk fluid. Curcumin kinetic release was studied by using hollow mesoporous silica (HMS) and HMS modified with poly (styrene sulfonate) (PSS) via radical polymerization (Wibowo et al., 2013). The results showed good agreement of PSS@HMS with Ritger−Peppas models with n values between 0.43 and 1, which indicates the non-Fickian drug-release mechanism, except for the curcumin released from HMS at pH 7.4 of PBS solution which follows the Fickian release mechanism. The Ritger−Peppas constant (k) of PSS@HMS nanoparticles is lower than that of unmodified-HMS nanoparticles at both pH 5.0 and 7.4, which indicates a slow release rate of curcumin. This is due to the presence of PSS on the surface of nanoparticles which increases the diffusion rate of curcumin from one site to another site until it is released into the PBS medium. The kinetic release models can be used to predict the distribution of drugs inside a matrix consisting of inorganic solids and polymers. (Taki et al., 2020) prepared an amorphous solid dispersion based on indomethacin layered with a pH-independent sustained-release polymer (Eudragit®RSPO) on spherical silicate using a fluidized bed granulator. The results showed that, despite increasing Eudragit®RSPO from 5 to 40 mass% in the solid dispersion, all formulations followed the Higuchi, indicating that the drug release could be associated with both diffusion from inner pores and diffusion within the Eudragit® RSPO-containing outer layer of the pellet. This can be used to confirm that indomethacin was uniformly distributed inside the matrix and released via diffusion from free paths in the matrix. Notably, sometimes, the best-fitting model may not truly represent the model's exactness concerning the matrix. Cis-Pt release kinetics were studied using mesoporous silica functionalized with folic acid (Ortiz-Islas et al., 2021). The correlation coefficient R^2 was fitted to Higuchi and Korsmeyer-Peppas models. A higher R^2 was followed by Korsmeyer-Peppas models with the release exponent (n) equal to 1, indicating the presence of a Super Case II, where drug transport is controlled mainly by the swelling of the drug-loaded systems, and this pattern regularly exhibited a longer period of increased swelling than the period of relaxation. This system cannot be applied to silica as it is not polymeric matrix that can suffer swelling processes. Therefore, the Higuchi model logically represents the release kinetic model from MSNs. A summary of further studies relevant to release kinetic models using MSNs can be found in Table 6.

Table 6
Release kinetics models of drug-loaded mesoporous silica and silica-based materials.

Carrier type	Drug type	Fitted kinetics	Observations	Ref.
MCM-41/12-tungstophosphoric acid	Camptothecin (CPT)	First order Higuchi	CPT release is a concentration-dependent process and follows the Fickian diffusion mechanism.	(Solanki et al., 2019)
Chitosan/Al-MCM-41	Levofloxacin (LVX)	Korsmeyer-Peppas	The LVX release is of Korsmeyer-Peppas kinetic behavior. The diffusion exponent is related to the operation of diffusion and erosion mechanisms during the release process.	(Dardir et al., 2021)
Silica Xerogel/Polymer Core-shell	Vancomycin	First order Baker-Lonsdale	Bare polymer nanoparticles exhibited a first-order degradation release. However, a composite of silica xerogel shifted the release kinetic to the Baker-Lonsdale model. The release constant of composite is much smaller than bare polymer, indicating the importance of the composite for long-term drug release applications.	(Huang et al., 2018)
Thiol-modified MCM41	5-fluorouracil	Hixson–Crowell	The agreement with the Hixson–Crowell regime may be attributed to the presence of the disulfide caps in the samples. These caps are saturated with the drug which leads to changes in the surface area during the release process.	(Murugan et al., 2013)
MSNs	Ruthenium-Polypyridyl (Ru-PIP)	Korsmeyer-Peppas	An acidic environment induced a diffusion-controlled release mechanism for Ru-PIP from MSN.	(Harun et al., 2021)
HMS-MgAl-hydrotalcite (HMS/LDH)	5-fluorouracil (5-FU)	Higuchi Korsmeyer-Peppas	In the pH 7.4 release medium, both FU/HMS and FU/HMS@LDH showed high correlation coefficients with Higuchi and K-P models with release exponent ($n \leq$ 0.45), indicating the release was governed by Fickian diffusion. This was because 5-FU molecules interacted with the pore surface through hydrogen bonding. At pH 4.6, the n value for the FU/HMS@LDH was 0.519, suggesting that the 5-FU release was non-Fickian diffusion. The possible reason was the partial dissolution of the LDH nanosheets coated on the surface of the FU/HMS in a weak acid solution.	(Jin et al., 2019)
NH2/MCM-41	Curcumin	Weibull Korsmeyer-Peppas	The immediate release appears to be caused by free drug molecules leached from the pure MCM-41 and NH_2/MCM-410 s pores, resulting in the drug diffusing from the system's mesochannels. As a result, the CUR was slowly dissolved into the liquid phase.	(Atiyah et al., 2022)
KIT-6-NH2	Ketoprofen 5-flurouracil	First order Korsmeyer-Peppas	The release mechanism might proceed as follows: (1) the initial release may occur due to the leaching of free drug molecules from the KIT-6-NH2 pore entrances, (2) afterward, KP and 5-FU continue to dissolve slowly into the liquid phase as the solvent diffuses from the system out of mesochannels, and (3) followed by the dissociation of hydrogen-bonded KP and 5-FU with the NH2 group of KIT-6-NH2.	(Ayad et al., 2016)
MCF/β-cyclodextrin	Doxorubicin (Dox)	Higuchi	MCF-$(\beta\text{-CD})_{20\ \%}$ at pH 5.0–7.4 and MCF-$(\beta\text{-CD})_{40\ \%}$ at pH 7.4) followed the Higuchi model. However, the MCF-$(\beta\text{-CD})_{40\ \%}$ sample at pH 5.0 adjusts more closely to the Korsmeyer-Peppas model with anomalous transport type (non-Fickian). This may be due to the pH buffer could be going through to the inclusion complex, dissolving, and releasing the charged Dox through the diffusion and relaxation of the material.	(Sánchez-Orozco et al., 2020)

6. Key considerations in designing MSN carriers

Prior to in-vivo application, MSNs should be designed to possess the following properties: a) small hydrodynamic size (<100 nm); b) large adsorption capacity; c) high colloidal stability; and d) low toxicity (Lin et al., 2011). The essential considerations for designing ideal MSNs for in-vivo biomedical use are illustrated in Fig. 9.

6.1. Particle stability

The nature of particle aggregation plays a vital role in drug release patterns and colloidal stability within biological fluids. The nanoparticles must interact individually with cells without forming polydispersed molecules of distinct sizes and properties. These molecules randomly behave when interacting with biological cells, leading to undesired reactions. Therefore, scientists must ensure that MSNs have colloidal stability from the initial stages of production to final in-vivo administration (Schneid et al., 2020). In practical biomedical applications, MSNs are always immersed in biological fluids such as simulated body fluids (SBFs) with different ionic strengths. The agglomeration of particles increases as the ionic strength increases. These ions always seek to neutralize the electrokinetic potential of silica, approaching the zeta potential value to the isoelectric point of silica. As a result, even if particles are initially produced with small sizes, the hydrodynamic size of silica can exceed the recommended value of <100 nm during exposure to these biological ionic fluids. Therefore, preventing or reducing agglomeration is crucial for designing systems with re-dispersible and stable colloids. There are many methods for increasing stability and minimizing agglomeration. One method involves grafting the surface of MSNs with functional groups to maintain the electrokinetic potential above >30mv, providing sufficient repulsion forces. Another method includes coating the surface with polymeric substances or using chemical aids like surfactants to preserve and stabilize the colloid in suspension (Cebrián et al., 2011). The experimental design of MSNs should include studying particle stability in different media such as water, buffered solution, and cell culture media. Furthermore, MSNs should retain their hydrodynamic sizes during the pretreatment of silica particles to show the effects of template removal, washing, and filtration steps on the aggregation and dispersity of particles in aqueous solutions (Lin et al., 2012).

6.2. Biocompatibility and cytotoxicity of MSNs

MSNs have a unique and multifunctional structure that can be used in different biological applications. These nanoparticles have a stable feature under various biological environments compared to other organic biomaterial such as polymers. However, the biocompatibility of MSNs in biological systems is still not completely understood. This is due to the interaction between biological systems and MSNs, which relies on a range of nanoscale features such as particle size, shape, surface area, pore size, surface chemistry, etc. These factors determine whether MSNs have a desired biological effect or are highly toxic when brought in contact with biological molecules (Asefa and Tao, 2012b). Particle size is a major critical factor that influences biological reactivity. In general, the surface reactivity and surface area are high for small-sized particles, which could lead to cellular interactions and toxicity issues. These interactions are generated mainly from surface silanol groups linked by hydrogen bonds or electrostatic forces with membrane cells. Furthermore, the smaller the particles are, the higher the ability to penetrate the cell membrane and cause damage inside the cells. In addition, due to the high surface area/volume ratio, particle aggregation may occur in cell culture media in a way that may alter the characteristics of MSNs and subsequently influence the biological outcomes (Dong et al., 2020; Tarn et al., 2013). The porous nature of MSNs has advantages over porous colloidal silica in terms of cytotoxicity and inflammatory response. In their study (S. Lee et al., 2011), although mesoporous silica has a higher surface area than colloidal silica, they showed a reduction in the inflammatory response and apoptosis elicited. Furthermore, in both the MTT assay and FACS analysis, MSNs showed less cytotoxicity and apoptotic cell death than that of colloidal silica nanoparticles. These positive features of MSNs may be attributed to the fact that mesoporosity reduces the contact area between silanol groups and membrane cells (Tarn et al., 2013). To demonstrate the influence of particle shape on cell behavior, (Huang et al., 2010) studied the effects of MSNs with different aspect ratios (ARs,1,2, and 4) having three different shapes (spheres, short and long rods) on the cellular uptake and behavior of A375 human melanoma cells. They suggested that particles with higher ARs have higher cellular uptake and faster internalization rates. Besides that, long rod-shaped MSNs have a higher cytotoxicity compared to other shaped particle. This could be explained by the differences in the curvature of the different shaped MSNs. For instance, particles with a rod shape have a higher contact area with the cell membrane than spherical particles.

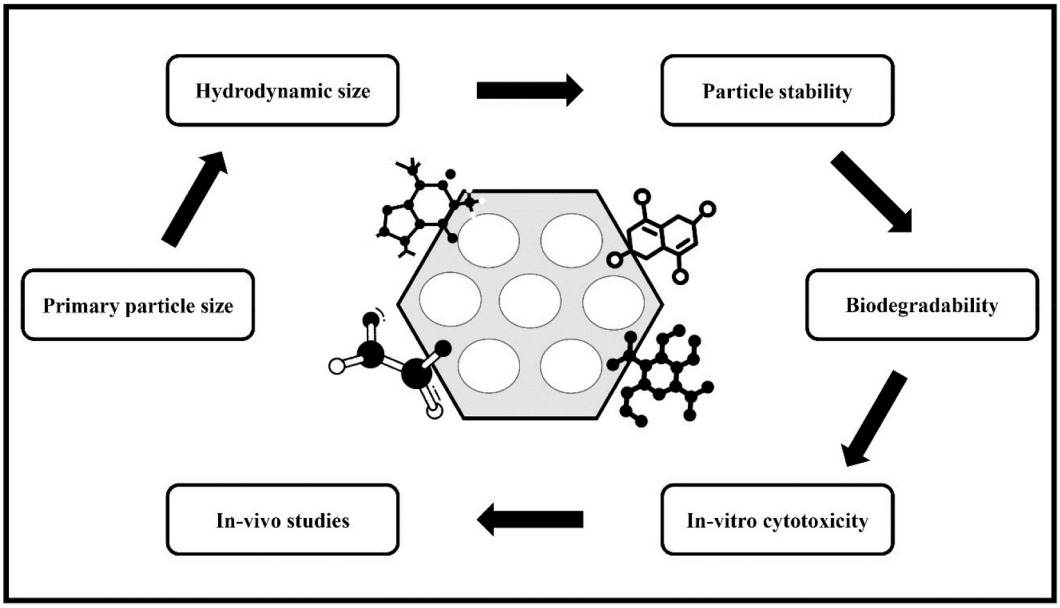

Fig. 9. Diagram of critical considerations in the design of MSNs for the biomedical applications.

Although, rod-like MSNs have a greater cellular internalization, (Shao et al., 2017) concluded that changes in the ARs of magnetic MSNs have negligible effects on cytotoxicity in tumor and normal cell lines. These contrary studies demonstrate that particle shape effects may vary or be complicated by cell types, culture media, particle concentration, and cytotoxicity assay. Therefore, a systematic analysis of variables should be conducted before examining the particle shape cytotoxicity (Hao et al., 2016). Besides particle and pore characteristics, the biocompatibility of MSNs can be enhanced by surface modification. For example, coating the surface with polymers can reduce the contact area between reactive silanol groups and cell membranes. Additionally, introducing PEG onto the surface can prolong the circulation time of nanoparticles, preventing their quick accumulation in the liver, spleen, and lung tissues. Moreover, modifying the surface chemistry can improve endocytosis, cellular uptake, and endosomal release (Florensa et al., 2022). Regardless of the above factors, the cytotoxicity assay strongly affects the accuracy of the collected data. Generally, MTT and WST-1 assays have been widely used for determining cytotoxicity of MSNs. MTT and WST-1 assays are based on the redox-driven transformation of tetrazolium salts into formazan salt by mitochondrial dehydrogenases in living cells (Braun et al., 2018). However, there is a possibility of directly reducing the MTT and WST-1 dyes by the redox activity of silica particles instead of the metabolic activity of living cells. Therefore, it is highly recommended to establish different cytotoxicity assays (e.g., ATP-based assays) to evaluate the correct cell counts during the experiments on MSN cytotoxicity (Laaksonen et al., 2007).

7. Conclusion and future perspectives

Drug loading is a promising strategy to produce highly stable amorphous drugs with improved dissolution rate, solubility, and bioavailability. The ideal loading process should be able to load large amounts of drugs, minimize the drug deposition on the external surface, maximize pore filling, and release the drug to the targeted sites in the desired pattern. Among various inorganic nanomaterials, mesoporous silica nanoparticles (MSNs) have attracted attention in oral drug delivery due to their tunable surface area, pore size, and pore volume. Besides that, it can be easily modified with functional groups to increase the loading capacity and enhance the release rate. Several loading methods have been used to encapsulate drugs. The main loading methods can be classified into solvent methods and solvent-free methods. The solvent methods use organic solvents to dissolve the drug, followed by adsorption/dispersion of these molecules. Solvent methods can selectively load drugs with a high degree of amorphousation. However, these methods can lead to unstable formulations and recrystallization of the drug in the case of exceeding the loading capacity. Scaling up these techniques presents numerous challenges due to the high consumption time, the use of large quantities of solvent, and additional steps of separation and purification are needed. However, spray techniques such as fluidized bed and co-spray drying, besides green solvent-based methods such as supercritical fluid technology, can be optimized to scale it to the industrial level. The solvent-free methods, including melting and milling, have the advantages of loading large amounts of drugs and are easy to scale up compared with solvent methods. Nevertheless, these methods result in less stable formulations and require severe conditions, such as high temperatures, high shear force, and high mechanical stresses, to force the drug inside the carrier matrix. In addition, using of polymer is necessary in the milling method to facilitate the process and avoid damage to the mechanical parts of the device. The ideal drug loading methods should be able to load large amounts of the drug, prevent drug crystallization, preserve the stability of the particles, be cost-effective, and be easy to scale up for industrial purposes. Identifying the release mechanism is crucial to ensure that drug carriers provide sustained or controlled drug release. It also provides a fundamental basis for simulating an in-vivo mechanism to maximize the efficiency of the formulation. Drug release mechanisms using MSNs can be classified into four categories: diffusion, dissolution, erosion, and ion exchange. By controlling these driven mechanisms, novel drug delivery systems can be synthesized. The use of mathematical models is important for predicting the release rates of active molecules and their diffusion patterns within delivery systems. This enables the design and development of new systems with more desired release patterns. Several kinetic release models have been proposed for the drug delivery sector. The most fit kinetics that may apply to mesoporous carriers are zero and first order, Higuchi, and Korsmeyer-Peppas. Although release kinetic models can predict the predominantly driven mechanism, these models do not provide a sufficient conception to explain the physical and chemical phenomena during the process. There is no single parameter related to the intrinsic dissolution rate and characteristics of the carrier matrix. In addition, there are no correlations in the case of mono or multilayered adsorption. Through adsorption isotherms and kinetics, it is possible to link the adsorption behavior with kinetic release models, providing a better explanation of the release process. Besides, new or modified kinetic models may be driven using Artificial Intelligence (AI) optimization tools. The mathematical models should include experimental variables related to the dissolution test parameters, drug physiochemical properties, and carrier characteristics. The development of new kinetic models can be beneficial for creating novel delivery systems that show a strong correlation between in-vitro and in-vivo applications. Consequently, drug loading and release kinetic models require further investigation and development to produce sustainable and effective systems.

CRediT authorship contribution statement

Ali H. Khalbas: Conceptualization, Methodology, Data curation, Investigation, Writing – original draft. **Talib M. Albayati:** Writing – original draft, Methodology, Supervision. **Nisreen S. Ali:** Visualization, Formal analysis, Writing – review & editing. **Issam K. Salih:** Conceptualization, Supervision.

Declaration of competing interest

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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