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## Exploiting recent trends for the synthesis and surface functionalization of mesoporous silica nanoparticles towards biomedical applications

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1 **Review article**

2 **Exploiting recent trends for the synthesis and surface functionalization of mesoporous**  
3 **silica nanoparticles towards biomedical applications**

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13 **Abstract**

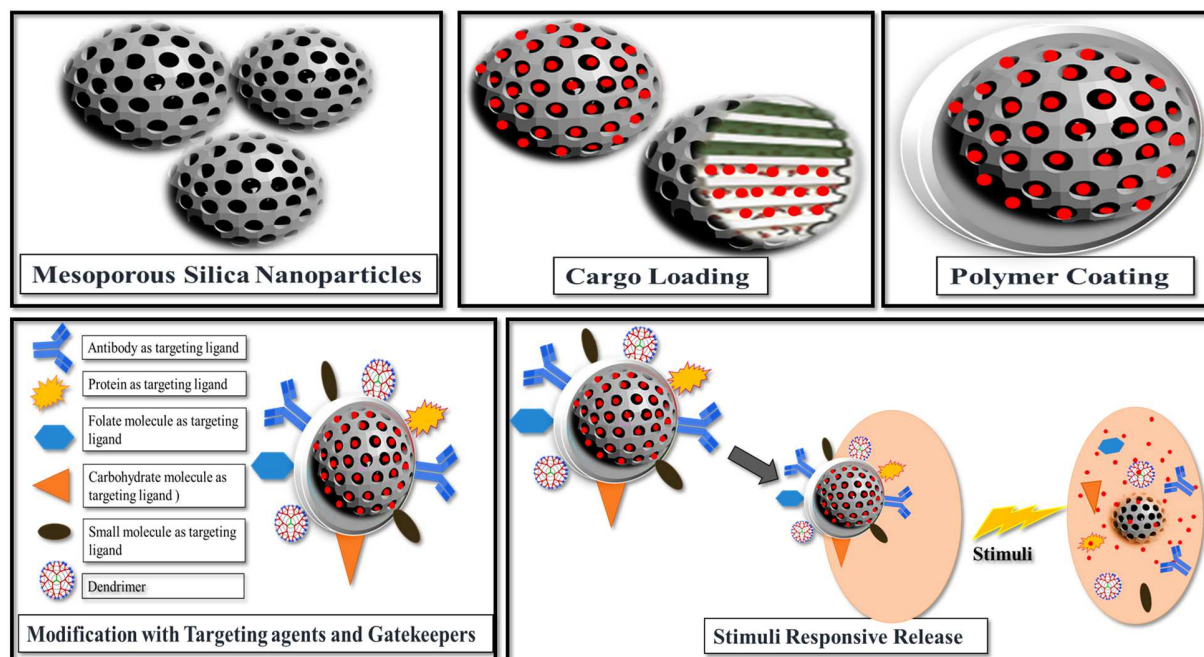
14 Rapid progress in developing multifunctional nanocarriers for drug delivery has been observed in  
15 recent years. Inorganic mesoporous silica nanocarriers (MSNs), emerged as an ideal candidate  
16 for gene/drug delivery with distinctive morphological features. These ordered carriers of porous  
17 nature have gained unique attention due to their distinctive features. Moreover, transformation  
18 can be made to these nanocarriers in terms of pores size, pores volume, and particle size by  
19 altering specific parameters during synthesis. These ordered porous materials have earned special  
20 attention as a drug carrier for treating multiple diseases. Herein, we highlight the strategies  
21 employed in synthesizing and functionalizing these versatile nanocarriers. In addition, the  
22 various factors that influence their sizes and morphological features were also discussed. The  
23 article also summarizes the recent advancements and strategies for drug and gene delivery by  
24 rendering smarter MSNs by incorporating functional groups on their surfaces. Averting off-target  
25 effects through various capping strategies is a massive milestone for the induction of stimuli-  
26 responsive nanocarriers that brings out a great revolution in the biomedical field.

27 **Highlights**

- 28 1. MSNs serve as an ideal candidate for gene/drug delivery with unique and excellent attributes.  
29 2. MSNs surface can be functionalized using specific materials to impart unique structural  
30 features.  
31 3. Functionalization of MSNs with stimuli-responsive molecules can act as gatekeepers by  
32 responding only to the desired stimulus after uncapping under physiochemical stimuli.  
33 4. These capping agents act as vital targeting agents in developing MSNs and can be employed  
34 in various biomedical applications.

35

## 36 Graphical Abstract



37

## 38 Keywords

39 Mesoporous silica nanoparticles; Gatekeepers; Capping agents; Targeted drug delivery; Stimuli-  
40 responsive; Chemical modification.

## 41 1. Introduction

42 Nanomedicine's advent in the field of nanotechnology has gained much escalation with the  
43 provision of promising solutions towards drug delivery for the treatment of several diseases  
44 (Bernal et al., 2021; Nagraik et al., 2021). The development of nanocarriers to transport and  
45 release a therapeutic agent at the diseased site in a controlled and selective manner has gained  
46 significant attention from researchers (Sciicluna and Vella-Zarb, 2020). Nanometric agents  
47 provide an effective alternative for treating diseases requiring the potent administration of  
48 cytotoxic drugs. These agents are mainly categorized as organic or inorganic nanocarriers and  
49 brought tremendous achievement in treating various infectious diseases. These organic  
50 nanometric agents include different polymeric agents (Begines et al., 2020; Kong et al., 2020;  
51 Palanikumar et al., 2020; Siddiqui et al., 2020), lipid-based carriers (Barkat et al., 2020; Plaza-  
52 Oliver et al., 2021), dendrimers (Mandal and Biomaterials, 2021; Nikzamid et al., 2021) and  
53 micelles (Atanase, 2021; Hwang et al., 2020). These agents are widely employed for the  
54 treatment of various dreadful diseases. However, in contrast to organic nanometric agents, the  
55 carriers composed of inorganic composition have gained remarkable attention owing to their  
56 higher mechanical, chemical, and thermal stabilities. These agents mainly include nanocarriers  
57 consisting of carbon, metal, or silica (Zhang et al., 2021)..

58 Nanoporous silica nanoparticles are the inorganic particles having pores in the nano-size  
59 of 1-100 nm. These nanopores are categorized as micropores having a diameter of < 2 nm,  
60 mesopores of 2-50 nm pore diameter, and macropores with a pore diameter of 50 nm or larger  
61 (Zhang et al., 2021). These agents also depict good biocompatibility but a relatively low  
62 degradation profile (Shi et al., 2020). Among different substances used for the composition of  
63 these agents, mesoporous silica nanocarriers (MSNs) acts as one of the astounding achievements.  
64 These carriers shared significant attributes of high loading and encapsulation efficiency, ease of  
65 production, biocompatibility, zero premature release, and increased capacity of tunability in  
66 terms of their size, pores diameter, and morphology (Alyassin et al., 2020; Manzano and Vallet-  
67 Regí, 2020). In the initial phase, they were only employed to increase the solubility of drugs  
68 having lower solubility. However, further exploration and advancement in their applications  
69 widens their purpose for improving bioavailability, designing controlled drug release, and  
70 targeting the active moieties at the desired site. In recent years, receptor-based targeting at the  
71 desired site through stimuli-responsive action has gained significant importance (Haddick et al.,  
72 2020; Kundu et al., 2020).

73 The most promising advantages of MSNs as a drug delivery system are their “zero  
74 premature controlled release” property (Slowing et al., 2008) by ensuring drugs be delivered  
75 without leakage. This property of the MSNs can be achieved by designing them as intelligent  
76 drug delivery carriers, which enables them to release the drug in the specified area of interest  
77 without any premature release at the off-target sites. Conventional polymeric nanocarriers  
78 suffered from the limited drug loading capacity and the abrupt departure of matrix-encapsulated  
79 agents due to poor stability profile. In contrast, MSNs are highly stable and can deliver large  
80 payloads of drugs with precise temporal control. This kind of release is particularly beneficial for  
81 the delivery of cytotoxic agents requiring precise drug control. For this purpose, various  
82 gatekeepers play a crucial role in controlling the release of drugs by capping the entrances of the  
83 carriers and can only be removed under specific conditions. The internal structure of these agents  
84 acts as a safer micro-environmental region that serves as effective loading of the therapeutic  
85 agent and at the same time its protection from deactivation or degradation from the external  
86 environment. These pores of the MSNs may act as drug reservoir systems and permit controlled  
87 diffusion of a drug to the surrounding tissues over specified intervals of time upon the influence  
88 of any internal (endogenous molecules, redox potential, pH, or biomolecules) or external  
89 triggering stimuli (Light, pH, heat, ultrasound, magnetic field or chemicals) (Chen et al., 2020a;  
90 Irshad et al., 2020; Kundu et al., 2020). The fabrication of such an intelligent carrier system  
91 demonstrated precise release of drug at a specified area, exhibiting zero premature release of  
92 drug in the systemic circulation. However, without capping or surface functionalization, these  
93 drug carriers may exhibit release of drug in the systemic circulation, having a premature release  
94 of a drug.

95 These different gatekeepers may include certain materials acting as hard caps or soft  
96 caps. The distinction is made based on the templating method which is being used for the

97 fabrication of porous MSNs. Two types of templating materials are commonly employed for  
98 their fabrication. The hard templating method, also called exotemplate, utilizes a porous solid  
99 agent, in which inorganic precursor is utilized to fill the hollow spaces of MSNs. These are  
100 synthesized from nanomaterials of non-silica sources such as polymeric beads, semiconductor  
101 NPs, metal or metal oxides (Cadmium sulfide (CdS), iron oxide (Fe<sub>3</sub>O<sub>4</sub>)), and gold nanocarriers  
102 (AuNPs). While in the soft templating method, also called endotemplate, a surfactant is usually  
103 utilized without use of any hard template. Soft capping agents include various biomolecular  
104 agents, micelles, organic molecules, microemulsions, or supramolecular assemblies. In  
105 comparison to hard MSNs, these agents are produced under mild reaction conditions following  
106 an easy method of synthesis (Ghaferi et al., 2021). The capping technique also influences the  
107 release pattern of the encapsulated agent. The templating agent affects the structural properties of  
108 NPs, which in turn affects the release of encapsulated material from their surface, *e.g.*, shell  
109 thickness of the carrier. For example, Lin et al. demonstrated the different release kinetics of  
110 ATP, encapsulated in various capped MSNs through real-time imaging. The hard-capped MSNs  
111 revealed the faster release of a small payload of the drug while the soft capped MSNs like  
112 polamidoamine demonstrated sustained and slow release for larger drug amounts (Gruenhagen et  
113 al., 2005).

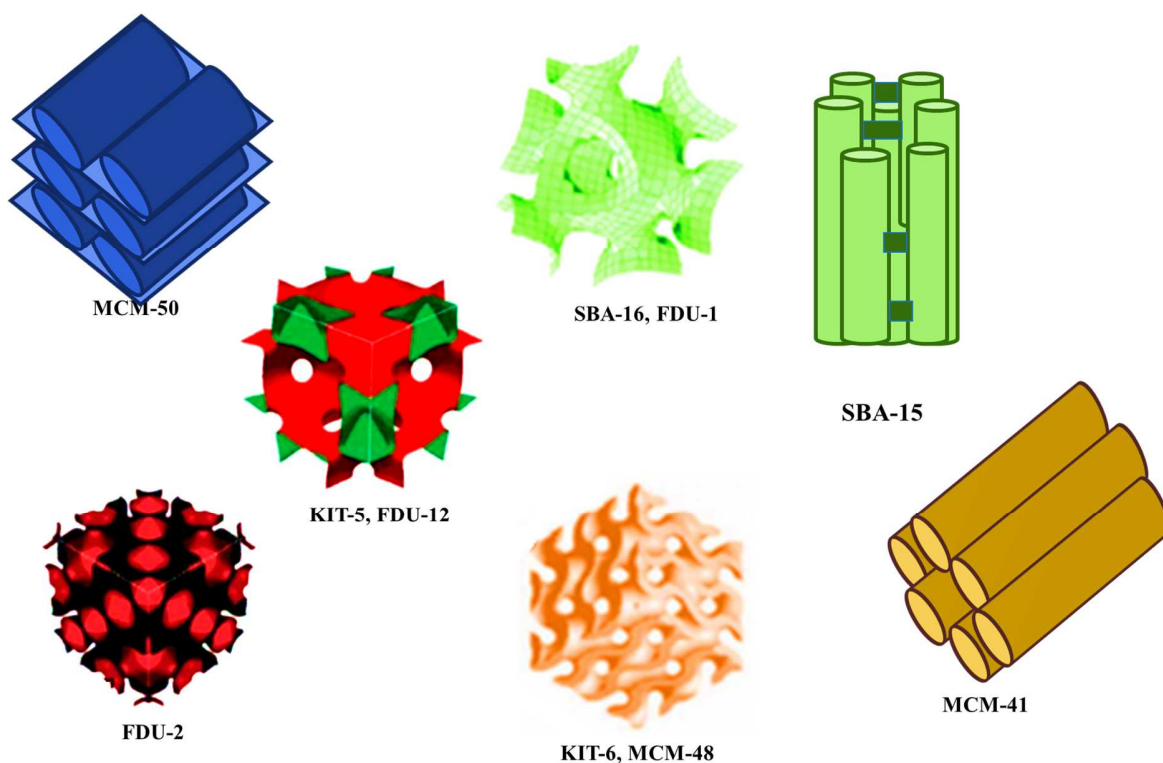
114 Moreover, functionalization of MSNs can be provided by decorating their external  
115 surfaces with ligands capable of active targeting at the diseased site. Attachment of one or more  
116 stimuli-responsive functional groups to the capped MSNs enables them to release drugs on  
117 command. For this purpose, modifications of the silanol groups have been made on the surface  
118 of MSNs to create highly modified nanocarriers with remarkable and efficient properties. In  
119 addition, all these materials can be phagocytosed by physiological cells without posing any  
120 cytotoxicity, which makes these multifunctional MSNs a superior candidate for the site-specific-  
121 controlled delivery of drug/gene or any other therapeutic moiety (Kankala et al., 2020). Herein,  
122 we will discuss the types, synthesis techniques, and the recent advancements in the development  
123 of novel stimuli-responsive MSNs by various capping molecules. Moreover, we will also focus  
124 on the surface modifications of these agents for release of a therapeutic agent at the target site,  
125 upon exposure to internal or external stimuli.

## 126 **2. Types of MSNs**

127 Synthesis of MSNs dates back to the 1970s, after which in 1992, Mobil Research and  
128 Development Corporation synthesized MSNs from gels of alumino-silicate. They utilized a  
129 template of liquid crystals and named these materials MCM-41 (Mobil Composition of Matter or  
130 Mobil Crystalline Materials). Usually, these MSNs are categorized into various types, such as  
131 Santa Bar-bara (SBA including SBA-1, 2, 3, 6, 12, 15, 16, etc.), Mobile Crystalline Materials  
132 that further includes (MCM-41, 48 and 50), Michigan State University (MSU), Fudan University  
133 (FDU) and Hexagonal Mesoporous Silica (HMS). According to IUPAC, MSNs are materials  
134 with an ordered presentation of pores with a 2-50 nm porous diameter. The sizes of the pores can

135 be altered by employing specific surfactants under suitable reaction conditions (Beck et al.,  
136 1992). These surfactants can be of four types based on charges present on them, including  
137 cationic surfactants (quaternary ammonium salts or cetyltrimethylammonium bromide (CTAB)),  
138 anionic type (compounds carrying sulfonic acid, phosphoric acid), non-ionic type polyethylene  
139 oxide (PEO), and ampholytic type. Apart from these, certain other carriers of mesoporous nature  
140 were also synthesized through variation in the starting templating agents and reaction conditions  
141 (Vallet-Regi et al., 2001). These materials have changed geometrical arrangements with  
142 variations in pores sizes.

143 Due to the availability of a wide variety of surfactants, different structures of MSNs have  
144 been introduced as shown in Fig 1.



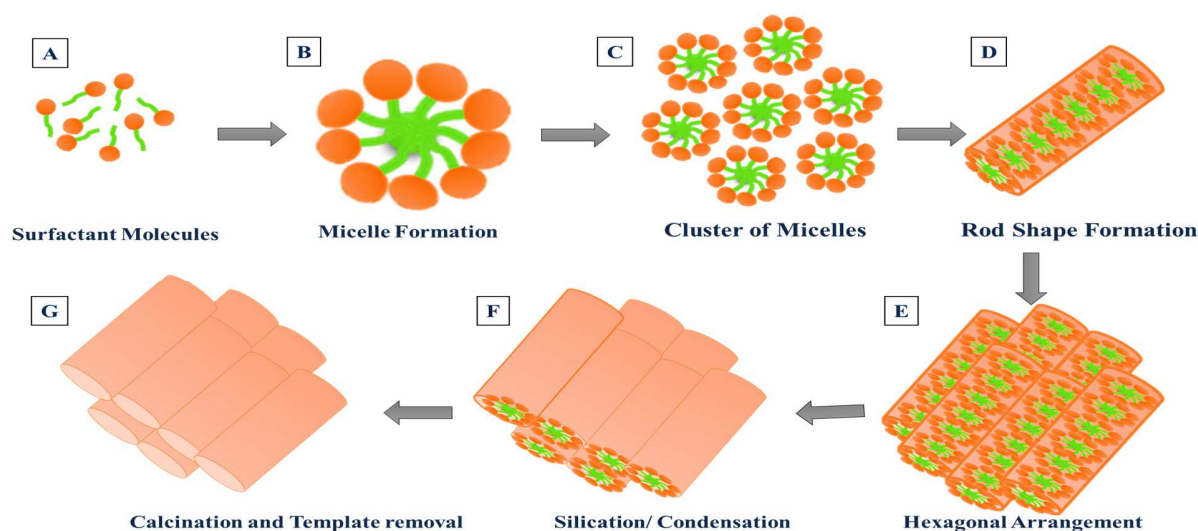
145  
146 Fig. 1. Different types of MSNs

147  
148 Different members have been fabricated among MCM families by utilizing different  
149 reaction conditions. Among these, MCM-41 are widely used carriers employing cationic  
150 surfactants as a templating agent. They are composed of the regular two-dimensional hexagonal  
151 arrangement having a pore size of 2.5 nm to 6 nm. By considering the importance of the MCM  
152 family, MCM-48, another member of the MCM family has also been designed as a drug carrier.



153 MCM-48 depicts a cubical arrangement with a three-dimensional structure. In contrast to MCM-  
 154 41, these materials displayed bi-continuous channels and offered quick materials transport.  
 155 MCM-50 is also designed among the MCM family which exhibited lamellar arrangement (Øye  
 156 et al., 2001). The general mechanism of MSM formation is depicted in Fig 2. Firstly, the  
 157 surfactant molecules self-aggregate themselves at alkaline pH above the critical micelle  
 158 concentration, resulting in the formation of micelles. Afterward, with the addition of  
 159 tetraethoxysilane (TEOS), the micellar packing started through the electrostatic interaction  
 160 between positively charged  $N^+(CH_3)_3$  and negatively charged silanes ( $Si-O^-$ ), which leads to the  
 161 formation of ordered architectures of silica. The silica precursors overlap at the polar head of  
 162 surfactant micelles by forming a wall around them. Removal of surfactant to expose the channels  
 163 of mesopores resulted in the formation of MSMs.

164



165

166 Fig. 2. Schematic representation of MCM-41 synthesis using cationic surfactant template

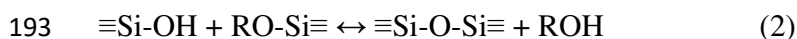
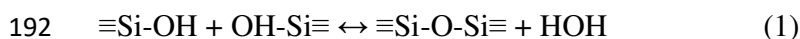
167 Another mesoporous structure of highly ordered nature is termed as SBA or Santa  
 168 Barbara; due to their synthesis at Santa Barbara, the University of California. These materials  
 169 possess thicker walls of silica and larger pores of 4.6 to 30 nm (Zhao et al., 1998). The initial  
 170 templating agent for their synthesis can influence the symmetry of these materials. Non-ionic co-  
 171 polymer alkyl poly (ethylene oxide) helps to design cubic mesopores named SBA-11 while  
 172 oligomeric surfactants result in the formation of three-dimensional hexagonal mesostructured  
 173 SBA-12. In the same way, poly (alkylene oxide) brings out a regular hexagonal mesostructured  
 174 carrier named SBA-15 or a cubic cage-like structure termed as SBA-16 (Zhao et al., 1998).

175 FSM-16 is another exciting type of mesoporous material that can be utilized for wide  
 176 pharmaceutical purposes, besides its use as a catalyst and adsorbent. (Tozuka et al., 2005). Some  
 177 other types of mesoporous materials are coined as Korea Advanced Institute of Science and

178 Technology (KIT) and Technical Delft University (TUD-1) with different symmetries and pore  
179 shapes (Heikkilä et al., 2007; Nandiyanto et al., 2009). Among the above-mentioned MSNs,  
180 MCM-41, 48, and SBA-15, 16 are employed widely for drug and gene delivery.

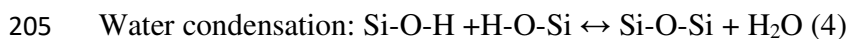
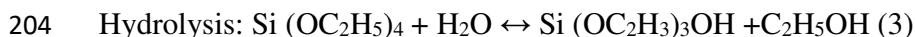
### 181 3. Advances in Synthesis Methods

182 MSNs can be synthesized through various methods, including soft or hard templating  
183 method, fast self-assembly, Stober method, modified aerogel methods, hydrothermal technique,  
184 and dissolving reconstruction method. Synthesis of spherical micron-sized silica nanocarriers  
185 was pioneered by Stöber, by employing specific chemical reactions, and the method was  
186 afterward named as 'Stöber synthesis' (Stöber et al., 1968). Mostly Stöber's method is followed  
187 for the fabrication of MSNs, which is also known as the sol-gel method. In the sol-gel method,  
188 the sol phase is generated by the reactions of hydrolysis and condensation with the production of  
189 colloidal particles at alkaline or acidic pH, while the condensation of colloidal particles results in  
190 the production of gel phase of three-dimensional structure through cross-linking of siloxane bond  
191 (Corbalan et al., 2012b). This general reaction is depicted in Equation 1 and 2 as:



194 Where R, maybe any alkyl group.

195 Hydrolysis of alkoxide groups depends upon the molar concentration of Si/H<sub>2</sub>O and other  
196 reaction conditions. The condensation process occurs only after hydrolysis reaction, in which  
197 repeated condensation forms a chain-like structure in the colloidal solution, while in gel form, it  
198 forms a huge network (Danks et al., 2016). Drying of this phase results in the formation of  
199 various biomolecules that were embedded in the silica gel matrix resulting in the formation of  
200 MCM-41. Through this technique, the produced MSNs are in the micron range, while the alkyl  
201 silicates hydrolysis and condensation control the particles' dispersity in the presence of alcohol.  
202 The method utilizes four components; silica source, water, alcohol, and base (Stöber et al.,  
203 1968). The expression of MSNs reaction through sol-gel reaction is:



207 Several other modifications can be made to get the particles of highly ordered nature in a  
208 nanometric range of different shapes (Wang et al., 2016). Further modifications were made to  
209 this method by utilization of cationic surfactant template to obtained spherical structure of MSN  
210 rather than hexagonal one, having same properties as provided by other methods. A lot of  
211 research has been conducted to obtain stable monodisperse particulates of MSNs (Grün et al.,



212 1997). This method is advantageous over others in terms of its simplicity and cost-effectiveness,  
 213 with a uniform structure and controlled properties. Also, the process utilizes fewer excipients and  
 214 is also time-saving (Bharti et al., 2015; Shahbazi et al., 2012).

215 The other technique for producing MSNs include soft and hard templating methods. In  
 216 the soft templating method, MSNs are produced through the use of organic templating agents to  
 217 create porosity. In the next step, heat is provided to remove the templating material and for the  
 218 isolation of pure mesoporous carriers (Wu et al., 2013). While, in hard templating method or  
 219 nano casting technique, the precursors of silica fills the templating mesopores through capillary  
 220 force, followed by the treatment of chemical or thermal removal of the templating agent, that  
 221 produces a mirror image of mesoporous silica structure (reverse structure) (Egger et al., 2015).

222 Hydrothermal technique for the development of MSNs was discovered by Roderick  
 223 Murchison, a British Geologist. He introduced it as the formation of minerals that were obtained  
 224 by the hot water solutions from cooling magmas. The process can be described as the reaction  
 225 occurring in the sealed container where the system's pressure and temperature are kept high  
 226 (Feng and Li, 2017). The method follows similar steps to that of the sol-gel process, except that  
 227 the mixture is transferred to an autoclave having a lining of Teflon at a certain temperature,  
 228 followed by the template removal. MSNs obtained through this method have improved regularity  
 229 and greater hydrothermal stability (Yu et al., 2012). Table 1 listed the distinguishing features of  
 230 the Sol-Gel and Hydrothermal process

231 Three important materials are necessary for the formation of MSNs; silica precursor  
 232 (tetramethylorthosilicate, tetraethylorthosilicate, tetrakis (2-hydroxyethyl) orthosilicate, and  
 233 sodium metasilicate), a surfactant that may act as a template directing agent (cationic or non-  
 234 ionic) and a catalyst. Other reagents may include co-solvents that are incorporated for the  
 235 prevention of aggregation.

236 **Table 1.** Distinguishing features of Sol-Gel and Hydrothermal process

Distinction	Sol-Gel Process	Hydrothermal Process	References
Process	This process involves two main steps of synthesis, including the formation of particles in solution followed by gel formation due to the 3D polymeric network.	In this process, an inorganic substance is added to the templating agent (acid or alkali), and the fabricated hydrogel is afterward subjected to autoclaving.	(Varshney et al., 2021)

<b>Reaction conditions</b>	In this process, the requirement of a sealed container is not required.	The reaction takes place in a sealed container, having maintained temperature and pressure.	(Mohamed Isa et al., 2021; Yu et al., 2012)
<b>Requirement of Autoclave</b>	The method doesn't require autoclaving or any other parameter of high temperature.	The method requires a Teflon-lined autoclave to maintain process parameters.	(Yu et al., 2012)
<b>Formation of mesoporous particles</b>	Desired morphology is obtained through simultaneous hydrolysis and condensation of metal oxide.	The powdered solid SiO <sub>2</sub> got dispersed during heat treatment, and the formation of mesophase assembly occurs after the removal of heat.	(Galabova, 2021).
<b>Morphology of MSNs</b>	Formulation parameters, such as temperature, pH, and reagent concentrations, affect the morphology and size of the particles.	Particle morphology and size have a significant influence on cooling rate after thermal treatment.	(Narayan et al., 2018)
<b>Advantages</b>	The main advantages include increased purity and ease of synthesis at moderate reaction conditions	The advantage of this method is to obtain MSNs having greater hydrothermal stability.	(Bharti et al., 2015; Shahbazi et al., 2012) (Lin et al., 2011).
<b>Disadvantages</b>	The method produces particles in micron size and requires further modifications	The process is complex and requires increased time.	(Miller et al., 2014).

237

238 **4. Factors that Affect Cellular uptake and Drug Loading in MSNs**

239 Mesoporous silica nanoparticles (MSNs) possess many attributes that make them  
240 beneficial for use in drug delivery due to their unique mesoporous structure. They also offer a  
241 high level of chemical stability, easy surface functionality, and biocompatibility that ensures  
242 controlled drug release and targeted delivery of various encapsulated agents. MSNs have gained  
243 attention in the scientific community due to the aforementioned properties: large pore volume,  
244 high surface area, narrow pore size distribution, and tunable pore diameter. Targeted drug  
245 delivery can also be achieved by surface modification of the MSNs.

246 Several factors influence the cellular uptake of MSNs by targeting cells, including  
247 particle size, pore size, shape, charge, and surface modification. In order to obtain MSNs to act  
248 as an ideal carrier for drug delivery, the particles must be of uniform shape with larger pore  
249 volume to maximize the loading capacity of the drug. The key properties of MSNs are affected  
250 by the following parameters.

#### 251 4.1. Size of MSNs

252 Particle size is one of the most crucial factors that affect the carrier properties and deliver  
253 the entrapped agent to the target site. Particles of smaller diameter are usually preferable for  
254 effective delivery of the agent with better cellular uptake properties. The particle size of the  
255 MSNs is affected by a variety of factors such as pH, temperature, reaction time, the addition of  
256 functional organo-silanes.

257 One of the foremost vital factors that contributes a significant role in controlling the  
258 particle size is the pH of the reaction medium. The hydrolysis process is affected by the initial  
259 pH that further controls the size of particles. In contrast, the particle's nucleation is determined  
260 by the silica condensation that affects the quality of nanoparticles. In a basic medium, the rate of  
261 hydrolysis increases with an increase in pH. In contrast, the rate of condensation is not  
262 proportional and is higher at pH 8.4 with a further decrease with an alteration of pH. A study  
263 demonstrated by Qiao et al. reported an increase in particles size from 30 to 85 nm with a  
264 subsequent reduction in pH from 10 to 6.8. These reports depicted that the minimum particle size  
265 can be attained at a pH of 9-10, showing the increased effect of condensation rates on the  
266 particles size compared to hydrolysis (Qiao et al., 2009). Moller et al. used triethanolamine as a  
267 base catalyst to create a basic environment instead of ammonium hydroxide (NH<sub>4</sub>OH) or sodium  
268 hydroxide (NaOH). Triethanolamine (TEA) may also perform its function as a complexing agent  
269 and prevent aggregates formation with a production of smaller discrete particles by affecting the  
270 pH of the system (Moeller et al., 2007). Another study reported by Bouchoucha et al. also  
271 demonstrated the control of particle size of MSNs particles by employing TEA as a base  
272 catalyzing additive and as a dispersing agent (Bouchoucha et al., 2016). Chiang et al.  
273 demonstrated the control of particle size of MSNs by observing different parameters. They  
274 concluded that among the various parameters that influence the size of the particles, pH plays the  
275 most important role, and the sequence of the influencing parameters is 57% for the pH, 29% for  
276 the reaction time, and 13% for the pH the amount of TEOS. They demonstrated the effect of

277 particle size by changing the pH values to 9.5, 12.16, or 13 and observed the smaller particle size  
278 of around 100 nm at pH 13.

279 The reaction time also has a notable influence on the particle size of MSNs. Chiang et al.  
280 also observed the effect of reaction time on particle size. They reported that the size of the  
281 particles increases at the start with a subsequent decrease as the reaction period increases from 2-  
282 10 h. (Chiang et al., 2011). Wang et al. developed virus-like MSNs having improved cellular  
283 uptake characteristics. The structural properties of these carriers changes at different reaction  
284 times. On prolonging the total reaction time, the walls of mesopores got thicker. After 18 h, the  
285 surface area of particles reduces due to the blocking of MSNs channels with excessive silicates  
286 growth. On further increasing the reaction time up to 24 h, the shorter nanotubes of silica adhere  
287 to the surface of nanoparticles without a noticeable change in the shape of nanoparticles. With a  
288 further increase of reaction time, these nanotubes increase in length up to ~5 nm with an increase  
289 in particle size of 130 nm. Finally, after 48 h, the total length of mesopores extends up to ~15 nm  
290 with particles size of 160 nm with elongation of nanotubes (Wang et al., 2017a).

291 Particle size can also be altered by the addition of certain solvents or other compounds.  
292 The effect of different co-solvents and mixtures on the sizes of the particles demonstrated a  
293 significant reduction of particle size by using ethylene glycol. It was proposed that the use of  
294 ethylene glycol decreases the interaction of surfactant with silica precursors and inhibits the  
295 growth of particles (Gu et al., 2007). Change in the composition of the alkoxy group ( $\text{Si}(\text{OR})_4$ )  
296 of tetraalkoxysilanes also brings out the change in the particle size. Also, the addition of certain  
297 additives like alcohols also influences the hydration rate of the reaction and causes alteration of  
298 particle size (Yamada et al., 2013). CTAB concentration also affects the process of hydrolysis  
299 and its micellization. Therefore the lower concentration of CTAB brings more homogenous and  
300 spherical distribution of particles sizes, while agglomerates were observed with variation in its  
301 concentration (Vazquez et al., 2017). The concentration of polymer F127 also plays a critical  
302 role in controlling the particle size of MSNs. Studies also reported the effect of  
303 tetramethylorthosilicate (TEOS) concentration on the particle size of MSNs. They observed that  
304 with the increasing value of TEOS, an increase in the particle size was observed. Although this  
305 increase in the particle size is not in proportion to the increase of TEOS, indicating a little effect  
306 of TEOS on particle size (Chiang et al., 2011). Also, increased concentration of TEOS is  
307 accountable for the change of monodisperse system to a heterogeneous system of particles size  
308 distribution. This is due to the presence of an excess quantity of silica precursor that leads to the  
309 production of new nuclei among the already formed particles (Zainala et al., 2013).

310 The introduction of some capping agent or functionalization of MSNs also affects the  
311 particle sizes. Capping of MSNs through polyethylene glycol (PEG)-silanes helps in the  
312 attenuation of the growth of particles, hence inhibiting their size through the process of steric  
313 stabilization. The addition of PEG-silane immediately to MSNs after the addition of tetramethyl  
314 orthosilicate (TMOS) limits its size up to 5 nm. Still, an increase in particle size of >13 nm was  
315 observed if there was a delay in addition after 50 minutes (Ma et al., 2013). Stirring rate is

316 another crucial factor in determining the particle size; slow stirring resulted in the formation of  
317 larger particles while fine particles were formed upon fast stirring (Beltrán-Osuna et al., 2017).

318 Temperature is another parameter that affects the particles sizes of MSNs. Increasing the  
319 temperature from 30°C to 70°C increases the particles size of MSNs from 28 to 113 nm. This  
320 may be due to polycondensation of silica precursors due to an increase in reaction rate, which  
321 results in the formation of a denser structure of silica with increased particle size (Zainala et al.,  
322 2013).

#### 323 4.2. Pore Size

324 Pore size is one of the essential parameters of MSNs for loading a variety of drug bio-  
325 macromolecules. Self-assembly of surfactant molecules with the silica precursor leads to the  
326 formation of MSNs with various pore sizes. These pores are formed upon the removal of charged  
327 surfactant molecules. In the case of non-ionic surfactants, the formed MSNs will have smaller  
328 pores sizes with low surface area. Several attempts have been made to synthesize MSNs with  
329 uniform pore sizes with highly ordered hexagonal regular structures. The persistent urge to  
330 obtain large pores of MSNs for the accommodation of carrier drug molecules brought the  
331 discovery of MSNs in 1992.

332 Surfactant selection plays a key role in ordering MSNs and affects their pore size. It was  
333 postulated that the sizes of the pores could be expanded by employing new templating materials.  
334 Pore sizes of the MSNs carriers can be varied by using surfactants of various chain lengths. The  
335 surfactants having longer chain lengths will form MSNs of larger pores in comparison to the  
336 surfactants of shorter chain lengths. Yano et al. developed monodispersed MSNs having highly  
337 ordered regularity by employing n- alkyl trimethylammonium chloride (C<sub>n</sub>TMACl) as a  
338 surfactant, where n =14, 16, and 18. The developed MSNs were aligned from the central point to  
339 outwards in a radial manner in the spherical particles (Yano and Fukushima, 2004).

340 For the generation of MSNs, usually, salts of dodecyl or cetyltrimethylammonium (CTA)  
341 were used, such as cetyltrimethylammonium chloride (CTAC) or cetyltrimethylammonium  
342 bromide (CTAB). A study reported the formation of MSNs with high porosity by employing a  
343 combination of surfactant (CTAB), co-surfactant (dimethyl hexadecyl amine), and oily phase  
344 (decane) to introduce new swelling strategies. The obtained carriers also exhibited high  
345 mechanical and thermal stability (Egger et al., 2015). In another study, PEG was employed as a  
346 stabilizer and added during the reaction process, which resulted in the formation of MSNs  
347 having larger cavities with high surface area (Ganguly et al., 2010). In addition, by changing the  
348 molar composition of the medium, the arrangement of pores can be changed to cubic (MCM-48)  
349 or hexagonal (MCM-41) type.

350 The ordering of mesostructures in the carriers is dependent on the concentration of  
351 TEOS. Increased concentration of TEOS resulted in the formation of a disordered structure of

352 MSNs. However, a lesser concentration of TEOS will not be sufficient that help in the formation  
353 of regular mesoporous structures (Chiang et al., 2011). The concentration of surfactant also  
354 significantly impacts the ordering of mesostructures. Less concentration of CTAB resulted in  
355 poor micellar structures, while its increased concentration may lead to the formation of a highly  
356 disordered structure.

357 Pores size also has a great influence on the release kinetics of drugs. Izquierdo et al.  
358 studied the release rate of erythromycin and ibuprofen by observing pore sizes and demonstrated  
359 the decreased release rate of the drug with a pore size of the matrix. They also observed a change  
360 in the delivery profile of hydrophobic drugs with modification of surface matrix (Izquierdo-  
361 Barba et al., 2005).

362 Further, different strategies were developed in order to change the morphological  
363 characteristics of MSNs (small pore size, non-uniformity). In this regard, research was conducted  
364 to synthesize monodisperse nanocarriers of silica with dendritic morphology and large porous  
365 structure. For this purpose, a partially fluorinated anionic fluorocarbon surfactant (Capstone FS-  
366 66) was mixed with CTAB through a sol-gel reaction. The increased concentration of Capstone  
367 FS-66 resulted in a larger particle size having a dendritic pore channel (Huang et al., 2017). This  
368 strategy was also employed by Yu and his co-workers. They designed MSNs using imidazolium  
369 ionic liquid with Pluronic F-127 as particle growth inhibitor and co-surfactants of various alkyl  
370 lengths and obtained dendritic MSNs with a particle size of < 200 nm (Yu et al., 2014).

#### 371 4.3. Shape of MSNs

372 The MSNs shape plays an important role in the cellular uptake and trafficking of MSNs  
373 into cells (Shao et al., 2017). Trewyn et al. showed that tubular MSNs achieve more efficient  
374 uptake by normal and cancerous cells than those of spherical shape. This suggests the impact of  
375 different shapes on cellular uptake behavior (Brian G. Trewyn, 2008). Huang et al. reported the  
376 influence of particle shape on *in vivo* bio-distribution of nanocarriers; by designing the  
377 fabrication of fluorescent MSNs of two different shapes. The distribution of MSNs in various  
378 organs has a high influence on shape effects. Rods of shorter MSNs showed more distribution in  
379 the liver, while rods of longer MSNs displayed more concentration in the spleen. Also, PEG  
380 modification on both types of MSNs makes their distribution higher in the lungs (Huang et al.,  
381 2011). Huang and his coworkers; also explained the relationship of shapes of MSNs and the  
382 observed cellular responses. They developed MSNs of the same chemical composition, surface  
383 charge, and diameter but different aspect ratios and observed the effect of particle shapes of three  
384 MSNs on cellular uptake studies. The results demonstrated different internalization behavior  
385 exhibited by particles of different shapes. Particles of larger aspect ratios demonstrated increased  
386 internalization in human melanoma cells (Huang et al., 2010).

387 The molar concentration of TEOS, surfactant, base catalyst, and water affects the  
388 morphology of MSNs. Non-spherical MSNs can be of cube shape, rod-like, ellipsoid, sheet or  
389 film-like materials. However, spherical MSNs have more potential in drug delivery in  
390 comparison to non-spherical MSNs. Zhang et al. studied the shape of MSNs on the delivery of  
391 Indomethacin. They prepared MSNs of various shapes by using different concentrations of  
392 surfactants and alkyl alcohols as co-surfactants. The result depicted different performances of  
393 MSNs due to the presence of different shapes (Zhang et al., 2019). Cai et al. synthesize MSNs of  
394 various shapes, including silica rods, oblate silica of nanometric size, or in spherical shape by  
395 changing the concentration of CTAB, TEOS, NH<sub>4</sub>OH/NaOH concentration (Cai et al., 2001).  
396 Another simple method for the preparation of MSNs was developed by using dodecanol (C<sub>12</sub>-  
397 OH) and CTAB as a soft templating agent. Six different shapes of MSNs were synthesized with  
398 modulation of temperature and C<sub>12</sub>-OH with the development of sphere-like, yolk-shell, hollow  
399 and peanut-like structures. The different morphologies were obtained through the use of  
400 dodecanol as a soft templating agent (Han et al., 2013). So, changing the micellar concentrations  
401 at initial levels may bring out changes in particles morphologies having different aspect ratio  
402 values. MSNs of rod-shape act as counterparts of MSNs of spherical shape and can be obtained  
403 through modulation of reaction parameters in a typical reaction. By adding the co-solvents in a  
404 reaction, *i.e.*, heptane, increasing the concentration of catalyst or by the change of temperature,  
405 rod-shaped MSNs can be obtained (Björk et al., 2013; Pang et al., 2005).

406 Another important shape of MSNs that take part in drug delivery includes ellipsoidal  
407 MSNs, but the major challenge associated with this shape is its inability to retain this shape and  
408 convert it into a spherical one in order to minimize the surface free energy. This kind of MSNs  
409 can be generated by employing ethanol, co-surfactant, and potassium chloride (Shen et al.,  
410 2012). Highly porous MSNs of platelet-shaped are designed by employing lower concentrations  
411 of heptane, ammonium fluoride, non-ionic block co-polymer P-104, Pluronic 123, sodium  
412 dodecyl sulfate, and CTAB (Björk et al., 2013; Chen et al., 2004; Cui et al., 2006). Certain  
413 organosilanes can also be used for the purpose of shape transformation. The morphological  
414 characteristics mostly depends upon the type and concentration of organoalkoxysilanes  
415 precursors. These morphological features of MSNs are generated due to the presence of different  
416 bonding and interactions among the chemical groups such as; hydrophobic interactions,  
417 hydrogen bonding, etc., between surfactant templates and organoalkoxysilanes (Huh et al.,  
418 2003).

## 419 **5. Surface Modification and Functionalization of MSNs for Drug Delivery**

420 The premature release of drugs is a great challenge for the delivery of drugs at the  
421 required site. Various modifications have been made on the surfaces of MSNs for imparting  
422 desired properties which may include controlling the drug release profile or improving the  
423 loading capacity of the drug, together with reduction of toxicity profile in comparison to free  
424 drug (Nik et al., 2020). Surface chemical modification in MSNs can significantly increase the



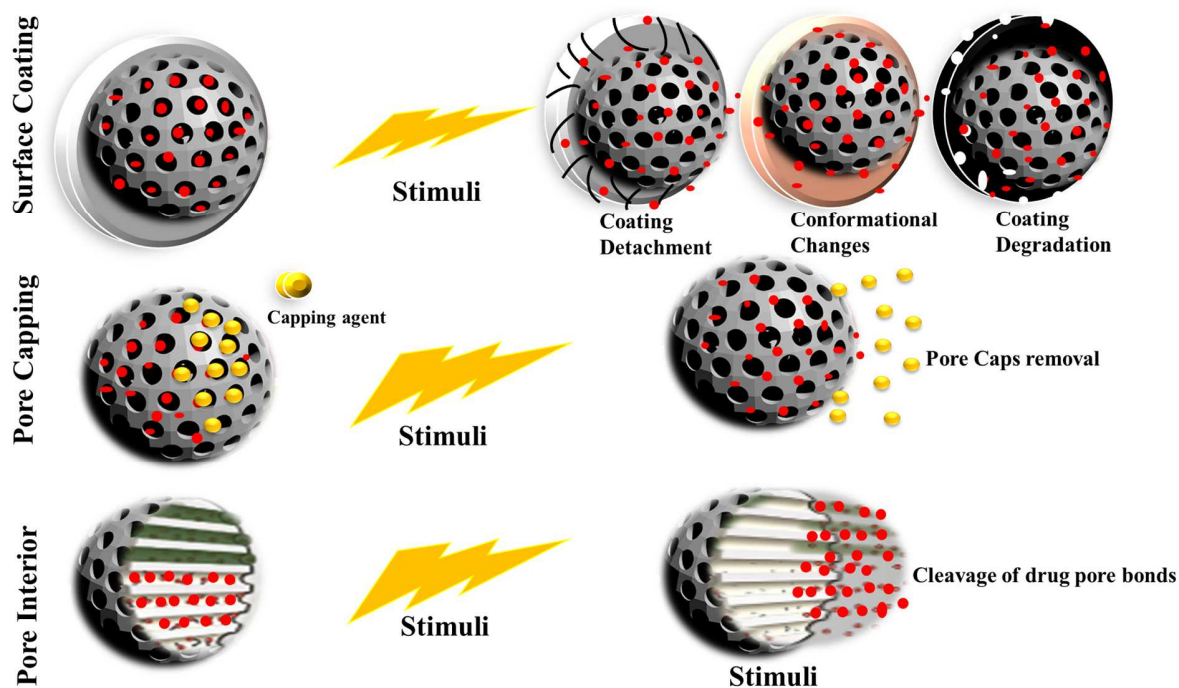
425 targeted delivery of drug with an increase uptake in affected cells. Modification can be  
426 performed by attaching different functional groups with characteristic features that alter the  
427 environmental interface of nanocarriers, thereby controlling their undesirable biological fluids  
428 interactions. These functional groups include amino groups containing polymers (polyethylene-  
429 glycol, dendrimers, polyethyleneimine, phospholipids), thiols, organic phosphates, etc. Chemical  
430 moieties can also be attached or adsorbed onto the external surface of MSNs, especially to the  
431 surface of silica, by either covalent linkage or electrostatic interactions. Positively charged  
432 moieties interact with the negatively charged silica surfaces to impart desirable features to the  
433 MSNs (Tarn et al., 2013). Modification can be made to their internal surface by grafting (post-  
434 synthesis functionalization) or co-condensation (in-situ functionalization), enabling their wider  
435 use in various applications. In comparison to the grafting modification, the technique of co-  
436 condensation provides improved bonding properties between the porous walls of MSNs with  
437 subsequent organic groups. This results in the development of a more homogenous structure of  
438 organic functional groups onto the porous structure of MSNs (Kobler et al., 2008).

439         The presence of silanol groups in the structures of MSNs allows greater modifications in  
440 order to make tremendous biomedical applications. Various modifications can be performed onto  
441 the hydroxyl groups of MSNs that can be amine, hydroxyl, thiols or other organic chain  
442 modifications. These modified surfaces perform an important role in the release of a drug under  
443 particular physiological conditions and control the release of the drug at particular stimuli. These  
444 modifications also improve various agents loading capacity, particularly siRNA and DNA,  
445 promoting targeted delivery of various cytotoxic agents (Natarajan and Selvaraj, 2014). The first  
446 capped MSN, developed in 2003, was coumarin-modified MSN, after which various MSNs were  
447 developed, decorated by capping agents of diverse properties. These agents can be proteins,  
448 polymeric supramolecules, or DNA fragments that respond to specific internal or external stimuli  
449 to release loaded cargo/drug. As glutathione (GSH) concentration is remarkably higher inside the  
450 cancerous cells (10 mM) as compared to extracellular matrix (2 μM), suggesting the presence of  
451 reduction potential for triggering drug release (Wang et al., 2015). Reduction potential provides  
452 selectivity by the splitation of disulfide bonding due to the presence of a large quantity of thiol  
453 groups as compared to the normal cellular environment (Karimi et al., 2016).

454         Capping of MSNs is mainly involved in two parts. In the first part, the gating mechanism  
455 is provided by certain immobilized molecular stalks that are covalently bonded to MSNs  
456 covering the pores of MSNs; while in the second part, certain labile molecular groups are non-  
457 covalently attached to the stalks. Alterations in the normal physiological conditions results in the  
458 reversible alteration of mobile molecular binding, resulting in the cleavage of weaker bonds  
459 between movable molecules and stalk that uncaps the mesoporous structures of MSNs,  
460 provoking drug release (Pan et al., 2012b, a). Tremendous work has been carried out in order to  
461 develop various materials that can be used as gate keepers. About a decade ago, nanoparticles of  
462 certain inorganic materials such as FeO and CdS were used to cap the pores through the  
463 formation of redox-sensitive disulfide bonds (Giri et al., 2005; Lai et al., 2003). On the addition

464 of a thiol-containing moiety dithiothreitol (DTT), the disulfide bonds break their interaction with  
 465 the nanoparticles while releasing the encapsulated agents. After that, other gatekeepers were  
 466 introduced, such as synthetic polymers (Hong et al., 2008), cyclodextrin or its supramolecular  
 467 systems (Zhou et al., 2014), biomacromolecules (Wen and Oh, 2014), inorganic nanoparticles  
 468 (Liu et al., 2010), peptides (Li et al., 2014), etc.

469 The cargo release from the MSNs carriers can be done through the use of three  
 470 approaches, as depicted in Fig 3. Among which, first can be achieved by coating the entire  
 471 surface of particles (Zhang et al., 2015), in the second approach, pores of MSNs can be sealed by  
 472 employing certain gatekeepers or molecular gates (Song and Yang, 2015), while the third  
 473 approach utilizes the coupling of drug cargo with the internal walls of the porous structure  
 474 (Moreira et al., 2016). All of these approaches will, in turn, undergo any of the two responses,  
 475 *i.e.*, conformational destruction or any change of the gate keeper covering the pores or the  
 476 cleavage of the pore covering agent upon required stimulus (Moreira et al., 2016; Peng et al.,  
 477 2013). In this respect, various approaches have been developed in order to control the release of  
 478 a drug; that may include applications of different polymeric combinations that may form firm  
 479 bonds covalently or either form surface adsorption onto the cargo. The carriers releases the drug  
 480 upon exposure to either external or internal stimuli by either uncoiling or swelling (Corbalan et  
 481 al., 2012a).



482  
 483 **Fig. 3.** Strategies utilized for the creation of stimuli-responsive MSNs and their release  
 484 mechanism

485 Different groups used in the functionalization of MSNs are discussed below:

#### 486 5.1. Chitosan

487 MSNs can be modified by using various materials that may act as a gate keeper such as  
488 polysaccharides, polymers, or biomolecules to obtain targeted drug release under the influence of  
489 specific stimuli. Polysaccharides have gained immense importance to be used as gate keepers  
490 due to a variety of attractive features (Wen and Oh, 2014). Among these polysaccharides,  
491 Chitosan is one of the remarkable polymer, that has been extensively utilized as gate keeping  
492 agent for MSNs. Chitosan, a linear polysaccharide having basic properties, is widely used as a  
493 capping agent for MSNs due to its higher biocompatibility and biodegradability (Qindeel et al.,  
494 2019). Moreover, the molecular weight and degree of deacetylation of chitosan also greatly  
495 affect its properties and functionalities. The molecular weight of chitosan generally ranges from  
496 10000 and 1 million Dalton, with a degree of deacetylation extending from 50 -95 %. As most of  
497 the polymer applications are mainly attributed to its properties based on protonation of amine  
498 groups molecules in the acidic medium. This protonation degree or pKa is dependent on  
499 molecular weight of the polymer and ultimately affect the particle size and release properties of  
500 drugs. Increase in the molecular weight of polymer permits faster release of drug (Fernández-Pan  
501 et al., 2015; Safdar et al., 2019). Cui et al. proposed the development of unique charge reversal  
502 MSNs through hybrid technology by using negatively charged carboxymethyl chitosan and  
503 positively charged chitosan. This charge reversal chitosan/carboxymethyl chitosan is designed as  
504 a pH stimuli-responsive trigger through the effect of protonation and deprotonation of respective  
505 polymer layers. This kind of surface charge reversal improves the delivery and retention time of  
506 Doxorubicin for the efficient treatment of breast cancer. He also demonstrated the effect of the  
507 molecular weight of chitosan on the particle size of nanocarriers. Increased particle size was  
508 observed with a molecular weight of 1000 kDa than with a molecular weight of 200 kDa (Cui et  
509 al., 2019). The deacetylation degree of chitosan also affects its properties related to cross-linking,  
510 solubility, degradation behavior, and release characteristics. The increased value of polymer's  
511 deacetylation degree decreases its crystallinity with increased degradation rate and higher release  
512 profile (Safdar et al., 2019).

513 Different studies reported the capping of MSNs with chitosan through the attachment of  
514 functional groups for targeting the drug at the required site by making it responsive to specific  
515 stimuli. Among these, the changing pH is extensively studied on account of the fact that most  
516 tumors have an acidic microenvironment. Therefore, chitosan is mostly studied as capping  
517 material for MSNs as a pH-responsive gatekeeper. Chitosan-capped MSNs can be activated by  
518 an environment of acidic pH and degraded under the action of lysozymes (enzymes of the  
519 immune system). As, the amino groups of chitosan became activated in acidic pH and converted  
520 into their cationic form, thereby acting as a positively charged polyelectrolyte. Zeiderman et al.  
521 designed gold nanorods that were coated with MSNs capped with chitosan for targeted delivery  
522 to pancreatic tumors. The pH-sensitive variant was attached with the chitosan to deliver the

523 carriers specifically at the acidic environment of tumors. The encapsulated drug gemcitabine  
524 displayed a greater cytotoxic effect when delivered through these carriers than free drugs  
525 (Zeiderman et al., 2016).

526 Chitosan being a cationic polymer, also improves the loading of genes and related  
527 molecules. Lin et al. reported the co-delivery of Doxorubicin and p53 gene through MSNs  
528 modified with dendronized chitosan that acts as a 'gate keeping agent' for the achievement of  
529 combination therapy with zero premature drug release. The drug was released from the carriers  
530 upon activation of a polymer through redox stimulus in the presence of GSH. Stimulus-induced  
531 release of the doxorubicin was reported with efficient gene delivery having increased expression  
532 of p-53 proteins in Hela cell culture (Lin et al., 2017).

533 The polymer also allows grafting of other active ligands for the design of site-specific  
534 targeted delivery. Yan et al. developed safe and biodegradable hollow MSNs by capping  
535 chitosan polymer on its outer surface that was further linked with glycidoxypropyl-tri-methoxy-  
536 silane (GPTMS) through siloxy bonding. Further targeting properties were provided by the folic  
537 acid attachment that allows the encapsulated agents, Doxorubicin and Pheophorbide  
538 (photosensitizer), to be available at the tumor site. The results demonstrated very efficient  
539 antitumor activity through the design of efficient delivery carriers (Yan et al., 2020). Shakeran et  
540 al. developed biodegradable MSNs by their modification with 3-triethoxysilylpropylamine  
541 (APTES) followed by chitosan modification through glutaraldehyde. This helps to increase the  
542 loading capacity of Methotrexate with more efficient uptake as an anti-cancer agent for the  
543 treatment of breast cancer (Shakeran et al., 2021).

544 Functionalization of MSNs through Chitosan is advantageous in terms of its natural  
545 origin, increase biocompatibility, and biodegradability with non-toxic profile, which imparts  
546 useful characteristics to MSNs in terms of biocompatibility and degradation. Also, the carrier is  
547 present with innate properties of anti-inflammatory, anti-bacterial, and mucoadhesive  
548 characteristics. Thus it is utilized in different biomedical fields in terms of targeting potential,  
549 anti-inflammatory, and wound healing properties (Jhaveri et al., 2021). However, the polymer is  
550 associated with a poor solubility profile at physiological pH and can only be dissolved at acidic  
551 pH. Moreover, the amino groups of the polymer become protonated at intestinal or basic pH and  
552 can be activated in the bloodstream through different enzymes (Heidari et al., 2021).

## 553 5.2. Multifunctional polymers

554 Various polysaccharides can be employed as gatekeepers due to the presence of their  
555 tunable surface, ease of synthesis, low toxicity profile, abundance in nature, and excellent  
556 biocompatibility. In this kind of approach, multiple layers of the polymers can be capped on the  
557 surface of MSNs for the implementation of the desired properties. These multilayered capping  
558 strategies are biocompatible and also allow functionalization to the MSNs surface.

559 Through the development of the stimuli-responsive system, the carriers prevent the  
560 release of cargo at the off-target site, as at higher pH values, the polymer remains present in a  
561 deprotonated state or in hydrophobic form causing a collapse of polymer onto the surface of  
562 silica. After their entry into endosomes or at acidic pH, the drug-loaded in the MSNs got released  
563 by switching the carriers into an open state. In a recent study, MSNs were constructed by  
564 utilizing the multiple layers of chitosan and alginate through a layer by layer technique for  
565 developing the pH-sensitive nanocargoes. Alginate is a polysaccharide of acidic properties that,  
566 when combined with the basic chitosan, provides multilayered coatings to the structure of MSNs.  
567 These kinds of MSNs displayed excellent bioavailability with low cytotoxicity and hemolytic  
568 activity compared to bare MSNs with the provision of the pH-dependent release of cytotoxic  
569 drug 'Doxorubicin' at the tumor site (Yang et al., 2010). In recent work, 5-fluorouracil was  
570 encapsulated in MSNs, and capping was done with the glucuronic acid-chitosan layers, for its  
571 delivery to the colorectal tumor environment. The drug was delivered to the targeted area by  
572 employing the strategy of the acidic tumor microenvironment, together with overexpression of  
573 lectin receptors. These lectins are proteinous in nature and bound specifically with the  
574 glycoproteins promoting active targeting of a drug (Narayan et al., 2021). Niedermayer et al.  
575 demonstrated multifunctional polymer capped MSNs for targeted delivery to cancer cells, in  
576 which a highly stable sequential attachment of specified functionalities to the surface of MSNs  
577 was presented. Through this approach, they developed multifunctional delivery carriers, having  
578 higher loading capacity through the presence of mesoporous silica core capped with poly-2-  
579 vinylpyridine (pH-responsive polymer). The bi-functional polymer was also functionalized with  
580 other groups, like PEG (for increasing permeation, retention and circulation time), additional  
581 endosomal opening groups (for release of drug in endosomal region), and targeting ligands.

582 In addition to pH, the introduction of photosensitizer polymer and magnetic nanocarriers  
583 were also developed. So, by developing this kind of multifunctional carriers, improved targeting  
584 was achieved through cellular uptake at acidic pH, photoactivation, or applying a magnetic field  
585 (Niedermayer et al., 2015). Hegazy et al. designed polymeric MSNs by modification with  
586 disulfide bonding and photoresponsive polymer, poly (2-nitrobenzyl acrylate) loaded with  
587 ibuprofen. Upon treatment with ultraviolet light, o-nitrobenzyl ester cleavage in the polymeric  
588 chains releases the loaded drug in a controlled manner (Hegazy et al., 2019). In another study,  
589 Zhang et al. developed polymeric MSNs that release the encapsulated drug upon the influence of  
590 triple stimuli of light, pH, and reducing agent (Zhang et al., 2015). The MSNs were modified  
591 with a capping of poly (2-(diethylamino) ethyl methacrylate, which is sensitive to pH and  
592 contains cleavable disulfide bonds and o-nitrobenzyl ester that is cleavable to light. The  
593 nanocarriers encapsulate Doxorubicin, demonstrating efficient cytotoxicity against HeLa cells,  
594 presented promising potential for cancer treatment (Zhang et al., 2015). Guisasola et al.  
595 developed iron oxide magnetic responsive MSNs and coated them with thermoresponsive  
596 polymer. Upon application of alternating magnetic field, these magnetic nanocarriers behave as  
597 an internal source of heat, increasing the surrounding temperature of a cancerous area with the

598 release of the entrapped drug. This kind of synergic action provides huge tumor treatment  
599 innovation (Guisasola et al., 2018).

600 Functionalizing MSNs with different polymeric agents helps design a more advanced  
601 nanocomplex, combining advantages of different polymers. Polycationic complexes with MSNs  
602 are more advantageous and versatile with promising biological applications. Alginate, an acidic  
603 polysaccharide that combines with the basic chitosan through multilayered coatings, provides  
604 increased protection to the loaded cargoes. In this way, this kind of polymeric system is not only  
605 advantageous to increase the biocompatibility of the polymer but is also helpful in effective  
606 functionalization with a more shielding effect (Feng et al., 2014). The layering of different  
607 polymers on the surface of MSNs helps provide enhanced biomedical activities, *i.e.*, a study  
608 demonstrated enhanced anti-cancerous activity after surface decoration of MSN with PEG and  
609 PEI than a single layer of chitosan (You et al., 2015). However, by implementing this strategy,  
610 the particle size and the release characteristics of the carrier can be altered. A detailed study  
611 should be performed to evaluate the *in vivo* fate of these carriers.

612

### 613 5.3. Dextrin

614 Dextrin is another low molecular weight starch derivative and has been widely used for  
615 the capping of MSNs surfaces. It is commonly used as a gate capping agent for the design of pH-  
616 sensitive MSNs with more water solubility. In recent years, various strategies have been  
617 developed for the design of dextrin capped MSNs. Research conducted by Chen et al. developed  
618 MSNs loaded with doxorubicin hydrochloride and capped them with dextrin. Afterward, dextrin  
619 was oxidized to obtain dextrin dialdehyde for its coupling with tetraethylenepentamine (pH  
620 sensitive Schiff's base) for 'closing the gate' to avoid the premature release of a drug. The  
621 aldehyde groups in the dextrin dialdehyde form cross-linking with the Schiff's base produced  
622 from tetraethylenepentamine to 'close the gate.' In this way, the modified dextrin capping of  
623 MSNs acts as a gatekeeper for the control of the release of drugs, particularly at the acidic tumor  
624 microenvironment, by acting as a pH-sensitive delivery system. Under a normal physiological  
625 environment, Schiff's base will remain stable, avoiding the premature release of a drug, while at  
626 low pH of tumor region (5-6.8), the Schiff's base will be hydrolyzed, allowing slow diffusion of  
627 the drug illustrating its controlled release behavior (Chen et al., 2016).

628 Dextrin-coated MSNs sensitive to glutathione and internal enzymes were also fabricated  
629 for targeted delivery in tumor cells. Chen et al. developed an on-demand drug delivery system by  
630 developing stimuli-responsive MSNs that were end-capped with dialdehyde dextrin that acts as a  
631 gate keeper for sealing the drug inside the pores of MSNs. The polymer is further interlinked  
632 with GSH sensitive disulfide bonds. The polymer tightly capped the surface of MSNs and  
633 responded only under acidic or GSH conditions for the release of the entrapped drug. These

634 Dextrin-modified dual responsive MSN carriers behave as promising nanocarriers for the release  
635 of on-demand drug delivery (Chen et al., 2018b). Another research reported that the capping of  
636 organic silica nanocarriers with dialdehyde dextrin through Schiff base bonding releases the drug  
637 upon stimulation of acidic pH and redox potential (Li et al., 2020). Graphene oxide nanocarriers  
638 were also conjugated with dextrin, which was stimulated by  $\alpha$ -amylase enzyme and released  
639 drug at the tumor site having higher permeability through the endothelial barrier with better  
640 penetration profile (Kiew et al., 2017).

641 Other starch derivatives of hydrolyzed form, *i.e.*, Glucidex 29, Glucidex 37, Glucidex,  
642 and 47, are also used for capping purposes having different concentrations of maltose and  
643 glucose. These were also degraded by enzymatic action for uncapping the surface of MSNs.

644 The advantage of dextrin functionalization helps to impart greater bio-compatibility and  
645 bio-degradability to the MSNs nanocarriers. Moreover, the polymer is also of lower molecular  
646 weight and can be utilized as a superior capping agent for the release of targeted drug delivery.  
647 However, the disadvantage associated with the polymers is their low stability profile (Kagami et  
648 al., 2003).

#### 649 5.4. Hyaluronic acid

650 In 1934, a chemical substance from bovine eyes containing two sugar molecules was  
651 isolated by Karl Meyer and John Palmer and was termed as 'hyaluronic acid' due to the presence  
652 of uronic acid (one sugar molecule) and its isolation from hyaloid (vitreous body) of bovine eyes  
653 (Meyer and Palmer, 1934). Further research demonstrated that the molecule is composed of non-  
654 sulfated glycosaminoglycan (polysaccharide composed of monomers of N-acetyl-D-glucosamine  
655 molecules joined together by -1, 3, and -1, 4 glycosidic linkages. It is considered as one of the  
656 vital biopolymers playing an important role in a number of physiological activities.

657 The polymer is negatively charged, having non-immunogenicity, increased  
658 biodegradability, and biocompatibility. Moreover, its increasing ability to target a variety of  
659 chemical receptors like CD-44 (Cluster of Differentiation 44), CD-168 (Cluster of  
660 Differentiation 168, playing a role in wound healing), RHAMM (receptor for hyaluronan  
661 mediated motility), Toll-like receptors, HARE (HA receptor for endocytosis) plays an important  
662 function in cellular internalization of nanocarriers at the targeted site. Moreover, the polymer  
663 degrades by the action of hyaluronidase-1 (lysosomal enzyme) into fragments of lower molecular  
664 weight.

665 The enveloping of hyaluronic acid to the surface of MSNs help them to act not only as  
666 the capping agent but also as a targeting agent to the targeted site. Massive research has been  
667 carried out to target hyaluronic acid capped MSNs at the diseased site with increased expression  
668 of its receptors (Chen et al., 2013b). Zhou et al. developed hollow MSNs and functionalized



669 them with dopamine-modified hyaluronic acid, which acts both as a gate keeper and a targeting  
670 agent. The system delivered the encapsulated drug ‘Doxorubicin hydrochloride’ together with  
671 the fluorescent dye ‘indocyanine green’ to the cancerous region. The developed system releases  
672 the enveloped agents at the targeted site by acting as a pH-sensitive system (Zhou et al., 2021).  
673 Chen et al. fabricated hybrid MSNs by capping with hyaluronic acid through hydrazine bonds.  
674 The system releases the drug in response to acidic pH with enhanced targeting towards CD-44  
675 expressed cells in Hela cells. The developed carriers displayed enhanced release of Doxorubicin  
676 in response to acidic pH, demonstrating effective treatment against cancer cells (Chen et al.,  
677 2018a).

678 Nairi et al. demonstrated the effect of chain length of hyaluronic acid on cellular  
679 internalization to achieve targeted drug delivery. For this purpose, they functionalized MSNs  
680 first with amino acids and then with hyaluronic acid of various molecular weights for targeting  
681 cancer cells (Nairi et al., 2018). A study was also conducted in which hydrophobic drug  
682 camptothecin was loaded in MSNs capped with hyaluronic acid for the treatment of cancer with  
683 enhanced cytotoxicity (Ma et al., 2012). A study was also conducted to target drugs through  
684 hyaluronic acid capped MSNs to treat human colon cancer by demonstrating their effective  
685 cytotoxicity against HCT-116 cell lines (Yu et al., 2013). Gary-Bobo et al. developed MSNs  
686 capped with a layer of poly-(L-lysine) together with hyaluronic acid through layer by layer  
687 technique for the treatment of colorectal cancerous cells. Polyelectrolyte multilayered system  
688 was developed by electrostatic interactions of oppositely charged polyelectrolytes consisting of  
689 positively charged poly (L-lysine) and negatively charged hyaluronic acid. These functionalized  
690 MSNs were targeted to the colorectal cancer cells having CD-44 overexpression, which is mainly  
691 involved in cancer progression with tumor angiogenesis (Gary-Bobo et al., 2012). Similarly,  
692 redox responsive drug delivery was developed based on hyaluronic acid capped MSNs, in which  
693 drug (6-mercaptopurine) was released in the presence of GSH (Zhao et al., 2014).

694 The advantage of functionalization of MSNs with hyaluronic acid resulted in the  
695 formation of MSNs with high bio-degradability and biocompatibility. Moreover, a study reported  
696 the effect of different chains of hyaluronic acid on MSN properties. The smaller diameter of  
697 particles was obtained with a high molecular weight of hyaluronic acid, with efficient  
698 internalization through the process of endocytosis. This is due to the multipoint attachment of  
699 longer hyaluronic acid chains and its entanglement on the MSN surface, which produces  
700 particles of smaller size (Chen et al., 2018a). However, the technique requires extensive *in vivo*  
701 studies for the determination of bio-distribution and fate of MSNs.

## 702 5.5. Amino groups

703 Functionalization with amino groups can be done on the matrices of MSNs for the control of  
704 drug interaction with the matrix surface that further controls its release rate. Amino-tagged  
705 MSNs were developed especially for the better interaction of siRNA. The MSNs shell having a

706 negative charge is being functionalized with the positively charged blocks of amino acid for the  
707 development of a highly efficient delivery system.

708 This method was utilized for modification of MCM-41 nanocarriers encapsulated with  
709 enrofloxacin hydrochloride by the grafting of amine carriers to inner channels while thiol groups  
710 were introduced onto the outer surface of MSNs through a stepwise approach. Introduction of –  
711 SH and –NH<sub>2</sub> groups form bonding with negatively charged carboxyl groups avoiding the  
712 premature drug release. Moreover, attachment of –NH<sub>2</sub> functional group promotes increased  
713 attachment of ibuprofen on MSNs facilitating sustained drug release and better relaxivity in MRI  
714 (Carniato et al., 2015). However, little control over final functional groups localization brings  
715 random distribution of functionalized groups on the surface of MSN (Linares et al., 2011). He et  
716 al. developed amino-functionalized MSNs by post grafting method for Doxorubicin delivery.  
717 Amino functionalized MSNs resulted in increased loading of drug and releases drug at acidic pH.  
718 Doxorubicin-loaded amino-functionalized MSNs displayed efficient cytotoxic potential against  
719 non-small cell lung cancerous cells (He et al., 2017). Geng et al. developed amino-functionalized  
720 MSNs for delivery of GLP-1AR (Glucagon-like peptide) and FGF-21 (Fibroblast growth factor  
721 21) plasmids for treatment of Diabetes mellitus type 2. Liraglutide is a glucagon-like agonist of  
722 peptide-1 receptors, and FGF-21 helps to treat insulin resistance and glucose metabolism. The  
723 developed amino-functionalized MSNs carrying both FGF-21 and liraglutide for transfection of  
724 Hepa 1-6 cells (Geng et al., 2021). Similarly, co-functionalization of MSNs by chelating it with  
725 gadolinium (Gd-DOTA) and amino groups provides better contrast for MRI by binding of amine  
726 groups with the terminal carboxylic moieties on gadolinium chelate (Carniato et al., 2015).

727 Amino functionalized MSNs are also used for improving the release profile of poorly  
728 water-soluble drugs. Wang et al. synthesized chiral MSNs and functionalized them with an  
729 amino group for enhancing the release profile of poorly water-soluble drug Indomethacin. The  
730 resultant 2-D hexagonal carriers with curled channels differed in morphological features from  
731 other 2D hexagonal MSNs with straight channels. After loading a drug through hydrogen  
732 bonding into silica carriers, the crystalline drug was converted into an amorphous form with  
733 improved drug dissolution. These chiral curvature channels hold more drugs in comparison to  
734 straight channels carriers. The loaded carriers displayed fast drug release with an improved  
735 dissolution profile (Wang et al., 2019).

736 The amino-functionalized MSNs are more frequently utilized for siRNA delivery. The MSN  
737 shell having a negative charge is normally functionalized with the cationic co-polymer with the  
738 production of an advanced capped system, having an efficient binding ability. The system helps  
739 in the delivery of loaded cargo at the targeted site by uncapping through an endosomal pathway.  
740 The presence of multi-amine moieties enhances the affinities of siRNA with the particles. The  
741 main disadvantage of this method is the hindrance of the release of siRNA in the cytoplasm due  
742 to the formation of strong polyplexes, which ultimately decreases the efficacy of siRNA, also

743 called 'vector unpacking.' The second main disadvantage of this method is polycation  
744 cytotoxicity, raising the concern about the nanocarrier's toxicity (Hartono et al., 2014).

## 745 5.6. Nucleic Acids

746 Nucleic acids are recognized as one of the most attractive building molecules due to their  
747 specific sequence, polymorphic conformation, and versatile physicochemical attributes. Due to  
748 their universal properties, DNA molecules are designed to fabricate stimuli-responsive MSNs  
749 with intelligent and on-demand delivery of the required therapeutic agent. Researchers developed  
750 various strategies for achieving targeted delivery using DNA molecules by complexing DNA  
751 molecules with agents that act as gatekeepers and release drugs at the target site in response to  
752 the specific stimuli as depicted in Fig 4 (Li et al., 2011).

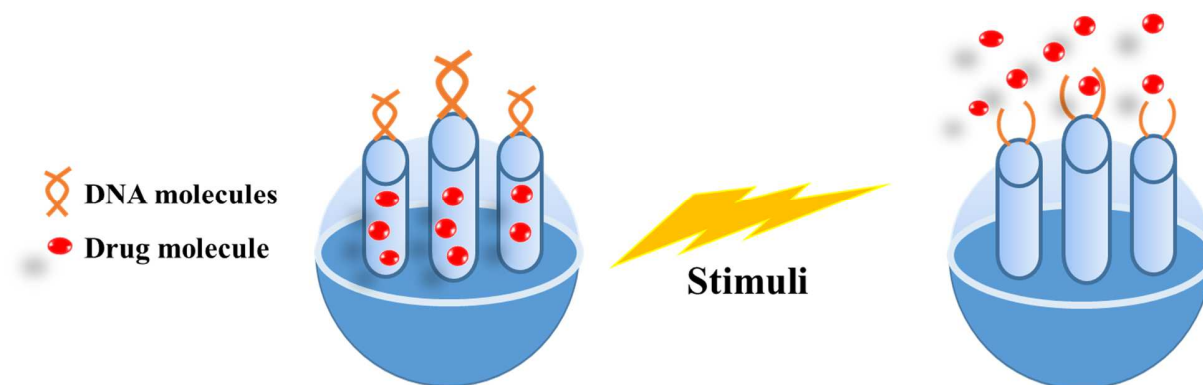
753 Controlled mechanisms for the release of encapsulated agents can be made by utilizing  
754 the principle of complex binding of metal ions, *i.e.*, silver or mercury with thymine and cytosine  
755 residues of DNA complexes. Functionalization of the pores of MSNs with DNA molecules is  
756 being made that are rich in cytosine and are further complexed by the binding of the Ag<sup>+</sup> ions  
757 that closes the outlet and acts as an intelligent molecule gated switch by forming a complex of C-  
758 Ag-C. The porous opening is controlled by the competitive reaction by the molecules that  
759 displaces the complex of C-Ag-C and converts it into the single-stranded molecule of DNA. This  
760 deformation of the DNA complex resulted in the presence of certain thiol molecules that resulted  
761 in the opening of the porous structure with site-specific release of the encapsulated drug  
762 molecule. So, the reversible opening and closing of the porous structures depend on the external  
763 concentrations of Ag linkers and the molecules containing thiol groups (He et al., 2012).

764 The development of highly selective MSNs carriers that are sensitive to GSH  
765 concentration has been developed; by employing thymine-rich DNA molecules coordinated with  
766 mercury (Hg<sup>+</sup>) ions. Hg<sup>+</sup> ions form stronger interaction with the thymine bases resulting in the  
767 formation of a complex of T-Hg<sup>+</sup>-T. Upon the detection of specific target GSH, this complex  
768 undergoes deformation into single-stranded DNA, with the release of active molecules of  
769 methylene blue (Wang et al., 2017b). Another study reported that DNA molecule acts as a very  
770 responsive stimuli for delivery of active moiety (Rhodamine) by employing quadruplex DNA  
771 with stretches of Cytosine base and act as gate keeper onto the pores of MSNs. It undergoes  
772 conformational changes upon a change of pH, providing unique property to function as a gate  
773 coupling agent. Under acidic conditions, the cytosine bases will remain present in their  
774 protonated form with the perseverance of closed DNA folds in a quadruplex form, while an  
775 increase in pH results in the deprotonation of the C<sup>+</sup> residues, resulting in the unfolding of DNA  
776 structure to single-stranded form. This leads to the release of entrapped moiety into the  
777 surrounding area through the inter-conversional opening and closing of the pores upon a change  
778 in the pH (Chen et al., 2011a).

779 Similarly, DNA-controlled molecular gate was also developed by attachment of DNA to  
780 the outer pores of MSNs carriers that were further operated by the melting of its strands upon  
781 certain temperature with the release of entrapped agent (Schlossbauer et al., 2010). Another  
782 study described the DNA-modified hollow MSNs for the treatment of cancer based on chemo-  
783 photothermal therapy (Hai et al., 2018). Researchers also reported the development of DNA  
784 functionalized MSNs carriers that release the cytotoxic agent upon exposure to visible light. In  
785 this context, MSNs based on Ruthenium polypyridyl complexed DNA were developed for the  
786 release of cytotoxic moieties including docetaxel and paclitaxel. This hybrid complex of  
787 ruthenium cleaved only under the exposure of visible light, releasing active moiety at the  
788 targeted site and present as a promising system that can be selectively used for the treatment of  
789 breast cancer (Frasconi et al., 2013).

790 Another study reported that DNA grafted MSNs that are sensitive to increasing the  
791 concentration of ATP, particularly in the tumor microenvironment. MSNs were modified with  
792 ATP and amine-modified aptamers of mucine that were covalently anchored onto the surface of  
793 MSNs. ATP aptamers were immobilized on MSNs surface with hybridization of mucine aptamer  
794 and resulting in the formation of a Y-shaped structure of DNA, acting as a gatekeeper on the  
795 surface of MSNs. The developed DNA grafted MSN carrier displayed an efficient loading  
796 capacity of Doxorubicin and released it at the tumor environment, where the concentration of  
797 ATP is high (10mM). This strategy displayed that the release of the drug occurs in the tumor  
798 region without its leakage at any undesired area or in the systemic circulation, where the  
799 concentration of ATP is less (1uM), and avoiding systemic toxicity of the cytotoxic drug  
800 (Bagheri et al., 2021). In this way, modification of MSNs with DNA by utilizing various  
801 approaches provides new insights for the treatment of a wide variety of dreadful diseases.

802 Functionalization of MSNs with nucleic acid helps in more precise manipulation of  
803 nanocarriers with the opportunity to develop MSNs in larger quantities. This allows the MSNs to  
804 combine with the nucleic acids with the development of a unique and more precise  
805 nanostructure, which removes only under the influence of specific stimulus. However, the  
806 method requires the determination of more sequences of reactions to identify specific  
807 interactions and binding properties of these agents with MSNs (Xu et al., 2021). General scheme  
808 of stimuli-responsive DNA gated release of drug from MSNs is shown in Fig. 4.



809

810 Fig. 4. Stimuli-responsive DNA gated release of drug from MSNs

811 Surface Modification of MSNs in response to specific stimuli are given in Table 2.

812 **Table 2.** Surface Modification of MSNs based Stimuli-Responsive Controlled release system of  
 813 various drugs.

Chemical modification/ Functionalization of MSNs	Drug Loaded in MSNs	Active stimulus	Effect of functionalization	References
Chemical modification of MSNs with Pegylated amino acid	Celastrol	pH	Targeted drug delivery to cancer by the release of drug at acidic pH, targeted delivery of drug to mitochondria	(Choi et al., 2018)
Chemical modification of MSNs with Calcium	siRNA, Chloroquine	pH	Targeted drug delivery to cancer cells at acidic pH	(Choi et al., 2020)
Chemical modification of MSNs with gold nanoparticles-biotin complexes	Doxorubicin	Enzyme	Cytotoxic potential against cells highly expressed with matrix metalloproteinase enzyme	(Eskandari et al., 2019)

<b>Chemical modification of MSNs with quadruplex DNA with stretches of the Cytosine base</b>	Rhodamine	pH	Targeted delivery to cancer cells having acidic pH	(Chen et al., 2011a)
<b>Chemical modification of MSNs with poly(amidoamine) dendrimer (PAMAM)</b>	Doxorubicin	pH	Increase mucoadhesive properties for bladder cancer therapy, Targeted delivery to cancer cells having acidic pH	(Wang et al., 2020a)
<b>Chemical modification of MSNs with cytochrome C and aptamer</b>	Doxorubicin	Redox potential	Targeted delivery to a liver tumor (HCT-116 cell lines) having increased GSH concentration	(Zhang et al., 2014)
<b>Phosphonated MSNs</b>	Ruthenium complexes	Hypoxic condition	Detection and quantification of molecular oxygen with targeted release at a reduced oxygen concentration	(Umehara et al., 2021)
<b>Chemical modification of MSNs with DNA molecules</b>	Fluorescein	Temperature	Targeted drug delivery upon increased temperature	(Schlossbauer et al., 2010)
<b>Chemical modification of MSNs with Thymine rich DNA molecules coordinated with mercury (Hg<sup>+</sup>) ions</b>	Methylene blue	Redox potential	Stimuli-responsive effect of changing in GSH concentration	(Wang et al., 2017b)
<b>MSNs modified with amino groups</b>	Octahedral Organoruthe	pH	Efficient cytotoxic potential against	(Martínez-Carmona et

	nim complex			glioblastoma cells having acidic pH, anti-cancerous activity	al., 2020)
<b>MSNs Ruthenium polypyridyl complexed DNA</b>	Docetaxel, Paclitaxel	Light		Stimuli-responsive effect to light for the treatment of breast cancer, drug release on application to light	(Frasconi et al., 2013)
<b>MSNs modified with the amino group</b>	Doxorubicin	pH		Efficient cytotoxic potential against non-small cell lung cancer cells having acidic pH	(He et al., 2017)
<b>MSNs capped with gold nanoparticles and linked with short single-stranded DNA as gatekeeping agent</b>	Doxorubicin	Laser stimulation, pH		Stimuli-responsive effect upon acidic pH and laser stimuli, for treatment of cancer	(Zhou et al., 2019)
<b>MSNs modified with an amino group</b>	Liraglutide, Fibroblast growth factor 21	-		Diabetes mellitus type 2	(Geng et al., 2021)
<b>MSNs modified with ruthenium complexes</b>	Safranin O	Light		Photochemical drug delivery system	(Salinas et al., 2020)
<b>Y-Shaped DNA grafted MSNs</b>	Doxorubicin	ATP		Stimuli-responsive effect to ATP for treatment of cancer	(Bagheri et al., 2021)
<b>Chemical modification of MSNs with Dextrin coupled with Schiff's base</b>	Doxorubicin hydrochloride	pH		Stimuli-responsive effect to acidic pH for treatment of cancer	(Chen et al., 2016)
<b>Chemical modification of MSNs with gold</b>	-	Redox potential		Anti-cancerous activity having increase GSH	(Augspurger et al., 2018)



<b>nanoparticles</b>			concentration, by A-549 cells
<b>Carboxyl functionalized MSNs capped with cerium oxide nanoparticles</b>	Doxorubicin	pH	Targeted delivery to Hela cells at acidic pH (Singh et al., 2018)
<b>Chemical modification of MSNs with dextrin</b>	Doxorubicin	Enzyme	Anti-cancerous activity with increased penetration having increased concentration of $\alpha$ -amylase enzyme (Kiew et al., 2017)
<b>Chemical modification of MSNs with peptide-based amphiphile</b>	Doxorubicin	Redox potential	Targeted drug delivery to tumor cells at increased GSH concentration (Cheng et al., 2017)
<b>Chemical modification of MSNs with gelatin</b>	Doxorubicin	pH	Targeted drug delivery to tumor cells at acidic pH (Zou et al., 2013)
<b>Chemical modification of MSNs with Cytosine rich DNA complexed with Ag<sup>+</sup> ions</b>	-	Thiol groups	Targeted drug delivery, stimuli-responsive effect to thiol groups (He et al., 2012)
<b>Chemical modification of MSNs with gelatin</b>	Doxorubicin	Enzyme	Cytotoxic potential against cells, highly expressed with matrix metalloproteinase enzyme (Xu et al., 2013)
<b>Multifunctional polymer capped MSNs (Chitosan and alginate)</b>	Doxorubicin hydrochloride	pH	Targeted delivery to cancer cells at acidic pH (Yang et al., 2010)

<b>Chitosan capped MSNs linked with glycidoxypropyl-tri-methoxy-silane</b>	Doxorubicin and Pheophorbide	pH	Targeted delivery to cancer cells at acidic pH	(Yan et al., 2020)
<b>MSNs modified with dendronized chitosan</b>	Doxorubicin and P-53 gene	Redox potential	Stimuli-responsive effect of increasing GSH concentration for treatment of cancer	(Lin et al., 2017)
<b>Gold nanorods coated with MSNs capped with chitosan attached with pH-sensitive variant 7</b>	Gemcitabine	pH	Targeted delivery to pancreatic tumors Targeted delivery to breast carcinoma cells at acidic pH	(Zeiderman et al., 2016)
<b>MSNs coated with chitosan</b>	Raloxifene hydrochloride	pH	Targeted delivery to breast carcinoma cells at acidic pH	(Shah and Rajput, 2018)
<b>MSNs modification with 3-triethoxysilylpropyl amine (APTES) followed by chitosan modification</b>	Methotrexate	pH	Increase the loading capacity of Methotrexate with more efficient uptake as an anti-cancer agent for breast cancer treatment. Targeted delivery to breast carcinoma cells at acidic pH	(Shakeran et al., 2021)
<b>MSNs modification with dextrin dialdehyde</b>	Doxorubicin	pH	Targeted delivery to cancer at acidic pH	(Chen et al., 2016)
<b>Charge reversal MSNs modified by using carboxymethyl/chit</b>	Doxorubicin	pH	Targeted delivery to breast carcinoma cells at acidic pH	(Cui et al., 2019)

<b>osan</b>				
<b>MSNs modification with Fe<sub>3</sub>O<sub>4</sub> nanoparticles</b>	Camptothecin	Magnetic field	Targeted delivery to cancer cells upon application of magnetic field	(Chen et al., 2011b)
<b>MSNs modification with dopamine modified hyaluronic acid</b>	Doxorubicin	pH	Targeted delivery to mammary carcinoma cells at acidic pH	(Zhou et al., 2021)
<b>MSNs modification with glucuronic acid-chitosan layer</b>	5-Fluorouracil	pH	Targeted delivery to colorectal cancer cells at acidic pH	(Narayan et al., 2021)
<b>MSNs modification with gelatin</b>	Paclitaxel	External magnetic field	Targeted delivery to tumor cells upon application of magnetic field	(Che et al., 2015)
<b>MSNs modification with protamine</b>	Curcumin	Enzyme	Targeted delivery to colorectal cancer cells having protease enzyme	(Radhakrishnan et al., 2014)
<b>Hollow MSNs modification with poly (3-acrylamidophenylboronic acid) (PAPBA)</b>	-	Glucose	Potential use in diabetes treatment, the release of a drug on glucose detection	(Wang et al., 2021)
<b>MSNs capped with hyaluronic acid</b>	Doxorubicin	pH	Targeted delivery to HeLa cells at acidic pH	(Chen et al., 2018a)
<b>MSNs capped with hyaluronic acid</b>	6-mercaptopurine	Redox potential	Targeted delivery to HCT-116 cell lines at increased GSH concentration	(Zhao et al., 2014)
<b>MSNs modified with multifunctional polymer</b>	-	pH	Targeted delivery to HeLa cells upon acidic pH	(Niedermayer et al., 2015)

<b>MSNs with dextrin</b>	<b>modified with dialdehyde</b>	Doxorubicin	pH and Redox potential	On-demand drug delivery increase acidic pH to cancer cells	(Chen et al., 2018b)
<b>MSNs with polyethyleneimine</b>	<b>modified</b>	Plasmid DNA	Ultrasound	Drug delivery to cancer cells	(Du et al., 2020)

814

815 **6. Mesoporous Silica Nanoparticles (MSNs) for Co-delivery of Nucleic Acids and Small-**  
816 **molecular Drugs for Cancer Therapy**

817 The use of nanocarriers for co-delivery of desirable gene/drug to the disease site is an  
818 attractive strategy for clinical therapy (Chen et al., 2017b; Shi et al., 2017). MSNs can also be  
819 utilized as a promising carrier for the transfection of genes besides conventional delivery of  
820 active agents. As naked genetic material is associated with poor penetration properties, these  
821 agents play a great role in the delivery of genetic material. Genetic delivery can be through viral  
822 or non-viral means. The viral genetic delivery system is a more efficient system in terms of  
823 various safety measures, such as non-specificity, gene recombination, and immunogenicity  
824 (Zhou et al., 2018b). Different cationic carriers, inorganic or organic molecules, and recombinant  
825 proteins have been served as vital carriers for the delivery of genetic carriers. Among various  
826 nanocarriers, liposomal agents displayed great attention to providing efficient transfection of  
827 genes but associated with greater instability. The inorganic nanocarriers displayed a greater  
828 advantage in terms of physicochemical stability, easy preparation, and surface functionalization.  
829 In this way, MSNs showed attractive features for gene delivery with efficient cellular uptake and  
830 enhanced transfection efficiency (Kesse et al., 2019). However, MSNS carry negative charge on  
831 their surfaces mainly due to the ionization of silanol groups, which ultimately reduces their  
832 binding efficiency to the molecules with negative surface charges such as DNA. In this way,  
833 modification is being made to the surface of MSNs with net positive charge through techniques  
834 such as functionalization with a cationic polymer, co-delivery of cationic metals, and through  
835 amination modification. These modifications bring out greater interactions of these MSNs with  
836 the negatively charged nucleic material. Stimuli responsive gene delivery for cancer therapy

837 Modification through amidation is one of the simplest and most common techniques for  
838 loading the genetic material in MSNs, in which aminopropyl trimethoxy silane (APTMS) and  
839 aminopropyltriethoxy silane (APTES) are commonly employed for modification. Studies also  
840 demonstrated increased adsorption efficiency of plasmid DNA with increasing amination degree.  
841 Modification of MSNs surface can also be modified with metal cations for facilitation of gene  
842 delivery. Metal counter ions such as  $Mg^{+2}$ ,  $Na^+$  or  $Ca^{+2}$  demonstrated efficient affinity with

843 genetic material. Moreover, cationic polymers such as poly-L-lysine, polyethyleneimine, poly-L-  
844 arginine, and polyamidoamine can bind effectively to the negatively charged nucleic acid. Yu et  
845 al. developed MSNs modified with poly-dimethylamino ethyl acrylate as an efficient nanocarrier  
846 for gene delivery. The polymer degrades in water to poly-acrylic acid, depicting controlled  
847 siRNA delivery (Hartono et al., 2014; Lin et al., 2014). Studies by Zhou and colleagues  
848 demonstrated an innovative approach for nucleic acids delivery into cancer cells, which  
849 enhanced the transfection efficiency. Their experiments revealed that encapsulation of Nucleic  
850 acids (pDNA siRNA) via ammonium salt (A) modified conical pores MSNs (CMSN-A) enabled  
851 intracellular trafficking enhanced gene transfection with the efficient release of cargos. The  
852 authors suggest this is due to the presence of increased positive charges of ammonium salts  
853 present in CMSN, which lead to an increase the gene loading capacity, gene binding stability and  
854 cellular uptake efficiency. This system was able to deliver the cargo at the site of action due to  
855 acidic pH and redox potential (Zhou et al., 2020).

856 MSNs have in general small porous diameter ( $< 3$  nm), due to which most of the  
857 plasmids and genes were being adsorbed on the surface of MSNs instead of being encapsulated.  
858 Also, the adsorbed genes can be degraded by the action of several enzymes such as lysosomes  
859 and nucleases. Therefore, the need of a suitable modification is desired in which MSNs can  
860 encapsulate the drug in their pores (Hartono et al., 2012; Wu et al., 2015). For this purpose, MSN  
861 carriers with large porous diameters have been prepared by use of pore expanding agents such as  
862 1, 3, 5 trimethylbenzene (Hao et al., 2021). This type of nanocarriers displays increased  
863 transfection efficiency with enhanced protection from the cellular environment. Kim et al.  
864 demonstrated delivery of chloroquine with plasmid DNA after modification of phosphonated  
865 MSNs having ultra-large pore size with polyethyleneimine of different molecular weights. The  
866 increased transfection efficiency of these MSNs was examined through green fluorescent protein  
867 (Kim et al., 2011). After efficient loading of the genetic material, the carriers respond to specific  
868 stimuli for the release of encapsulated genetic material. A recent study reported the release of  
869 plasmid DNA from MSNs microbubbles for efficient cancer therapy (Du et al., 2020).

870 In order to enhance the MSN's biocompatibility, bio-distribution, accumulation, binding  
871 affinity, and cellular uptake at the tumor site, widely explored strategies have been developed.  
872 Mickler et al. targeted epidermal growth factor receptor (EGFR), a protein commonly expressed  
873 on tumor cells, by decorated MSNs with natural EGF or artificial EGFR-binding peptide (GE11).  
874 The authors were able to successfully prove that this complex effectively accelerates MSNs  
875 endocytosis by tumor cells due to ligand-receptor binding. Folate receptor (FR), a  
876 glycosylphosphatidylinositol (GPI)-anchored membrane protein, over-expressed in tumor cells  
877 and is an attractive target for drug delivery. López et al. (López et al., 2017) developed an  
878 asymmetrically decorated MSN particle with targeting moieties [folic acid (FA) and  
879 Triphenylphosphine (TPP)]. The authors demonstrated successful MSN particle accumulation  
880 inside tumor cells and binding to mitochondria membrane by the action of FA and TPP moieties,  
881 respectively (Mickler et al., 2012). Babaei et al. developed PEGylated rod-shaped MSNs as a

882 nanocarrier for the co-delivery of an anticancer drug (camptothecin) and surviving shRNA-  
 883 expressing plasmid (iSur-DNA) to colorectal cancer. Moreover, these MSNs were tagged with  
 884 AS1411 aptamer, which has high affinity and specificity to nucleolin protein, facilitating  
 885 increased drug uptake into the nucleolin positive colorectal cancer cells and suppressing tumor  
 886 growth (Babaei et al., 2020). Wanger et al. demonstrated MSNs loaded anticancer immune-  
 887 stimulant R-848 (resiquimod), which were rapidly taken up by specialized antigen-presenting  
 888 cells (APCs), with potent activation of the dendritic immune cells (DCs) (Wagner et al., 2021).  
 889 This suggests that MSNs hold significant potential as a carrier for cancer vaccine delivery.  
 890 General scheme for stimuli responsive gene delivery for cancer therapy is shown in Fig 5.

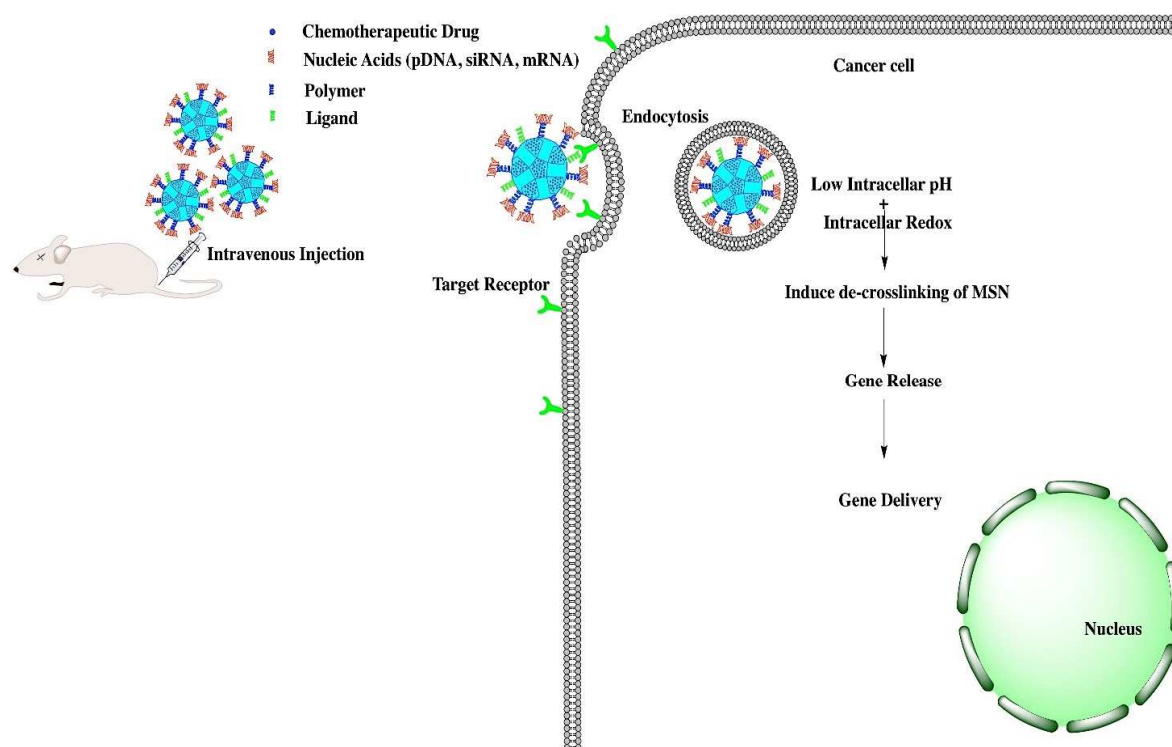
891 In Table 3, various molecules decorated on MSNs surface that are able to interact  
 892 selectively with specific membrane receptors overexpressed in tumor cells are shown.

893 **Table 3.** Summary of targeting drug delivery system based on MSNs.

Targeting receptor	Targeting ligand	Target cell type	Refs.
<b>EGFR</b>	Epidermal growth factor	HuH-7	(Mickler et al., 2012)
<b><math>\alpha</math>-Folate receptor</b>	Folic acid	MDA-MB 435 MDA-MB-231 PANC-1, MiaPaCa-2 MCF-7, HeLa HeLa	(Wang et al., 2010) (Tao et al., 2010) (Sarkar et al., 2016) (Lu et al., 2012) (Prasad et al., 2016)
<b><math>\alpha</math>-Folate receptor Mitochondria membrane</b>	Folic acid Triphenylphosphine	LnCAP	(López et al., 2017)
<b>Mannose receptor</b>	Mannose	MCF-7, HCT-116, MDA-MB-231	(Brevet et al., 2009)
<b>Galactose receptor</b>	Galactose	HeLa, A549	(Niemelä et al., 2015)
<b>Mucin-1 glycoprotein</b>	Mucin-1 antibody	MMT, Mtag	(Dréau et al., 2016)
<b>CD105 protein</b>	TRC105 antibody	4T1	(Wang et al., 2013)
<b>CD44 protein</b>	Hyaluronic Acid	MCF-7, MDA-MB-321, 4T1	(Kang et al., 2019)

$\alpha_v\beta_3$ integrins	cRGD	MDA-MB 435	(Ferris et al., 2011)
Transferrin receptor	Transferrin	HepG2	(Montalvo-Quiros et al., 2019)

894



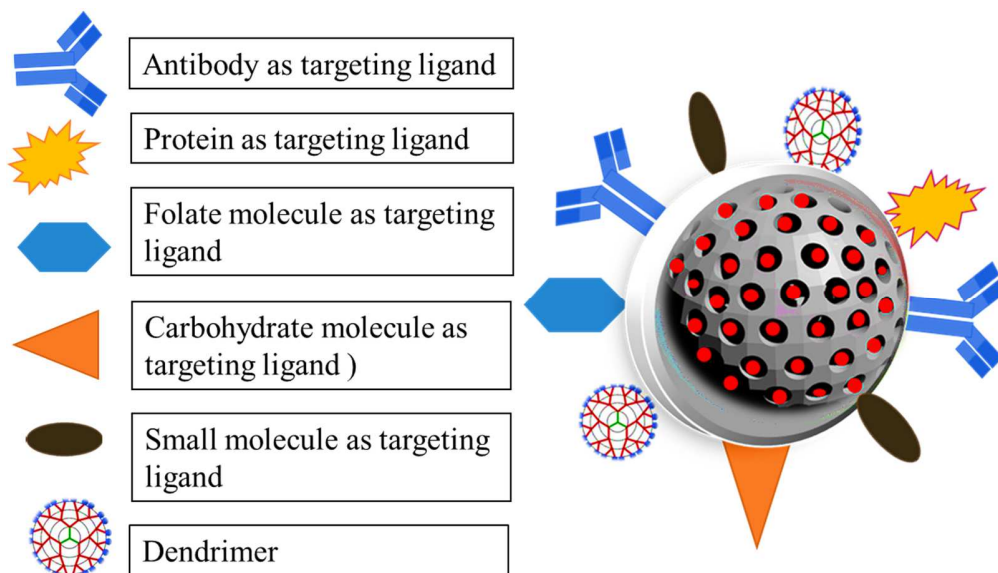
895

896 Fig. 5. Stimuli responsive gene delivery for cancer therapy

## 897 7. Biomedical applications of MSNs

898 It is becoming increasingly evident that MSNs hold strong potential as carriers for  
 899 biomedical applications. Multifunctional MSNs, which typically range from 50 to 3000 nm in  
 900 diameter, exhibit numerous outstanding properties, including large surface areas and pore  
 901 volume with high loading efficiency, tunable release mechanisms, and easy surface decoration  
 902 by attaching ligands for active targeting. These characteristics of MSNs created a vast era of  
 903 formulation development in the field of nanomedicine. MSNs found their immense importance  
 904 in different areas of drug targeting (Bagheri et al., 2021; Murugan et al., 2013), tissue  
 905 engineering (Nekounam et al., 2021; Pouroutzidou et al., 2021), cell tracking (Kim et al., 2021;  
 906 Umehara et al., 2021), and genes transfection (Hosseinpour et al., 2021) due to their peculiar  
 907 characteristics of large surface properties, tremendous internal volume and unique channels that  
 908 facilitate the adsorption of various protein and drugs. Capping agents can control the behavior of

909 pores opening and closing, hence controlling the precise spatial and temporal release of  
 910 encapsulated material with characteristics of lower degradation kinetics (Manzano and Vallet-  
 911 Regí, 2020). These controlled gatekeepers capping the pore entrances of MSNs play prominent  
 912 and crucial roles in achieving specific drug release and avoiding premature leakage in the  
 913 delivery process before the target is reached. The perfect gatekeepers can only be removed under  
 914 specific internal or external stimuli, such as pH, redox potential, temperature, biomolecules,  
 915 light, magnetic field and ultrasound, or a combination of these stimuli, which is significant for  
 916 precise therapeutic treatments and potential applications in human bodies. Further, their intrinsic  
 917 ability of functionalization at interior or exterior surfaces, along with biocompatible profile make  
 918 these delivery vesicles ideal for biomedical applications (Gruenhagen et al., 2005). Fig 6. shows,  
 919 some of the targeting ligands used for the functionalization of MSNs.



920

921 Fig 6. MSNs modifications with targeting ligands

922 Attachment of these moieties results in the modification of drug loading, protein  
 923 adsorption, biocompatibility, protein adsorption, imaging ability, and immune system  
 924 interactions (Bürglová et al., 2014). For example, surface functionalization of MSNs with amino  
 925 acids improves the drug's loading capacity and provides sustained delivery of therapeutic  
 926 moieties (Liu et al., 2015). Similarly, carboxylic group addition to the surface of MSNs improves  
 927 drug dispersion and release due to the creation of more negative charges. It also aids in the  
 928 attachment of fluorescent probes for the facilitation of imaging and diagnosis (Liu et al., 2015).  
 929 Ibuprofen adsorption on MSNs functionalized surface is extensively studied, in which carbonyl  
 930 groups formed bonding with the silanol groups. However, in the case of non-functionalized  
 931 surfaces, Ibuprofen dimer formation has taken place through concomitant interaction of drug  
 932 molecules through intermolecular bonding through hydrogen bonding. A study conducted by  
 933 Babonneau et al. demonstrated the incompatibility of ibuprofen loaded in MSNs through an



934 NMR study by observing increased drug on the pore walls of MSNs, showing higher drug  
935 motility (Babonneau et al., 2003; Babonneau et al., 2004). Researchers have made numerous  
936 innovations for delivering various drugs through MSNs in order to make them more efficient  
937 while reducing their unwanted effects.

938 Notably, MSNs possess advantages over traditional nanocarriers, especially for cancer  
939 immunotherapies. Small interference RNA (siRNA) has shown great promise in gene therapy  
940 because it can efficiently silence the expression of the desired target with high specificity and  
941 minimal side effects. Despite the great promise of siRNA in biomedical application, there have  
942 been several obstacles that restrict their clinical application, which includes: (i) naked siRNA is  
943 easily degradable by endogenous nucleases with rapid clearance by the renal route and (ii) they  
944 cannot be internalized efficiently by target cells due to polar nature of phospholipid bilayer  
945 membrane (Chen et al., 2015; de Fougerolles et al., 2007; Liu et al., 2016; van den Brand et al.,  
946 2018). Nowadays, enormous efforts have been devoted to developing nanoparticles for gene  
947 therapeutics. Ideal gene carriers should meet critical clinical criteria for successful  
948 implementation in clinical studies. The most important points are encapsulation efficiency, gene  
949 loading capacity, gene protection from degradation, stability of nanoparticles, endocytosis by  
950 target cells, controlled gene release at the target site, and lesser cytotoxic effect (Descamps and  
951 Benihoud, 2009; Duerner et al., 2008; Li and Huang, 2006; Yue and Wu, 2013).  
952 Polyethyleneimine-coated MSN nanocarrier has been demonstrated to be a promising  
953 intracellular carrier for glucuronidase (GUS)-encoding plasmid DNA or siRNA due to its high  
954 loading efficiency. Since, polyethyleneimine create a homogenous coating on MSN particles to  
955 adsorb the negatively charged siRNA. (Cha et al., 2017; Pinese et al., 2018). Pinese et al.  
956 described a novel approach for the scaffold-mediated sustained release of siRNA/MSN  
957 polyethyleneimine complexes. This system's successful uptake of siRNA downregulated the  
958 expression of collagen-1 compared to conventional bolus delivery. Together, these studies  
959 provided new insights into MSNs mediated nanoparticle-cell communication and intracellular  
960 trafficking (Pinese et al., 2018).

961 Further, MSNs also help in the monitoring of the targeted chemotherapeutic agent in  
962 order to avoid systemic toxicity. Different molecules such as carbon dots, FITC, chlorin,  
963 Hoechst, and multicolored up-conversion nanocarriers are generally utilized for the fabrication of  
964 nanocarriers. These agents transport the chemotherapeutic agent to the target site and are  
965 advantageous in monitoring nanocarrier's bio-distribution (Hu et al., 2016; Wang et al., 2020b;  
966 Zhou et al., 2018a). Yu et al. designed an interesting strategy for the real-time tracking of a drug  
967 by employing chitosan capped MSNs loaded with fluorescent dye. These novel nanocarriers  
968 mainly consisted of three components: the MSNs for encapsulating the drug molecule, chitosan  
969 as a gate keeper for the opening and closing of pores of MSNs and the fluorophore 1 8-  
970 naphthalimide for a signal of fluorescence. Pores will remain closed under the absence of GSH  
971 concentration as the sulfone blocks the intramolecular transfer of charge, leading to no  
972 fluorescence emission. However, in the presence of GSH, its nucleophilic attack removes the

973 chitosan with the opening of pores, triggering drug release and emission of green fluorescence.  
974 This strategy helps the researchers in expanding the knowledge of gating the nanocarriers for  
975 monitoring the real-time release of drugs for various ailments (Chen et al., 2020b).

976 MSNs are also ideal candidates as bio-catalysts due to their increased adsorption capacity  
977 and increased surface area. The enzymes can be encapsulated efficiently with high stability and  
978 act as bio-catalysts for intercellular bioanalysis. Luciferin-loaded nanocarriers in MSN pores  
979 through disulfide bonding with conjugation of PEGylated luciferase enzyme were developed for  
980 identification of self-catalyst luminescence for detection of the tumor. In the presence of redox  
981 potential and ATP, the release of luciferase catalyzed luciferin with the emission of  
982 luminescence. This system provides a unique platform for tumor development and its therapeutic  
983 response to treatment (Sun et al., 2011).

## 984 **8. Safety, Biodistribution, and fate of the MSNs**

985 Despite various biomedical applications of MSNs, the Food and Drug Administration  
986 hasn't approved MSNs for medical applications until their final fate, bio-distribution, and  
987 clearance routes have been addressed. In general, any administered agent undergoes the process  
988 of absorption, distribution, metabolism, and clearance. Most commonly, the nanocarriers are  
989 administered through subcutaneous or intravenous routes. The injection of these nanocarriers  
990 into the bloodstream prompts rapid bio-distribution of these agents through the bloodstream.  
991 However, the stability of these nanocarriers is an important determinant factor that decides their  
992 ultimate biomedical use (Bourquin et al., 2018). These carriers must be robust enough for the  
993 protection of loaded carriers in the bloodstream and degrade after delivering the cargo at the  
994 target site. As, MSNs are composed of SiO<sub>2</sub> matrix, which is susceptible to OH<sup>-</sup> (nucleophilic  
995 attack) by water molecules present in the aqueous media, leading to the production of orthosilicic  
996 acid in the dissolution media and can be excreted by the urine. The produced acid is water-  
997 soluble and helps in the maintenance of bones integrity. Thus FDA announces silica as a safe  
998 biomolecule for over 50 years (Bourquin et al., 2018; Croissant et al., 2018; Croissant et al.,  
999 2017a).

1000 The dissolution rate of MSNs mainly depends upon different parameters of particle  
1001 properties, such as pores size, surface area, particle size, condensation degree, and  
1002 functionalization molecules. The incorporation of different additives such as drugs,  
1003 photosensitizer molecules, or other in-organic agents also affects its dissolution characteristics.  
1004 The addition of the covalent addition of organic agents leads to the production of a new category  
1005 of MSNs, termed periodic mesoporous organosilica (PMOs). These materials share the same  
1006 protocols of synthesis but differ in the degradation rates. In this way, the mesoporosity of the  
1007 silica molecules can be protected for longer periods of time. In these PMOs, different cleavable  
1008 organic moieties are introduced, such as lysine, oxamide, disulfide, tetrasulfide, etc., to introduce  
1009 their on-demand degradation (Croissant et al., 2017b). The dissolution also depends on the

1010 properties of degradation or dissolution media, such as its temperature, concentration, and pH,  
1011 etc. In this way, the MSNs dissolution process can range from a few hours up to several weeks,  
1012 depending upon its characteristics and final application. The *in vitro* degradation rate of the  
1013 MSNs molecules revealed their long-term stability long enough to guarantee the release of  
1014 loaded cargo at the site of action (Braun et al., 2016). While the *in vivo* biodegradation of MSNs  
1015 in different animal models demonstrated increase biodegradation behavior of the carriers having  
1016 polymeric coatings on outer surfaces. This increases their circulation time in the bloodstream  
1017 with an increased stability profile.

1018 The bio-distribution profile of MSNs demonstrated their accumulation in the  
1019 reticuloendothelial system, including the liver, lungs, and spleen (Zhang et al., 2016). This is due  
1020 to the adsorption of proteins on their external surfaces. These proteins are normally derived from  
1021 serum and sometimes can also enhance the selectivity of targeted MSNs, indicating the effect of  
1022 proteins corona on the bio-distribution of nanocarriers (Beck et al., 2017). However, in order to  
1023 avoid this phenomenon, the surfaces of MSNs are normally coated with hydrophilic polymers  
1024 such as poly (ethylene glycol) (PEG). . Functionalization of MSNs was also observed,  
1025 demonstrating increased circulation time of MSNs functionalized with PEG molecule (Chen et  
1026 al., 2017a; Goel et al., 2016). Also, the non-pegylated nanocarriers demonstrated high  
1027 accumulation in the spleen, liver, and kidneys. In another recent study, Kang et al. developed  
1028 hydroxyapatite (HAP) hybrid MSNs, loaded with anticancer drug doxorubicin (DOX) to target  
1029 tumor cells. HAP departs excellent features of biocompatibility and nontoxicity, to MSNs with  
1030 further coating of hyaluronic acid (HA), which is a ligand that can bind specifically to CD-44  
1031 receptor with enhanced cellular uptake. These strategies improve the biodegradability, drug  
1032 loading, and drug release and eventually lead to better therapeutic outcomes (Kang et al., 2019).

1033 Bio-distribution of MSNs has also been investigated after their radiolabeling with  $^{64}\text{Cu}$   
1034 through positron emission tomography in BALB/c mice having xenografted breast and  
1035 glioblastoma tumors. The bio-distribution in the liver is presented in the highest concentration,  
1036 regardless of the presence or absence of targeting ligands. The lower amount of concentrations  
1037 was also present in the spleen, lungs, kidney, and intestines (Chen et al., 2013a; Goel et al.,  
1038 2014). In another bio-distribution study, it was concluded that by an increase in particles from 80  
1039 to 160 nm, a higher accumulation of nanocarriers was observed in spleen in comparison to the  
1040 liver The particle shape of MSNs also has a strong influence on MSNs bio-distribution. The  
1041 particles having elongated and spherical morphology showed higher accumulation in the spleen  
1042 in comparison to spherical particles (Huang et al., 2011). Different studies have been performed  
1043 regarding renal clearance of MSNs from the body. These studies confirmed the increase  
1044 elimination of these nanocarriers from the renal route. In addition, hepatobiliary excretion and  
1045 excretion through bile are normally under the influence of proteins adsorption, while excretion  
1046 through feces is normally governed by aggregation and accumulation of smaller particles  
1047 (Manzano and Vallet-Regí, 2020).

## 1048 **9. Conclusions and Future perspectives**

1049 MSNs are one of the most promising approaches in the biomedical field and introduced  
1050 as superior carriers to cope with the hurdles of limited drug release and premature release of  
1051 cargo with a better stability profile. Research has been conducted in controlling the structural  
1052 properties of MSNs, including their morphology, pore size, particle size, and structure ordering.  
1053 Further, to achieve increased loading of drugs with their precise control of release at a target site,  
1054 functionalization of MSNs' surface by an external or internal decoration of functional groups is  
1055 being explored. The combination of MSNs with other agents and functional groups, including  
1056 polymeric substances, chemical moieties or nucleic acids, helps to create hybrid MSNs having  
1057 great potential for various biomedical applications. Surface treatment of MSNs also improves the  
1058 interaction of nanocarriers with the biological environment and improves the biocompatibility of  
1059 the carriers. These modified MSNs can be utilized in various biomedical applications for  
1060 achieving targeted drug delivery and facilitating controlled release kinetics.

1061 However, despite numerous physio-chemical advantages that led the researchers to  
1062 develop MSNs for various biomedical applications, especially cancer, there are still some  
1063 prominent challenges that need to be addressed before achieving any clinical translation. First of  
1064 all, standardizing the protocols of scalability with reproducibility in the production of MSNs is  
1065 very important. The carriers should be produced on a larger scale with the same colloidal  
1066 stability, particle size, and pore area. Any functionalization strategy must be standardized with a  
1067 depiction of an appropriate stability profile and drug loading capacity. Secondly, the bio-  
1068 distribution studies must be carried out in different animal models in order to predict the final  
1069 fate of MSNs. A mandatory step is to evaluate the toxicological profile of these nanocarriers in  
1070 human models. In general, it is quite evident that there is a requirement of proper clinical  
1071 evaluation of these nanocarriers together with the collaboration of interdisciplinary industrial  
1072 efforts and other scientists to accelerate the entire process from bench to bed translation.

## 1073 **References**

- 1074 Alyassin, Y., Sayed, E.G., Mehta, P., Ruparelia, K., Arshad, M.S., Rasekh, M., Shepherd, J.,  
1075 Kucuk, I., Wilson, P.B., Singh, N., 2020. Application of mesoporous silica nanoparticles as drug  
1076 delivery carriers for chemotherapeutic agents. *Drug discovery today*.  
1077 Atanase, L.I., 2021. Micellar Drug Delivery Systems Based on Natural Biopolymers. *Polymers*  
1078 13, 477.  
1079 Augspurger, A.E., Sun, X., Trewyn, B.G., Fang, N., Stender, A.S., 2018. Monitoring the  
1080 stimulated uncapping process of gold-capped mesoporous silica nanoparticles. *Analytical*  
1081 *chemistry* 90, 3183-3188.  
1082 Babaei, M., Abnous, K., Taghdisi, S.M., Taghavi, S., Sh Saljooghi, A., Ramezani, M.,  
1083 Alibolandi, M., 2020. Targeted rod-shaped mesoporous silica nanoparticles for the co-delivery of  
1084 camptothecin and survivin shRNA in to colon adenocarcinoma in vitro and in vivo. *Eur J Pharm*  
1085 *Biopharm* 156, 84-96.

1086 Babonneau, F., Camus, L., Steunou, N., Ramila, A., Vallet-Regi, M.J.M.O.P.L., 2003.  
1087 Encapsulation of ibuprofen in mesoporous silica: solid state NMR characterization. *MRS Online*  
1088 *Proceedings Library* 775, 3261-3266.

1089 Babonneau, F., Yeung, L., Steunou, N., Gervais, C., Ramila, A., Vallet-Regi, M., 2004. Solid  
1090 state NMR characterisation of encapsulated molecules in mesoporous silica. *Journal of sol-gel*  
1091 *science and technology* 31, 219-223.

1092 Bagheri, E., Alibolandi, M., Abnous, K., Taghdisi, S.M., Ramezani, M., 2021. Targeted delivery  
1093 and controlled release of doxorubicin to cancer cells by smart ATP-responsive Y-shaped DNA  
1094 structure-capped mesoporous silica nanoparticles. *Journal of Materials Chemistry B* 9, 1351-  
1095 1363.

1096 Barkat, M.A., Das, S.S., Pottou, F.H., Beg, S., Rahman, Z., 2020. Lipid-based nanosystem as  
1097 intelligent carriers for versatile drug delivery applications. *Current pharmaceutical design* 26,  
1098 1167-1180.

1099 Beck, J.S., Vartuli, J., Roth, W.J., Leonowicz, M., Kresge, C., Schmitt, K., Chu, C., Olson, D.H.,  
1100 Sheppard, E., McCullen, S., 1992. A new family of mesoporous molecular sieves prepared with  
1101 liquid crystal templates. *Journal of the American Chemical Society* 114, 10834-10843.

1102 Beck, M., Mandal, T., Buske, C., Linden, M., 2017. Serum protein adsorption enhances active  
1103 leukemia stem cell targeting of mesoporous silica nanoparticles. *ACS applied materials and*  
1104 *interfaces* 9, 18566-18574.

1105 Begines, B., Ortiz, T., Pérez-Aranda, M., Martínez, G., Merinero, M., Argüelles-Arias, F.,  
1106 Alcudia, A., 2020. Polymeric nanoparticles for drug delivery: Recent developments and future  
1107 prospects. *Nanomaterials* 10, 1403.

1108 Beltrán-Osuna, Á.A., Ribelles, J.L.G., Perilla, J.E., 2017. A study of some fundamental  
1109 physicochemical variables on the morphology of mesoporous silica nanoparticles MCM-41 type.  
1110 *Journal of Nanoparticle Research* 19, 1-14.

1111 Bernal, A., Calcagno, C., Mulder, W.J., Pérez-Medina, C., 2021. Imaging-guided nanomedicine  
1112 development. *Current Opinion in Chemical Biology* 63, 78-85.

1113 Bharti, C., Nagaich, U., Pal, A.K., Gulati, N., 2015. Mesoporous silica nanoparticles in target  
1114 drug delivery system: A review. *International journal of pharmaceutical investigation* 5, 124.

1115 Björk, E.M., Söderlind, F., Odén, M., 2013. Tuning the shape of mesoporous silica particles by  
1116 alterations in parameter space: from rods to platelets. *Langmuir* 29, 13551-13561.

1117 Bouchoucha, M., Cote, M.-F., C.-Gaudreault, R., Fortin, M.-A., Kleitz, F., 2016. Size-controlled  
1118 functionalized mesoporous silica nanoparticles for tunable drug release and enhanced anti-  
1119 tumoral activity. *Chemistry of Materials* 28, 4243-4258.

1120 Bourquin, J., Milosevic, A., Hauser, D., Lehner, R., Blank, F., Petri-Fink, A., Rothen-  
1121 Rutishauser, B., 2018. Biodistribution, clearance, and long-term fate of clinically relevant  
1122 nanomaterials. *Advanced materials* 30, 1704307.

1123 Braun, K., Pochert, A., Beck, M., Fiedler, R., Gruber, J., Lindén, M., 2016. Dissolution kinetics  
1124 of mesoporous silica nanoparticles in different simulated body fluids. *Journal of Sol-Gel Science*  
1125 *and Technology* 79, 319-327.

1126 Brevet, D., Gary-Bobo, M., Raehm, L., Richeter, S., Hocine, O., Amro, K., Loock, B., Couleaud,  
1127 P., Frochot, C., Morère, A., Maillard, P., Garcia, M., Durand, J.O., 2009. Mannose-targeted  
1128 mesoporous silica nanoparticles for photodynamic therapy. *Chem Commun (Camb)*, 1475-1477.

1129 Brian G. Trewyn, J.A.N., Yannan Zhao, Victor S.-Y. Lin, 2008. Biocompatible mesoporous  
1130 silica nanoparticles with different morphologies for animal cell membrane penetration. *Chemical*  
1131 *Engineering Journal* 137, 23-29.

1132 Bürglová, K., Noureddine, A., Hodačová, J., Toquer, G., Cattoën, X., Wong Chi Man,  
1133 M.J.C.A.E.J., 2014. A general method for preparing bridged organosilanes with pendant  
1134 functional groups and functional mesoporous organosilicas. 20, 10371-10382.

1135 Cai, Q., Luo, Z.-S., Pang, W.-Q., Fan, Y.-W., Chen, X.-H., Cui, F.-Z., 2001. Dilute solution  
1136 routes to various controllable morphologies of MCM-41 silica with a basic medium. Chemistry  
1137 of materials 13, 258-263.

1138 Carniato, F., Muñoz-Úbeda, M., Tei, L., Botta, M., 2015. Selective functionalization of  
1139 mesoporous silica nanoparticles with ibuprofen and Gd (III) chelates: a new probe for potential  
1140 theranostic applications. Dalton Transactions 44, 17927-17931.

1141 Cha, W., Fan, R., Miao, Y., Zhou, Y., Qin, C., Shan, X., Wan, X., Li, J., 2017. Mesoporous  
1142 Silica Nanoparticles as Carriers for Intracellular Delivery of Nucleic Acids and Subsequent  
1143 Therapeutic Applications. Molecules 22.

1144 Che, E., Gao, Y., Wan, L., Zhang, Y., Han, N., Bai, J., Li, J., Sha, Z., Wang, S., 2015.  
1145 Paclitaxel/gelatin coated magnetic mesoporous silica nanoparticles: Preparation and antitumor  
1146 efficacy in vivo. Microporous and Mesoporous Materials 204, 226-234.

1147 Chen, B.C., Lin, H.P., Chao, M.C., Mou, C.Y., Tang, C.Y., 2004. Mesoporous silica platelets  
1148 with perpendicular nanochannels via a ternary surfactant system. Advanced Materials 16, 1657-  
1149 1661.

1150 Chen, C., Pu, F., Huang, Z., Liu, Z., Ren, J., Qu, X., 2011a. Stimuli-responsive controlled-  
1151 release system using quadruplex DNA-capped silica nanocontainers. Nucleic acids research 39,  
1152 1638-1644.

1153 Chen, C., Sun, W., Wang, X., Wang, Y., Wang, P., 2018a. pH-responsive nanoreservoirs based  
1154 on hyaluronic acid end-capped mesoporous silica nanoparticles for targeted drug delivery.  
1155 International journal of biological macromolecules 111, 1106-1115.

1156 Chen, C., Sun, W., Yao, W., Wang, Y., Ying, H., Wang, P., 2018b. Functional polymeric  
1157 dialdehyde dextrin network capped mesoporous silica nanoparticles for pH/GSH dual-controlled  
1158 drug release. RSC advances 8, 20862-20871.

1159 Chen, F., Hong, H., Zhang, Y., Valdovinos, H.F., Shi, S., Kwon, G.S., Theuer, C.P., Barnhart,  
1160 T.E., Cai, W., 2013a. In vivo tumor targeting and image-guided drug delivery with antibody-  
1161 conjugated, radiolabeled mesoporous silica nanoparticles. ACS nano 7, 9027-9039.

1162 Chen, F., Valdovinos, H.F., Hernandez, R., Goel, S., Barnhart, T.E., Cai, W.J.A.P.S., 2017a.  
1163 Intrinsic radiolabeling of Titanium-45 using mesoporous silica nanoparticles. 38, 907-913.

1164 Chen, H., Zhang, W., Zhu, G., Xie, J., Chen, X., 2017b. Rethinking cancer nanotheranostics. Nat  
1165 Rev Mater 2.

1166 Chen, H., Zheng, D., Liu, J., Kuang, Y., Li, Q., Zhang, M., Ye, H., Qin, H., Xu, Y., Li, C., 2016.  
1167 pH-Sensitive drug delivery system based on modified dextrin coated mesoporous silica  
1168 nanoparticles. International journal of biological macromolecules 85, 596-603.

1169 Chen, J., Dong, X., Feng, T., Lin, L., Guo, Z., Xia, J., Tian, H., Chen, X., 2015. Charge-  
1170 conversional zwitterionic copolymer as pH-sensitive shielding system for effective tumor  
1171 treatment. Acta Biomater 26, 45-53.

1172 Chen, K., Chang, C., Liu, Z., Zhou, Y., Xu, Q., Li, C., Huang, Z., Xu, H., Xu, P., Lu, B., 2020a.  
1173 Hyaluronic acid targeted and pH-responsive nanocarriers based on hollow mesoporous silica  
1174 nanoparticles for chemo-photodynamic combination therapy. Colloids and Surfaces B:  
1175 Biointerfaces 194, 111166.

1176 Chen, P.-J., Hu, S.-H., Hsiao, C.-S., Chen, Y.-Y., Liu, D.-M., Chen, S.-Y., 2011b.  
1177 Multifunctional magnetically removable nanogated lids of Fe<sub>3</sub>O<sub>4</sub>-capped mesoporous silica

1178 nanoparticles for intracellular controlled release and MR imaging. *Journal of Materials*  
1179 *Chemistry* 21, 2535-2543.

1180 Chen, Y., Lu, W., Guo, Y., Zhu, Y., Song, Y., 2020b. Chitosan-Gated Fluorescent Mesoporous  
1181 Silica Nanocarriers for the Real-Time Monitoring of Drug Release. *Langmuir* 36, 6749-6756.

1182 Chen, Z., Li, Z., Lin, Y., Yin, M., Ren, J., Qu, X., 2013b. Bioresponsive hyaluronic acid-capped  
1183 mesoporous silica nanoparticles for targeted drug delivery. *Chemistry—A European Journal* 19,  
1184 1778-1783.

1185 Cheng, Y.-J., Zhang, A.-Q., Hu, J.-J., He, F., Zeng, X., Zhang, X.-Z., 2017. Multifunctional  
1186 peptide-amphiphile end-capped mesoporous silica nanoparticles for tumor targeting drug  
1187 delivery. *ACS applied materials and interfaces* 9, 2093-2103.

1188 Chiang, Y.-D., Lian, H.-Y., Leo, S.-Y., Wang, S.-G., Yamauchi, Y., Wu, K.C.-W., 2011.  
1189 Controlling particle size and structural properties of mesoporous silica nanoparticles using the  
1190 Taguchi method. *The Journal of Physical Chemistry C* 115, 13158-13165.

1191 Choi, E., Lim, D.-K., Kim, S., 2020. Calcium-doped mesoporous silica nanoparticles as a  
1192 lysosomolytic nanocarrier for amine-free loading and cytosolic delivery of siRNA. *Journal of*  
1193 *Industrial and Engineering Chemistry* 81, 71-80.

1194 Choi, J.Y., Gupta, B., Ramasamy, T., Jeong, J.-H., Jin, S.G., Choi, H.-G., Yong, C.S., Kim, J.O.,  
1195 2018. PEGylated polyaminoacid-capped mesoporous silica nanoparticles for mitochondria-  
1196 targeted delivery of celastrol in solid tumors. *Colloids and Surfaces B: Biointerfaces* 165, 56-66.

1197 Corbalan, J.J., Medina, C., Jacoby, A., Malinski, T., Radomski, M.W., 2012a. Amorphous silica  
1198 nanoparticles aggregate human platelets: potential implications for vascular homeostasis.  
1199 *International journal of nanomedicine* 7, 631.

1200 Corbalan, J.J., Medina, C., Jacoby, A., Malinski, T., Radomski, M.W., 2012b. Amorphous silica  
1201 nanoparticles aggregate human platelets: potential implications for vascular homeostasis.  
1202 *International journal of nanomedicine* 7, 631.

1203 Croissant, J.G., Fatieiev, Y., Almalik, A., Khashab, N.M., 2018. Mesoporous silica and  
1204 organosilica nanoparticles: physical chemistry, biosafety, delivery strategies, and biomedical  
1205 applications. *Advanced healthcare materials* 7, 1700831.

1206 Croissant, J.G., Fatieiev, Y., Khashab, N.M., 2017a. Degradability and clearance of silicon,  
1207 organosilica, silsesquioxane, silica mixed oxide, and mesoporous silica nanoparticles. *Advanced*  
1208 *materials* 29, 1604634.

1209 Croissant, J.G., Fatieiev, Y., Khashab, N.M., 2017b. Functional Nanoparticles: Degradability and  
1210 Clearance of Silicon, Organosilica, Silsesquioxane, Silica Mixed Oxide, and Mesoporous Silica  
1211 Nanoparticles *Advanced Materials* 29.

1212 Cui, L., Liu, W., Liu, H., Qin, Q., Wu, S., He, S., Pang, X., Zhu, C., Shen, P., 2019. pH-triggered  
1213 charge-reversal mesoporous silica nanoparticles stabilized by chitosan  
1214 oligosaccharide/carboxymethyl chitosan hybrids for effective intracellular delivery of  
1215 doxorubicin. *ACS Applied Bio Materials* 2, 1907-1919.

1216 Cui, X., Moon, S.-W., Zin, W.-C., 2006. High-yield synthesis of monodispersed SBA-15  
1217 equilateral hexagonal platelet with thick wall. *Materials Letters* 60, 3857-3860.

1218 Danks, A.E., Hall, S.R., Schnepf, Z., 2016. The evolution of 'sol-gel' chemistry as a technique  
1219 for materials synthesis. *Materials Horizons* 3, 91-112.

1220 de Fogerolles, A., Vornlocher, H.P., Maraganore, J., Lieberman, J., 2007. Interfering with  
1221 disease: a progress report on siRNA-based therapeutics. *Nat Rev Drug Discov* 6, 443-453.

1222 Descamps, D., Benihoud, K., 2009. Two key challenges for effective adenovirus-mediated liver  
1223 gene therapy: innate immune responses and hepatocyte-specific transduction. *Curr Gene Ther* 9,  
1224 115-127.

1225 Dréau, D., Moore, L.J., Alvarez-Berrios, M.P., Tarannum, M., Mukherjee, P., Vivero-Escoto,  
1226 J.L., 2016. Mucin-1-Antibody-Conjugated Mesoporous Silica Nanoparticles for Selective Breast  
1227 Cancer Detection in a Mucin-1 Transgenic Murine Mouse Model. *J Biomed Nanotechnol* 12,  
1228 2172-2184.

1229 Du, M., Chen, Y., Tu, J., Liufu, C., Yu, J., Yuan, Z., Gong, X., Chen, Z., 2020. Ultrasound  
1230 responsive magnetic mesoporous silica nanoparticle-loaded microbubbles for efficient gene  
1231 delivery. *ACS Biomaterials Science and Engineering* 6, 2904-2912.

1232 Duerner, L.J., Schwantes, A., Schneider, I.C., Cichutek, K., Buchholz, C.J., 2008. Cell entry  
1233 targeting restricts biodistribution of replication-competent retroviruses to tumour tissue. *Gene*  
1234 *Ther* 15, 1500-1510.

1235 Egger, S.M., Hurley, K.R., Datt, A., Swindlehurst, G., Haynes, C.L., 2015. Ultraporous  
1236 mesostructured silica nanoparticles. *Chemistry of Materials* 27, 3193-3196.

1237 Eskandari, P., Bigdeli, B., Porgham Daryasari, M., Baharifar, H., Bazri, B., Shourian, M.,  
1238 Amani, A., Sadighi, A., Goliaei, B., Khoobi, M., 2019. Gold-capped mesoporous silica  
1239 nanoparticles as an excellent enzyme-responsive nanocarrier for controlled doxorubicin delivery.  
1240 *Journal of drug targeting* 27, 1084-1093.

1241 Feng, S.-H., Li, G.-H., 2017. Hydrothermal and solvothermal syntheses, *Modern inorganic*  
1242 *synthetic chemistry*. Elsevier, pp. 73-104.

1243 Feng, W., Nie, W., He, C., Zhou, X., Chen, L., Qiu, K., Wang, W., Yin, Z.J.A.A.M., 2014.  
1244 Effect of pH-responsive alginate/chitosan multilayers coating on delivery efficiency, cellular  
1245 uptake and biodistribution of mesoporous silica nanoparticles based nanocarriers. *ACS Applied*  
1246 *Materials and Interfaces* 6, 8447-8460.

1247 Fernández-Pan, I., Maté, J.I., Gardrat, C., Coma, V., 2015. Effect of chitosan molecular weight  
1248 on the antimicrobial activity and release rate of carvacrol-enriched films. *Food hydrocolloids* 51,  
1249 60-68.

1250 Ferris, D.P., Lu, J., Gothard, C., Yanes, R., Thomas, C.R., Olsen, J.C., Stoddart, J.F., Tamanoi,  
1251 F., Zink, J.I., 2011. Synthesis of biomolecule-modified mesoporous silica nanoparticles for  
1252 targeted hydrophobic drug delivery to cancer cells. *Small* 7, 1816-1826.

1253 Frasconi, M., Liu, Z., Lei, J., Wu, Y., Strelakova, E., Malin, D., Ambrogio, M.W., Chen, X.,  
1254 Botros, Y.Y., Cryns, V.L., 2013. Photoexpulsion of surface-grafted ruthenium complexes and  
1255 subsequent release of cytotoxic cargos to cancer cells from mesoporous silica nanoparticles.  
1256 *Journal of the American Chemical Society* 135, 11603-11613.

1257 Galabova, B.B., 2021. Mesoporous silica nanoparticles: Synthesis, functionalization, drug  
1258 loading and release-A review. *Tropical Journal of Pharmaceutical Research* 20.

1259 Ganguly, A., Ahmad, T., Ganguli, A.K., 2010. Silica mesostructures: Control of pore size and  
1260 surface area using a surfactant-templated hydrothermal process. *Langmuir* 26, 14901-14908.

1261 Gary-Bobo, M., Brevet, D., Benkirane-Jessel, N., Raehm, L., Maillard, P., Garcia, M., Durand,  
1262 J.-O., 2012. Hyaluronic acid-functionalized mesoporous silica nanoparticles for efficient  
1263 photodynamic therapy of cancer cells. *Photodiagnosis and photodynamic therapy* 9, 256-260.

1264 Geng, S., Qin, L., He, Y., Li, X., Yang, M., Li, L., Liu, D., Li, Y., Niu, D., Yang, G., 2021.  
1265 Effective and safe delivery of GLP-1AR and FGF-21 plasmids using amino-functionalized dual-  
1266 mesoporous silica nanoparticles in vitro and in vivo. *Biomaterials* 271, 120763.



1267 Ghaferi, M., Koohi Moftakhari Esfahani, M., Raza, A., Al Harthi, S., Ebrahimi Shahmabadi, H.,  
1268 Alavi, S.E., 2021. Mesoporous silica nanoparticles: synthesis methods and their therapeutic use-  
1269 recent advances. *Journal of Drug Targeting* 29, 131-154.

1270 Giri, S., Trewyn, B.G., Stellmaker, M.P., Lin, V.S.Y., 2005. Stimuli-responsive controlled-  
1271 release delivery system based on mesoporous silica nanorods capped with magnetic  
1272 nanoparticles. *Angewandte Chemie* 117, 5166-5172.

1273 Goel, S., Chen, F., Hong, H., Valdovinos, H.F., Hernandez, R., Shi, S., Barnhart, T.E., Cai, W.,  
1274 2014. VEGF121-conjugated mesoporous silica nanoparticle: a tumor targeted drug delivery  
1275 system. *ACS applied materials and interfaces* 6, 21677-21685.

1276 Goel, S., Chen, F., Luan, S., Valdovinos, H.F., Shi, S., Graves, S.A., Ai, F., Barnhart, T.E.,  
1277 Theuer, C.P., Cai, W., 2016. Engineering Intrinsically Zirconium-89 Radiolabeled Self-  
1278 Destructing Mesoporous Silica Nanostructures for In Vivo Biodistribution and Tumor Targeting  
1279 Studies. *Advanced Science* 3, 1600122.

1280 Gruenhagen, J.A., Lai, C.-Y., Radu, D.R., Lin, V.S.-Y., Yeung, E.S., 2005. Real-time imaging of  
1281 tunable adenosine 5-triphosphate release from an MCM-41-type mesoporous silica nanosphere-  
1282 based delivery system. *Applied spectroscopy* 59, 424-431.

1283 Grün, M., Lauer, I., Unger, K.K., 1997. The synthesis of micrometer-and submicrometer-size  
1284 spheres of ordered mesoporous oxide MCM-41. *Advanced Materials* 9, 254-257.

1285 Gu, J., Fan, W., Shimojima, A., Okubo, T., 2007. Organic-inorganic mesoporous nanocarriers  
1286 integrated with biogenic ligands. *Small* 3, 1740-1744.

1287 Guisasola, E., Asín, L., Beola, L., de la Fuente, J.M., Baeza, A., Vallet-Regí, M., 2018. Beyond  
1288 traditional hyperthermia: in vivo cancer treatment with magnetic-responsive mesoporous silica  
1289 nanocarriers. *ACS applied materials and interfaces* 10, 12518-12525.

1290 Haddick, L., Zhang, W., Reinhard, S., Möller, K., Engelke, H., Wagner, E., Bein, T., 2020.  
1291 Particle-Size-Dependent Delivery of Antitumoral miRNA Using Targeted Mesoporous Silica  
1292 Nanoparticles. *Pharmaceutics* 12, 505.

1293 Hai, L., Jia, X., He, D., Zhang, A., Wang, T., Cheng, H., He, X., Wang, K., 2018. DNA-  
1294 functionalized hollow mesoporous silica nanoparticles with dual cargo loading for near-infrared-  
1295 responsive synergistic chemo-photothermal treatment of cancer cells. *ACS Applied Nano*  
1296 *Materials* 1, 3486-3497.

1297 Han, L., Zhou, Y., He, T., Song, G., Wu, F., Jiang, F., Hu, J., 2013. One-pot morphology-  
1298 controlled synthesis of various shaped mesoporous silica nanoparticles. *Journal of Materials*  
1299 *Science* 48, 5718-5726.

1300 Hao, Y., Tian, R., Lv, K., Liu, Z., Ni, J., Yuan, P., Bai, Y., Chen, X., 2021. Stimuli responsive  
1301 co-delivery of celecoxib and BMP2 from micro-scaffold for periodontal disease treatment.  
1302 *Journal of Materials Science and Technology* 75, 216-224.

1303 Hartono, S.B., Gu, W., Kleitz, F., Liu, J., He, L., Middelberg, A.P., Yu, C., Lu, G.Q., Qiao, S.Z.,  
1304 2012. Poly-L-lysine functionalized large pore cubic mesostructured silica nanoparticles as  
1305 biocompatible carriers for gene delivery. *Acs Nano* 6, 2104-2117.

1306 Hartono, S.B., Phuoc, N.T., Yu, M., Jia, Z., Monteiro, M.J., Qiao, S., Yu, C., 2014.  
1307 Functionalized large pore mesoporous silica nanoparticles for gene delivery featuring controlled  
1308 release and co-delivery. *Journal of Materials Chemistry B* 2, 718-726.

1309 He, D., He, X., Wang, K., Chen, M., Cao, J., Zhao, Y., 2012. Reversible stimuli-responsive  
1310 controlled release using mesoporous silica nanoparticles functionalized with a smart DNA  
1311 molecule-gated switch. *Journal of Materials Chemistry B* 22, 14715-14721.

1312 He, Y., Luo, L., Liang, S., Long, M., Xu, H., 2017. Amino-functionalized mesoporous silica  
1313 nanoparticles as efficient carriers for anticancer drug delivery. *Journal of biomaterials*  
1314 *applications* 32, 524-532.

1315 Hegazy, M., Zhou, P., Rahoui, N., Wu, G., Taloub, N., Lin, Y., Huang, X., Huang, Y.J.C., 2019.  
1316 A facile design of smart silica nanocarriers via surface-initiated RAFT polymerization as a dual-  
1317 stimuli drug release platform. *Colloids and Surfaces A: Physicochemical and Engineering*  
1318 *Aspects* 581, 123797.

1319 Heidari, R., Khosravian, P., Mirzaei, S.A., Elahian, F.J.S.r., 2021. siRNA delivery using  
1320 intelligent chitosan-capped mesoporous silica nanoparticles for overcoming multidrug resistance  
1321 in malignant carcinoma cells. *Scientific reports* 11, 1-14.

1322 Heikkilä, T., Salonen, J., Tuura, J., Hamdy, M., Mul, G., Kumar, N., Salmi, T., Murzin, D.Y.,  
1323 Laitinen, L., Kaukonen, A.M., 2007. Mesoporous silica material TUD-1 as a drug delivery  
1324 system. *International journal of pharmaceutics* 331, 133-138.

1325 Hong, C.-Y., Li, X., Pan, C.-Y., 2008. Smart Core– Shell Nanostructure with a Mesoporous  
1326 Core and a Stimuli-Responsive Nanoshell Synthesized via Surface Reversible Addition–  
1327 Fragmentation Chain Transfer Polymerization. *The Journal of Physical Chemistry C* 112, 15320-  
1328 15324.

1329 Hosseinpour, S., Cao, Y., Liu, J., Xu, C., Walsh, L.J., 2021. Efficient transfection and long-term  
1330 stability of rno-miRNA-26a-5p for osteogenic differentiation by large pore sized mesoporous  
1331 silica nanoparticles. *Journal of Materials Chemistry B* 9, 2275-2284.

1332 Hu, J.-J., Liu, L.-H., Li, Z.-Y., Zhuo, R.-X., Zhang, X.-Z., 2016. MMP-responsive theranostic  
1333 nanoplatfrom based on mesoporous silica nanoparticles for tumor imaging and targeted drug  
1334 delivery. *Journal of Materials Chemistry B* 4, 1932-1940.

1335 Huang, M., Liu, L., Wang, S., Zhu, H., Wu, D., Yu, Z., Zhou, S., 2017. Dendritic mesoporous  
1336 silica nanospheres synthesized by a novel dual-templating micelle system for the preparation of  
1337 functional nanomaterials. *Langmuir* 33, 519-526.

1338 Huang, X., Li, L., Liu, T., Hao, N., Liu, H., Chen, D., Tang, F., 2011. The shape effect of  
1339 mesoporous silica nanoparticles on biodistribution, clearance, and biocompatibility in vivo. *ACS*  
1340 *nano* 5, 5390-5399.

1341 Huang, X., Teng, X., Chen, D., Tang, F., He, J., 2010. The effect of the shape of mesoporous  
1342 silica nanoparticles on cellular uptake and cell function. *Biomaterials* 31, 438-448.

1343 Huh, S., Wiench, J.W., Yoo, J.-C., Pruski, M., Lin, V.S.-Y., 2003. Organic functionalization and  
1344 morphology control of mesoporous silicas via a co-condensation synthesis method. *Chemistry of*  
1345 *materials* 15, 4247-4256.

1346 Hwang, D., Ramsey, J.D., Kabanov, A.V., 2020. Polymeric micelles for the delivery of poorly  
1347 soluble drugs: from nanoformulation to clinical approval. *Advanced drug delivery reviews*.

1348 Irshad, S., Siddiqui, B., ur. Rehman, A., Farooq, R.K., Ahmed, N., 2020. Recent trends and  
1349 development in targeted delivery of therapeutics through enzyme responsive intelligent  
1350 nanoplatfrom. *International Journal of Polymeric Materials and Polymeric Biomaterials*, 1-11.

1351 Izquierdo-Barba, I., Martinez, Á., Doadrio, A.L., Pérez-Pariente, J., Vallet-Regí, M., 2005.  
1352 Release evaluation of drugs from ordered three-dimensional silica structures. *European Journal*  
1353 *of Pharmaceutical Sciences* 26, 365-373.

1354 Jhaveri, J., Raichura, Z., Khan, T., Momin, M., Omri, A.J.M., 2021. Chitosan nanoparticles-  
1355 insight into properties, functionalization and applications in drug delivery and theranostics.  
1356 *Molecules* 26, 272.

1357 Kagami, Y., Sugimura, S., Fujishima, N., Matsuda, K., Kometani, T., Matsumura, Y., 2003.  
1358 Oxidative stability, structure, and physical characteristics of microcapsules formed by spray  
1359 drying of fish oil with protein and dextrin wall materials. *Journal of food science* 68, 2248-2255.  
1360 Kang, Y., Sun, W., Li, S., Li, M., Fan, J., Du, J., Liang, X.J., Peng, X., 2019. Oligo Hyaluronan-  
1361 Coated Silica/Hydroxyapatite Degradable Nanoparticles for Targeted Cancer Treatment. *Adv Sci*  
1362 (Weinh) 6, 1900716.  
1363 Kankala, R.K., Han, Y.H., Na, J., Lee, C.H., Sun, Z., Wang, S.B., Kimura, T., Ok, Y.S.,  
1364 Yamauchi, Y., Chen, A.Z.J.A.M., 2020. Nanoarchitected structure and surface biofunctionality  
1365 of mesoporous silica nanoparticles. *Advanced Materials* 32, 1907035.  
1366 Karimi, M., Sahandi Zangabad, P., Ghasemi, A., Amiri, M., Bahrami, M., Malekzad, H.,  
1367 Ghahramanzadeh Asl, H., Mahdieh, Z., Bozorgomid, M., Ghasemi, A., 2016. Temperature-  
1368 responsive smart nanocarriers for delivery of therapeutic agents: applications and recent  
1369 advances. *ACS applied materials and interfaces* 8, 21107-21133.  
1370 Kesse, S., Boakye-Yiadom, K.O., Ochete, B.O., Opoku-Damoah, Y., Akhtar, F., Filli, M.S.,  
1371 Asim Farooq, M., Aquib, M., Maviah Mily, B.J., Murtaza, G., 2019. Mesoporous silica  
1372 nanomaterials: Versatile nanocarriers for cancer theranostics and drug and gene delivery.  
1373 *Pharmaceutics* 11, 77.  
1374 Kiew, S.F., Ho, Y.T., Kiew, L.V., Kah, J.C.Y., Lee, H.B., Imae, T., Chung, L.Y., 2017.  
1375 Preparation and characterization of an amylase-triggered dextrin-linked graphene oxide  
1376 anticancer drug nanocarrier and its vascular permeability. *International journal of pharmaceutics*  
1377 534, 297-307.  
1378 Kim, J.-S., Lee, S.K., Doh, H., Kim, M.Y., Kim, D.K., 2021. Real-Time Tracking of Highly  
1379 Luminescent Mesoporous Silica Particles Modified with Europium  $\beta$ -Diketone Chelates in  
1380 Living Cells. *Nanomaterials* 11, 343.  
1381 Kim, M.-H., Na, H.-K., Kim, Y.-K., Ryoo, S.-R., Cho, H.S., Lee, K.E., Jeon, H., Ryoo, R., Min,  
1382 D.-H., 2011. Facile synthesis of monodispersed mesoporous silica nanoparticles with ultralarge  
1383 pores and their application in gene delivery. *ACS nano* 5, 3568-3576.  
1384 Kobler, J., Möller, K., Bein, T., 2008. Colloidal suspensions of functionalized mesoporous silica  
1385 nanoparticles. *Acs Nano* 2, 791-799.  
1386 Kong, M., Peng, X., Cui, H., Liu, P., Pang, B., Zhang, K., 2020. pH-responsive polymeric  
1387 nanoparticles with tunable sizes for targeted drug delivery. *RSC Advances* 10, 4860-4868.  
1388 Kundu, M., Chatterjee, S., Ghosh, N., Manna, P., Das, J., Sil, P.C., 2020. Tumor targeted  
1389 delivery of umbelliferone via a smart mesoporous silica nanoparticles controlled-release drug  
1390 delivery system for increased anticancer efficiency. *Materials Science and Engineering: C* 116,  
1391 111239.  
1392 Lai, C.-Y., Trewyn, B.G., Jeftinija, D.M., Jeftinija, K., Xu, S., Jeftinija, S., Lin, V.S.-Y., 2003. A  
1393 mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle  
1394 caps for stimuli-responsive controlled release of neurotransmitters and drug molecules. *Journal*  
1395 *of the American Chemical Society* 125, 4451-4459.  
1396 Li, S.D., Huang, L., 2006. Gene therapy progress and prospects: non-viral gene therapy by  
1397 systemic delivery. *Gene Ther* 13, 1313-1319.  
1398 Li, X., Chen, Y., Zhang, X., Zhao, Y., 2020. Fabrication of biodegradable auto-fluorescent  
1399 organosilica nanoparticles with dendritic mesoporous structures for pH/redox-responsive drug  
1400 release. *Materials Science and Engineering: C* 112, 110914.  
1401 Li, X., Zhang, J., Gu, H., 2011. Adsorption and desorption behaviors of DNA with magnetic  
1402 mesoporous silica nanoparticles. *Langmuir* 27, 6099-6106.

1403 Li, Z.-Y., Liu, Y., Hu, J.-J., Xu, Q., Liu, L.-H., Jia, H.-Z., Chen, W.-H., Lei, Q., Rong, L.,  
1404 Zhang, X.-Z., 2014. Stepwise-acid-active multifunctional mesoporous silica nanoparticles for  
1405 tumor-specific nucleus-targeted drug delivery. *ACS applied materials and interfaces* 6, 14568-  
1406 14575.

1407 Lin, J.-T., Liu, Z.-K., Zhu, Q.-L., Rong, X.-H., Liang, C.-L., Wang, J., Ma, D., Sun, J., Wang,  
1408 G.-H., 2017. Redox-responsive nanocarriers for drug and gene co-delivery based on chitosan  
1409 derivatives modified mesoporous silica nanoparticles. *Colloids and Surfaces B: Biointerfaces*  
1410 155, 41-50.

1411 Lin, J.-T., Wang, C., Zhao, Y., Wang, G.-H., 2014. Mesoporous silica nanoparticles with  
1412 controlled loading of cationic dendrimer for gene delivery. *Materials Research Express* 1,  
1413 035403.

1414 Lin, Y.-S., Abadeer, N., Hurley, K.R., Haynes, C.L., 2011. Ultrastable, redispersible, small, and  
1415 highly organomodified mesoporous silica nanotherapeutics. *Journal of the American Chemical*  
1416 *Society* 133, 20444-20457.

1417 Linares, N., Serrano, E., Rico, M., Balu, A.M., Losada, E., Luque, R., García-Martínez, J., 2011.  
1418 Incorporation of chemical functionalities in the framework of mesoporous silica. *Chemical*  
1419 *Communications* 47, 9024-9035.

1420 Liu, F., Wang, J., Huang, P., Zhang, Q., Deng, J., Cao, Q., Jia, J., Cheng, J., Fang, Y., Deng,  
1421 D.Y., 2015. Outside-in stepwise functionalization of mesoporous silica nanocarriers for matrix  
1422 type sustained release of fluoroquinolone drugs. *Journal of Materials Chemistry B* 3, 2206-2214.

1423 Liu, R., Zhang, Y., Zhao, X., Agarwal, A., Mueller, L.J., Feng, P., 2010. pH-responsive  
1424 nanogated ensemble based on gold-capped mesoporous silica through an acid-labile acetal linker.  
1425 *Journal of the American Chemical Society* 132, 1500-1501.

1426 Liu, Y., Du, J., Choi, J.S., Chen, K.J., Hou, S., Yan, M., Lin, W.Y., Chen, K.S., Ro, T., Lipshutz,  
1427 G.S., Wu, L., Shi, L., Lu, Y., Tseng, H.R., Wang, H., 2016. A High-Throughput Platform for  
1428 Formulating and Screening Multifunctional Nanoparticles Capable of Simultaneous Delivery of  
1429 Genes and Transcription Factors. *Angew Chem Int Ed Engl* 55, 169-173.

1430 López, V., Villegas, M.R., Rodríguez, V., Villaverde, G., Lozano, D., Baeza, A., Vallet-Regí,  
1431 M., 2017. Janus Mesoporous Silica Nanoparticles for Dual Targeting of Tumor Cells and  
1432 Mitochondria. *ACS Appl Mater Interfaces* 9, 26697-26706.

1433 Lu, J., Li, Z., Zink, J.I., Tamanoi, F., 2012. In vivo tumor suppression efficacy of mesoporous  
1434 silica nanoparticles-based drug-delivery system: enhanced efficacy by folate modification.  
1435 *Nanomedicine* 8, 212-220.

1436 Ma, K., Werner-Zwanziger, U., Zwanziger, J., Wiesner, U., 2013. Controlling growth of  
1437 ultrasmall sub-10 nm fluorescent mesoporous silica nanoparticles. *Chemistry of Materials* 25,  
1438 677-691.

1439 Ma, M., Chen, H., Chen, Y., Zhang, K., Wang, X., Cui, X., Shi, J., 2012. Hyaluronic acid-  
1440 conjugated mesoporous silica nanoparticles: excellent colloidal dispersity in physiological fluids  
1441 and targeting efficacy. *Journal of Materials Chemistry* 22, 5615-5621.

1442 Mandal, A.K.J.I.J.o.P.M., Biomaterials, P., 2021. Dendrimers in targeted drug delivery  
1443 applications: A review of diseases and cancer. 70, 287-297.

1444 Manzano, M., Vallet-Regí, M., 2020. Mesoporous silica nanoparticles for drug delivery.  
1445 *Advanced Functional Materials* 30, 1902634.

1446 Martínez-Carmona, M., Ho, Q.P., Morand, J., García, A., Ortega, E., Erthal, L.C., Ruiz-  
1447 Hernandez, E., Santana, M.D., Ruiz, J., Vallet-Regí, M., 2020. Amino-Functionalized

1448 Mesoporous Silica Nanoparticle-Encapsulated Octahedral Organoruthenium Complex as an  
1449 Efficient Platform for Combatting Cancer. *Inorganic Chemistry* 59, 10275-10284.  
1450 Meyer, K., Palmer, J.W., 1934. The polysaccharide of the vitreous humor. *Journal of Biological*  
1451 *Chemistry* 107, 629-634.  
1452 Mickler, F.M., Möckl, L., Ruthardt, N., Ogris, M., Wagner, E., Bräuchle, C., 2012. Tuning  
1453 nanoparticle uptake: live-cell imaging reveals two distinct endocytosis mechanisms mediated by  
1454 natural and artificial EGFR targeting ligand. *Nano Lett* 12, 3417-3423.  
1455 Miller, L., Winter, G., Baur, B., Witulla, B., Solbach, C., Reske, S., Lindén, M., 2014. Synthesis,  
1456 characterization, and biodistribution of multiple <sup>89</sup>Zr-labeled pore-expanded mesoporous silica  
1457 nanoparticles for PET. *Nanoscale* 6, 4928-4935.  
1458 Moeller, K., Kobler, J., Bein, T., 2007. Colloidal suspensions of nanometer-sized mesoporous  
1459 silica. *Advanced Functional Materials* 17, 605-612.  
1460 Mohamed Isa, E.D., Ahmad, H., Abdul Rahman, M.B., Gill, M.R., 2021. Progress in  
1461 mesoporous silica nanoparticles as drug delivery agents for cancer treatment. *Pharmaceutics* 13,  
1462 152.  
1463 Montalvo-Quiros, S., Aragonese-Cazorla, G., Garcia-Alcalde, L., Vallet-Regí, M., González,  
1464 B., Luque-Garcia, J.L., 2019. Cancer cell targeting and therapeutic delivery of silver  
1465 nanoparticles by mesoporous silica nanocarriers: insights into the action mechanisms using  
1466 quantitative proteomics. *Nanoscale* 11, 4531-4545.  
1467 Moreira, A.F., Dias, D.R., Correia, I.J., 2016. Stimuli-responsive mesoporous silica  
1468 nanoparticles for cancer therapy: A review. *Microporous and Mesoporous Materials* 236, 141-  
1469 157.  
1470 Murugan, B., Ramana, L.N., Gandhi, S., Sethuraman, S., Krishnan, U.M., 2013. Engineered  
1471 chemoswitchable mesoporous silica for tumor-specific cytotoxicity. *Journal of Materials*  
1472 *Chemistry B* 1, 3494-3505.  
1473 Nagraik, R., Sharma, A., Kumar, D., Mukherjee, S., Sen, F., Kumar, A.P., 2021. Amalgamation  
1474 of biosensors and nanotechnology in disease diagnosis: Mini-Review. *Sensors International*,  
1475 100089.  
1476 Nairi, V., Magnolia, S., Piludu, M., Nieddu, M., Caria, C.A., Sogos, V., Vallet-Regí, M.,  
1477 Monduzzi, M., Salis, A., 2018. Mesoporous silica nanoparticles functionalized with hyaluronic  
1478 acid. Effect of the biopolymer chain length on cell internalization. *Colloids and Surfaces B:*  
1479 *Biointerfaces* 168, 50-59.  
1480 Nandiyanto, A.B.D., Kim, S.-G., Iskandar, F., Okuyama, K., 2009. Synthesis of spherical  
1481 mesoporous silica nanoparticles with nanometer-size controllable pores and outer diameters.  
1482 *Microporous and Mesoporous Materials* 120, 447-453.  
1483 Narayan, R., Gadag, S., Mudakavi, R.J., Garg, S., Raichur, A.M., Nayak, Y., Kini, S.G., Pai,  
1484 K.S.R., Nayak, U.Y., 2021. Mesoporous silica nanoparticles capped with chitosan-glucuronic  
1485 acid conjugate for pH-responsive targeted delivery of 5-fluorouracil. *Journal of Drug Delivery*  
1486 *Science and Technology* 63, 102472.  
1487 Narayan, R., Nayak, U.Y., Raichur, A.M., Garg, S., 2018. Mesoporous silica nanoparticles: A  
1488 comprehensive review on synthesis and recent advances. *Pharmaceutics* 10, 118.  
1489 Natarajan, S.K., Selvaraj, S., 2014. Mesoporous silica nanoparticles: importance of surface  
1490 modifications and its role in drug delivery. *RSC advances* 4, 14328-14334.  
1491 Nekounam, H., Kandi, M.R., Shaterabadi, D., Samadian, H., Mahmoodi, N., Hasanzadeh, E.,  
1492 Faridi-Majidi, R., 2021. Silica nanoparticles-incorporated carbon nanofibers as bioactive  
1493 biomaterial for bone tissue engineering. *Diamond and Related Materials*, 108320.

1494 Niedermayer, S., Weiss, V., Herrmann, A., Schmidt, A., Datz, S., Müller, K., Wagner, E., Bein,  
1495 T., Bräuchle, C., 2015. Multifunctional polymer-capped mesoporous silica nanoparticles for pH-  
1496 responsive targeted drug delivery. *Nanoscale* 7, 7953-7964.

1497 Niemelä, E., Desai, D., Nkizinkiko, Y., Eriksson, J.E., Rosenholm, J.M., 2015. Sugar-decorated  
1498 mesoporous silica nanoparticles as delivery vehicles for the poorly soluble drug celastrol enables  
1499 targeted induction of apoptosis in cancer cells. *Eur J Pharm Biopharm* 96, 11-21.

1500 Nik, A.B., Zare, H., Razavi, S., Mohammadi, H., Ahmadi, P.T., Yazdani, N., Bayandori, M.,  
1501 Rabiee, N., Mobarakeh, J.I., 2020. Smart drug delivery: Capping strategies for mesoporous silica  
1502 nanoparticles. *Microporous and Mesoporous Materials* 299, 110115.

1503 Nikzamir, M., Hanifehpour, Y., Akbarzadeh, A., Panahi, Y., 2021. Applications of Dendrimers  
1504 in Nanomedicine and Drug Delivery: A Review. *Journal of Inorganic and Organometallic*  
1505 *Polymers and Materials*, 1-16.

1506 Øye, G., Sjöblom, J., Stöcker, M.J.A.i.c., science, i., 2001. Synthesis, characterization and  
1507 potential applications of new materials in the mesoporous range. 89, 439-466.

1508 Palanikumar, L., Al-Hosani, S., Kalmouni, M., Nguyen, V.P., Ali, L., Pasricha, R., Barrera, F.N.,  
1509 Magzoub, M., 2020. pH-responsive high stability polymeric nanoparticles for targeted delivery  
1510 of anticancer therapeutics. *Communications biology* 3, 1-17.

1511 Pan, L., He, Q., Liu, J., Chen, Y., Ma, M., Zhang, L., Shi, J., 2012a. Nuclear-targeted drug  
1512 delivery of TAT peptide-conjugated monodisperse mesoporous silica nanoparticles. *Journal of*  
1513 *the American Chemical Society* 134, 5722-5725.

1514 Pan, L., He, Q., Liu, J., Chen, Y., Ma, M., Zhang, L., Shi, J., 2012b. Nuclear-targeted drug  
1515 delivery of TAT peptide-conjugated monodisperse mesoporous silica nanoparticles. *Journal of*  
1516 *the American Chemical Society* 134, 5722-5725.

1517 Pang, X., Gao, J., Tang, F., 2005. Controlled preparation of rod-and top-like MCM-41  
1518 mesoporous silica through one-step route. *Journal of non-crystalline solids* 351, 1705-1709.

1519 Peng, H., Dong, R., Wang, S., Zhang, Z., Luo, M., Bai, C., Zhao, Q., Li, J., Chen, L., Xiong, H.,  
1520 2013. A pH-responsive nano-carrier with mesoporous silica nanoparticles cores and poly (acrylic  
1521 acid) shell-layers: Fabrication, characterization and properties for controlled release of  
1522 salidroside. *International journal of pharmaceutics* 446, 153-159.

1523 Pinese, C., Lin, J., Milbreta, U., Li, M., Wang, Y., Leong, K.W., Chew, S.Y., 2018. Sustained  
1524 delivery of siRNA/mesoporous silica nanoparticle complexes from nanofiber scaffolds for long-  
1525 term gene silencing. *Acta Biomater* 76, 164-177.

1526 Plaza-Oliver, M., Santander-Ortega, M.J., Lozano, M.V., 2021. Current approaches in lipid-  
1527 based nanocarriers for oral drug delivery. *Drug Delivery and Translational Research*, 1-27.

1528 Pouroutzidou, G.K., Liverani, L., Theocharidou, A., Tsamesidis, I., Lazaridou, M.,  
1529 Christodoulou, E., Beketova, A., Pappa, C., Triantafyllidis, K.S., Anastasiou, A.D., 2021.  
1530 Synthesis and Characterization of Mesoporous Mg-and Sr-Doped Nanoparticles for  
1531 Moxifloxacin Drug Delivery in Promising Tissue Engineering Applications. *International*  
1532 *Journal of Molecular Sciences* 22, 577.

1533 Prasad, R., Aiyer, S., Chauhan, D.S., Srivastava, R., Selvaraj, K., 2016. Bioresponsive carbon  
1534 nano-gated multifunctional mesoporous silica for cancer theranostics. *Nanoscale* 8, 4537-4546.

1535 Qiao, Z.-A., Zhang, L., Guo, M., Liu, Y., Huo, Q., 2009. Synthesis of mesoporous silica  
1536 nanoparticles via controlled hydrolysis and condensation of silicon alkoxide. *Chemistry of*  
1537 *Materials* 21, 3823-3829.

1538 Qindeel, M., Ahmed, N., Khan, G.M., Rehman, A.u., 2019. Ligand decorated chitosan as an  
1539 advanced nanocarrier for targeted delivery: a critical review. *Nanomedicine* 14, 1623-1642.

1540 Radhakrishnan, K., Gupta, S., Gnanadhas, D.P., Ramamurthy, P.C., Chakravorty, D., Raichur,  
1541 A.M.J.P., 2014. Protamine-capped mesoporous silica nanoparticles for biologically triggered  
1542 drug release. *Particle and Particle Systems Characterization* 31, 449-458.

1543 Safdar, R., Omar, A.A., Arunagiri, A., Regupathi, I., Thanabalan, M., 2019. Potential of  
1544 Chitosan and its derivatives for controlled drug release applications—A review. *Journal of drug  
1545 delivery science and technology* 49, 642-659.

1546 Salinas, Y., Brüggemann, O., Monkowius, U., Teasdale, I., 2020. Visible light photocleavable  
1547 ruthenium-based molecular gates to reversibly control release from mesoporous silica  
1548 nanoparticles. *Nanomaterials* 10, 1030.

1549 Sarkar, A., Ghosh, S., Chowdhury, S., Pandey, B., Sil, P.C., 2016. Targeted delivery of quercetin  
1550 loaded mesoporous silica nanoparticles to the breast cancer cells. *Biochim Biophys Acta* 1860,  
1551 2065-2075.

1552 Schlossbauer, A., Warncke, S., Gramlich, P.M., Kecht, J., Manetto, A., Carell, T., Bein, T.,  
1553 2010. A programmable DNA-based molecular valve for colloidal mesoporous silica. *A journal of  
1554 German Chemical Society* 49, 4734-4737.

1555 Scicluna, M.C., Vella-Zarb, L., 2020. Evolution of nanocarrier drug-delivery systems and recent  
1556 advancements in covalent organic framework–drug systems. *ACS Applied Nano Materials* 3,  
1557 3097-3115.

1558 Shah, P.V., Rajput, S.J.J.A.P., 2018. Facile synthesis of chitosan capped mesoporous silica  
1559 nanoparticles: a pH responsive smart delivery platform for raloxifene hydrochloride. 19, 1344-  
1560 1357.

1561 Shahbazi, M.-A., Herranz, B., Santos, H.A., 2012. Nanostructured porous Si-based nanoparticles  
1562 for targeted drug delivery. *Biomatter* 2, 296-312.

1563 Shakeran, Z., Keyhanfar, M., Varshosaz, J., Sutherland, D.S., 2021. Biodegradable nanocarriers  
1564 based on chitosan-modified mesoporous silica nanoparticles for delivery of methotrexate for  
1565 application in breast cancer treatment. *Materials Scienc and Engineering: C* 118, 111526.

1566 Shao, D., Lu, M.-m., Zhao, Y.-w., Zhang, F., Tan, Y.-f., Zheng, X., Pan, Y., Xiao, X.-a., Wang,  
1567 Z., Dong, W.-f., 2017. The shape effect of magnetic mesoporous silica nanoparticles on  
1568 endocytosis, biocompatibility and biodistribution. *Acta biomaterialia* 49, 531-540.

1569 Shen, S., Gu, T., Mao, D., Xiao, X., Yuan, P., Yu, M., Xia, L., Ji, Q., Meng, L., Song, W., 2012.  
1570 Synthesis of nonspherical mesoporous silica ellipsoids with tunable aspect ratios for magnetic  
1571 assisted assembly and gene delivery. *Chemistry of Materials* 24, 230-235.

1572 Shi, J., Kantoff, P.W., Wooster, R., Farokhzad, O.C., 2017. Cancer nanomedicine: progress,  
1573 challenges and opportunities. *Nat Rev Cancer* 17, 20-37.

1574 Shi, Z., Zhou, Y., Fan, T., Lin, Y., Zhang, H., Mei, L., 2020. Inorganic nano-carriers based smart  
1575 drug delivery systems for tumor therapy. *Smart Materials in Medicine* 1, 32-47.

1576 Siddiqui, B., Rehman, A.U., Haq, I.-U., Ahmad, N.M., Ahmed, N., 2020. Development,  
1577 optimisation, and evaluation of nanoencapsulated diacerein emulgel for potential use in  
1578 osteoarthritis. *Journal of Microencapsulation* 37, 595-608.

1579 Singh, R.K., Patel, K.D., Mahapatra, C., Parthiban, S.P., Kim, T.-H., Kim, H.-W., 2018.  
1580 Combinatory cancer therapeutics with nanoceria-capped mesoporous silica nanocarriers through  
1581 pH-triggered drug release and redox activity. *ACS applied materials and interfaces* 11, 288-299.

1582 Slowing, II, Vivero-Escoto, J.L., Wu, C.W., Lin, V.S., 2008. Mesoporous silica nanoparticles as  
1583 controlled release drug delivery and gene transfection carriers. *Adv Drug Deliv Rev* 60, 1278-  
1584 1288.

1585 Song, N., Yang, Y.-W., 2015. Molecular and supramolecular switches on mesoporous silica  
1586 nanoparticles. *Chemical Society Reviews* 44, 3474-3504.

1587 Stöber, W., Fink, A., Bohn, E., 1968. Controlled growth of monodisperse silica spheres in the  
1588 micron size range. *Journal of colloid and interface science* 26, 62-69.

1589 Sun, X., Zhao, Y., Lin, V.S.-Y., Slowing, I.I., Trewyn, B.G.J.J.o.t.A.C.S., 2011. Luciferase and  
1590 luciferin co-immobilized mesoporous silica nanoparticle materials for intracellular biocatalysis.  
1591 133, 18554-18557.

1592 Tao, Z., Toms, B., Goodisman, J., Asefa, T., 2010. Mesoporous silica microparticles enhance the  
1593 cytotoxicity of anticancer platinum drugs. *ACS Nano* 4, 789-794.

1594 Tarn, D., Ashley, C.E., Xue, M., Carnes, E.C., Zink, J.I., Brinker, C.J., 2013. Mesoporous silica  
1595 nanoparticle nanocarriers: biofunctionality and biocompatibility. *Accounts of chemical research*  
1596 46, 792-801.

1597 Tozuka, Y., Wongmekiat, A., Kimura, K., Moribe, K., Yamamura, S., Yamamoto, K., 2005.  
1598 Effect of pore size of FSM-16 on the entrapment of flurbiprofen in mesoporous structures.  
1599 *Chemical and pharmaceutical bulletin* 53, 974-977.

1600 Umehara, Y., Kimura, Y., Kleitz, F., Nishihara, T., Kondo, T., Tanabe, K., 2021. Phosphonated  
1601 mesoporous silica nanoparticles bearing ruthenium complexes used as molecular probes for  
1602 tracking oxygen levels in cells and tissues. *RSC Advances* 11, 5865-5873.

1603 Vallet-Regi, M., Rámila, A., Del Real, R., Pérez-Pariente, J., 2001. A new property of MCM-41:  
1604 drug delivery system. *Chemistry of Materials* 13, 308-311.

1605 van den Brand, D., Mertens, V., Massuger, L.F., Brock, R., 2018. siRNA in ovarian cancer–  
1606 Delivery strategies and targets for therapy. *Journal of Controlled Release* 283, 45-58.

1607 Varshney, S., Nigam, A., Pawar, S.J., Mishra, N., 2021. An overview on biomedical applications  
1608 of versatile silica nanoparticles, synthesized via several chemical and biological routes: A  
1609 review. *Phosphorus, Sulfur, Silicon and the Related Elements* a, 1-17.

1610 Vazquez, N.I., Gonzalez, Z., Ferrari, B., Castro, Y., 2017. Synthesis of mesoporous silica  
1611 nanoparticles by sol–gel as nanocontainer for future drug delivery applications. *Boletín de la*  
1612 *Sociedad Española de Cerámica y Vidrio* 56, 139-145.

1613 Wagner, J., Gößl, D., Ustyanovska, N., Xiong, M., Hauser, D., Zhuzhgova, O., Hočevár, S.,  
1614 Taskoparan, B., Poller, L., Datz, S., Engelke, H., Daali, Y., Bein, T., Bourquin, C., 2021.  
1615 Mesoporous Silica Nanoparticles as pH-Responsive Carrier for the Immune-Activating Drug  
1616 Resiquimod Enhance the Local Immune Response in Mice. *ACS Nano* 15, 4450-4466.

1617 Wang, B., Zhang, K., Wang, J., Zhao, R., Zhang, Q., Kong, X., 2020a. Poly (amidoamine)-  
1618 modified mesoporous silica nanoparticles as a mucoadhesive drug delivery system for potential  
1619 bladder cancer therapy. *Colloids and Surfaces B: Biointerfaces* 189, 110832.

1620 Wang, J., Li, Z., Yin, Y., Liu, H., Tang, G., Ma, Y., Feng, X., Mei, H., Bi, J., Wang, K., 2020b.  
1621 Mesoporous silica nanoparticles combined with MoS<sub>2</sub> and FITC for fluorescence imaging and  
1622 photothermal therapy of cancer cells. *Journal of Materials Science* 55, 15263-15274.

1623 Wang, L., Liu, Y., Zhang, W., Chen, X., Yang, T., Ma, G., 2013. Microspheres and  
1624 microcapsules for protein delivery: strategies of drug activity retention. *Current pharmaceutical*  
1625 *design* 19, 6340-6352.

1626 Wang, L.S., Wu, L.C., Lu, S.Y., Chang, L.L., Teng, I.T., Yang, C.M., Ho, J.A., 2010.  
1627 Biofunctionalized phospholipid-capped mesoporous silica nanoshuttles for targeted drug  
1628 delivery: improved water suspensibility and decreased nonspecific protein binding. *ACS Nano* 4,  
1629 4371-4379.



1630 Wang, W., Wang, P., Tang, X., Elzatahry, A.A., Wang, S., Al-Dahyan, D., Zhao, M., Yao, C.,  
1631 Hung, C.-T., Zhu, X., 2017a. Facile synthesis of uniform virus-like mesoporous silica  
1632 nanoparticles for enhanced cellular internalization. *ACS central science* 3, 839-846.  
1633 Wang, X., Li, C., Fan, N., Li, J., Zhang, H., Shang, L., He, Z., Sun, J., 2019. Amino  
1634 functionalized chiral mesoporous silica nanoparticles for improved loading and release of poorly  
1635 water-soluble drug. *Asian journal of pharmaceutical sciences* 14, 405-412.  
1636 Wang, X., Zhang, Y., Luo, W., Elzatahry, A.A., Cheng, X., Alghamdi, A., Abdullah, A.M.,  
1637 Deng, Y., Zhao, D., 2016. Synthesis of ordered mesoporous silica with tunable morphologies and  
1638 pore sizes via a nonpolar solvent-assisted stober method. *Chemistry of Materials* 28, 2356-2362.  
1639 Wang, Y., Cheng, S., Hu, W., Lin, X., Cao, C., Zou, S., Tong, Z., Jiang, G., Kong, X., 2021.  
1640 Polymer-grafted hollow mesoporous silica nanoparticles integrated with microneedle patches for  
1641 glucose-responsive drug delivery. *Frontiers of Materials Science* 15, 98-112.  
1642 Wang, Y., Cui, Y., Huang, J., Di, D., Dong, Y., Zhang, X., Zhao, Q., Han, N., Gao, Y., Jiang, T.,  
1643 2015. Redox and pH dual-responsive mesoporous silica nanoparticles for site-specific drug  
1644 delivery. *Applied Surface Science* 356, 1282-1288.  
1645 Wang, Y., Jiang, L., Chu, L., Liu, W., Wu, S., Wu, Y., He, X., Wang, K., 2017b.  
1646 Electrochemical detection of glutathione by using thymine-rich DNA-gated switch  
1647 functionalized mesoporous silica nanoparticles. *Biosensors and Bioelectronics* 87, 459-465.  
1648 Wen, Y., Oh, J.K., 2014. Recent strategies to develop polysaccharide-based nanomaterials for  
1649 biomedical applications. *Macromolecular rapid communications* 35, 1819-1832.  
1650 Wu, M., Meng, Q., Chen, Y., Du, Y., Zhang, L., Li, Y., Zhang, L., Shi, J., 2015. Large-pore  
1651 ultrasmall mesoporous organosilica nanoparticles: micelle/precursor co-templating assembly and  
1652 nuclear-targeted gene delivery. *Advanced Materials* 27, 215-222.  
1653 Wu, S.-H., Mou, C.-Y., Lin, H.-P., 2013. Synthesis of mesoporous silica nanoparticles. *Chemical*  
1654 *Society Reviews* 42, 3862-3875.  
1655 Xu, J.-H., Gao, F.-P., Li, L.-L., Ma, H.L., Fan, Y.-S., Liu, W., Guo, S.-S., Zhao, X.-Z., Wang,  
1656 H., 2013. Gelatin-mesoporous silica nanoparticles as matrix metalloproteinases-degradable drug  
1657 delivery systems in vivo. *Microporous and mesoporous materials* 182, 165-172.  
1658 Xu, W., He, W., Du, Z., Zhu, L., Huang, K., Lu, Y., Luo, Y., 2021. Functional nucleic acid  
1659 nanomaterials: Development, properties, and applications. *Angewandte Chemie International*  
1660 *Edition* 60, 6890-6918.  
1661 Yamada, H., Urata, C., Ujiie, H., Yamauchi, Y., Kuroda, K., 2013. Preparation of aqueous  
1662 colloidal mesostructured and mesoporous silica nanoparticles with controlled particle size in a  
1663 very wide range from 20 nm to 700 nm. *Nanoscale* 5, 6145-6153.  
1664 Yan, T., He, J., Liu, R., Liu, Z., Cheng, J., 2020. Chitosan capped pH-responsive hollow  
1665 mesoporous silica nanoparticles for targeted chemo-photo combination therapy. *Carbohydrate*  
1666 *polymers* 231, 115706.  
1667 Yang, Y.-J., Tao, X., Hou, Q., Ma, Y., Chen, X.-L., Chen, J.-F., 2010. Mesoporous silica  
1668 nanotubes coated with multilayered polyelectrolytes for pH-controlled drug release. *Acta*  
1669 *Biomaterialia* 6, 3092-3100.  
1670 Yano, K., Fukushima, Y., 2004. Synthesis of mono-dispersed mesoporous silica spheres with  
1671 highly ordered hexagonal regularity using conventional alkyltrimethylammonium halide as a  
1672 surfactant. *Journal of Materials Chemistry* 14, 1579-1584.  
1673 You, Y., Hu, H., He, L., Chen, T., 2015. Differential Effects of Polymer-Surface Decoration on  
1674 Drug Delivery, Cellular Retention, and Action Mechanisms of Functionalized Mesoporous Silica  
1675 Nanoparticles. *Chemistry-An Asian Journal* 10, 2744-2754.

1676 Yu, M., Jambhrunkar, S., Thorn, P., Chen, J., Gu, W., Yu, C., 2013. Hyaluronic acid modified  
1677 mesoporous silica nanoparticles for targeted drug delivery to CD44-overexpressing cancer cells.  
1678 *Nanoscale* 5, 178-183.

1679 Yu, Q., Hui, J., Wang, P., Xu, B., Zhuang, J., Wang, X., 2012. Hydrothermal synthesis of  
1680 mesoporous silica spheres: effect of the cooling process. *Nanoscale* 4, 7114-7120.

1681 Yu, Y.-J., Xing, J.-L., Pang, J.-L., Jiang, S.-H., Lam, K.-F., Yang, T.-Q., Xue, Q.-S., Zhang, K.,  
1682 Wu, P., 2014. Facile synthesis of size controllable dendritic mesoporous silica nanoparticles.  
1683 *ACS applied materials interfaces* 6, 22655-22665.

1684 Yue, Y., Wu, C., 2013. Progress and perspectives in developing polymeric vectors for in vitro  
1685 gene delivery. *Biomater Sci* 1, 152-170.

1686 Zainala, N.A., Shukor, S., Wabb, H.A.A., Razakb, K., 2013. Study on the effect of synthesis  
1687 parameters of silica nanoparticles entrapped with rifampicin. *Chemical Engineering* 32.

1688 Zeiderman, M.R., Morgan, D.E., Christein, J.D., Grizzle, W.E., McMasters, K.M., McNally,  
1689 L.R.J.A.b.s., 2016. Acidic pH-targeted chitosan-capped mesoporous silica coated gold nanorods  
1690 facilitate detection of pancreatic tumors via multispectral optoacoustic tomography. *ACS*  
1691 *biomaterials science and engineering* 2, 1108-1120.

1692 Zhang, B., Luo, Z., Liu, J., Ding, X., Li, J., Cai, K., 2014. Cytochrome c end-capped mesoporous  
1693 silica nanoparticles as redox-responsive drug delivery vehicles for liver tumor-targeted triplex  
1694 therapy in vitro and in vivo. *Journal of Controlled Release* 192, 192-201.

1695 Zhang, R., Hua, M., Liu, H., Li, J., 2021. How to design nanoporous silica nanoparticles in  
1696 regulating drug delivery: Surface modification and porous control. *Materials Science and*  
1697 *Engineering: B* 263, 114835.

1698 Zhang, W., Zheng, N., Chen, L., Xie, L., Cui, M., Li, S., Xu, L., 2019. Effect of shape on  
1699 mesoporous silica nanoparticles for oral delivery of indomethacin. *Pharmaceutics* 11, 4.

1700 Zhang, Y.-N., Poon, W., Tavares, A.J., McGilvray, I.D., Chan, W.C., 2016. Nanoparticle–liver  
1701 interactions: cellular uptake and hepatobiliary elimination. *Journal of controlled release* 240,  
1702 332-348.

1703 Zhang, Y., Ang, C.Y., Li, M., Tan, S.Y., Qu, Q., Luo, Z., Zhao, Y., 2015. Polymer-coated  
1704 hollow mesoporous silica nanoparticles for triple-responsive drug delivery. *ACS applied*  
1705 *materials and interfaces* 7, 18179-18187.

1706 Zhao, D., Feng, J., Huo, Q., Melosh, N., Fredrickson, G.H., Chmelka, B.F., Stucky, G.D., 1998.  
1707 Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 angstrom pores.  
1708 *science* 279, 548-552.

1709 Zhao, Q., Geng, H., Wang, Y., Gao, Y., Huang, J., Wang, Y., Zhang, J., Wang, S., 2014.  
1710 Hyaluronic acid oligosaccharide modified redox-responsive mesoporous silica nanoparticles for  
1711 targeted drug delivery. *ACS applied materials and interfaces* 6, 20290-20299.

1712 Zhou, L., Liu, G., Wang, Y., Liu, J., Zhang, Y., Ma, Y., 2019. AuNP and ssDNA capped  
1713 mesoporous silica nanoparticles for laser controlled drug release. *RSC advances* 9, 34958-34962.

1714 Zhou, R., Sun, S., Li, C., Wu, L., Hou, X., Wu, P., 2018a. Enriching Mn-doped ZnSe quantum  
1715 dots onto mesoporous silica nanoparticles for enhanced fluorescence/magnetic resonance  
1716 imaging dual-modal bio-imaging. *ACS applied materials and interfaces* 10, 34060-34067.

1717 Zhou, S., Ding, C., Wang, C., Fu, J., 2020. UV-light cross-linked and pH de-cross-linked  
1718 coumarin-decorated cationic copolymer grafted mesoporous silica nanoparticles for drug and  
1719 gene co-delivery in vitro. *Mater Sci Eng C Mater Biol Appl* 108, 110469.

1720 Zhou, Y., Chang, C., Liu, Z., Zhao, Q., Xu, Q., Li, C., Chen, Y., Zhang, Y., Lu, B., 2021.  
1721 Hyaluronic Acid-Functionalized Hollow Mesoporous Silica Nanoparticles as pH-Sensitive  
1722 Nanocarriers for Cancer Chemo-Photodynamic Therapy. *Langmuir* 37, 2619-2628.  
1723 Zhou, Y., Quan, G., Wu, Q., Zhang, X., Niu, B., Wu, B., Huang, Y., Pan, X., Wu, C., 2018b.  
1724 Mesoporous silica nanoparticles for drug and gene delivery. *Acta pharmaceutica sinica B* 8, 165-  
1725 177.  
1726 Zhou, Y., Tan, L.L., Li, Q.L., Qiu, X.L., Qi, A.D., Tao, Y., Yang, Y.W., 2014. Acetylcholine-  
1727 triggered cargo release from supramolecular nanovalves based on different macrocyclic  
1728 receptors. *Chemistry—A European Journal* 20, 2998-3004.  
1729 Zou, Z., He, D., He, X., Wang, K., Yang, X., Qing, Z., Zhou, Q., 2013. Natural gelatin capped  
1730 mesoporous silica nanoparticles for intracellular acid-triggered drug delivery. *Langmuir* 29,  
1731 12804-12810.  
1732