



# Mesoporous Silica Nanoparticles for Bio-Applications

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Mesoporous materials with high specific surface, pores volume and unique pore size were recently intensively studied as bio-materials, such as carriers for controlled bio-active principles delivery. Mesoporous silica materials exhibit greater capacity for drugs loading and insure a controlled bio-active compound release if they are functionalized, in comparison with amorphous colloidal silica. Mesoporous silica nanomaterials have lately earned increasing interest also due to their substantial capability to be used in tumors treatment and imaging. Recently, functionalized mesoporous silica materials known a rapid development in imagistic and curative applications. This review summarizes the recent advancement in the obtaining and biological properties of mesoporous silica nanomaterials, emphasizing the synthesis methods and drug delivery application. Commonly used synthetic strategies are discussed, followed by a systematic review of applicability in optical and MRI imaging.

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## INTRODUCTION

In 1906, Paul Ehrlich introduced the term “magic bullet,” referring to an antigen capability to specific select “side chains” on the cells surface (Strebhardt and Ullrich, 2008; Li et al., 2012). In the cytotoxic chemotherapy, the design of a targeted component is essential if an efficient dose of a drug must attack only the damaged region, without affecting healthy cells. Hypothetically, this “magic bullet” must contain a nanoscale delivery system able to specifically targeting tumor, avoiding premature degradation (Peer et al., 2007). This integrated concept could result in a controlled-release upon activation.

Various theranostic drugs have been developed over the past 30 years, the most clinically used being multifunctional liposomes and polymeric micelles. However, the aim of this investigation is to draw special attention to the use of silica-based mesoporous nanomaterials as drugs robust and tuneable delivery systems.

Nanotherapeutics have been intensively studied in the last years, as a consequence of the capability to be used as effective drug delivery frameworks with decreased unwanted secondary effects (Lin et al., 2012). Contrary to the classical therapies, nanomaterials can be designed properly to target affected sites (tumors) and selectively deliver their load. Until now, different nanomaterials (polymers, metal, metal oxide, etc.) have been obtained and used as systems for integrating active principles and diagnostic functions in a single nanomaterial, called multifunctional nanotheranostic (Sanvicens and Marco, 2008; Lammers et al., 2010; Xie et al., 2010).

The unstoppable nanotechnology development resulted in the design of various nanomaterials with important therapeutic potential. For example, there have been discovered many materials suitable for treating various pathologies (Anselmo and Mitragotri, 2015, 2016), such as: magnetic (Hao et al., 2010; Lin et al., 2012; Wu et al., 2016) or plasmonic compounds

(Lin et al., 2012; Liu et al., 2016), that can be isolated excited with a magnetic field and light, resulting a thermic reaction able to induce cell death (Lin et al., 2012).

Mesoporous silica gained a raised interest, due to its extensive multi-functionality, based on its high specific surface, uniform and tuneable pore size, high pore volume, and facile functionalization (Rosenholm et al., 2011; Lin et al., 2012).

The first surfactant-assisted synthesis of MCM-41 mesoporous silica (Mobil Composition of Matter No. 41) was achieved by Mobil Company in 1992 (Kresge et al., 1992), but MCM-41 begun to be studied for bio-applications since 2001 as a matrix for drugs release (Vallet-Regi et al., 2001; Lin et al., 2012). Also, other studies reported silica derivates with reduced dimensions for drugs release (Cai et al., 2001; Fowler et al., 2001; Lin et al., 2012). Since then, extensive research have been carried out in order to improve nanosilica synthesis, its functionalization and to study *in vitro/in vivo* activity. **Figure 1** reflects a scheme used for highlighting the development of mesoporous silica nanomaterials used in biomedical-applications (Lin et al., 2012).

First modified mesoporous silica nanomaterials for stimuli-reactive guided liberation of active compounds through chemically extractible nanoparticles as coatings were obtained in 2003 (Lai et al., 2003; Lin et al., 2012). Since then, research focused on the addition of different compounds to obtain various diagnostic or therapeutic effects, which include: controlled drug delivery (Lai et al., 2003; Schlossbauer et al., 2009; Shen et al., 2017) and targeting (Wang et al., 2010; Shen et al., 2017).

Multifunctional mesoporous silica with imaging capabilities were synthesized and reported in 2006 (Kim et al., 2006; Lin et al., 2006). Until now, various routes to incorporate imaging agents were designed, for example fluorophores (for fluorescence imaging, Lin et al., 2005; Wu et al., 2008), or superparamagnetic nanoparticles (Kim et al., 2006; Lin et al., 2006).

From 2008, *in vivo* investigations have been achieved for the identification of mesoporous silica biodistribution

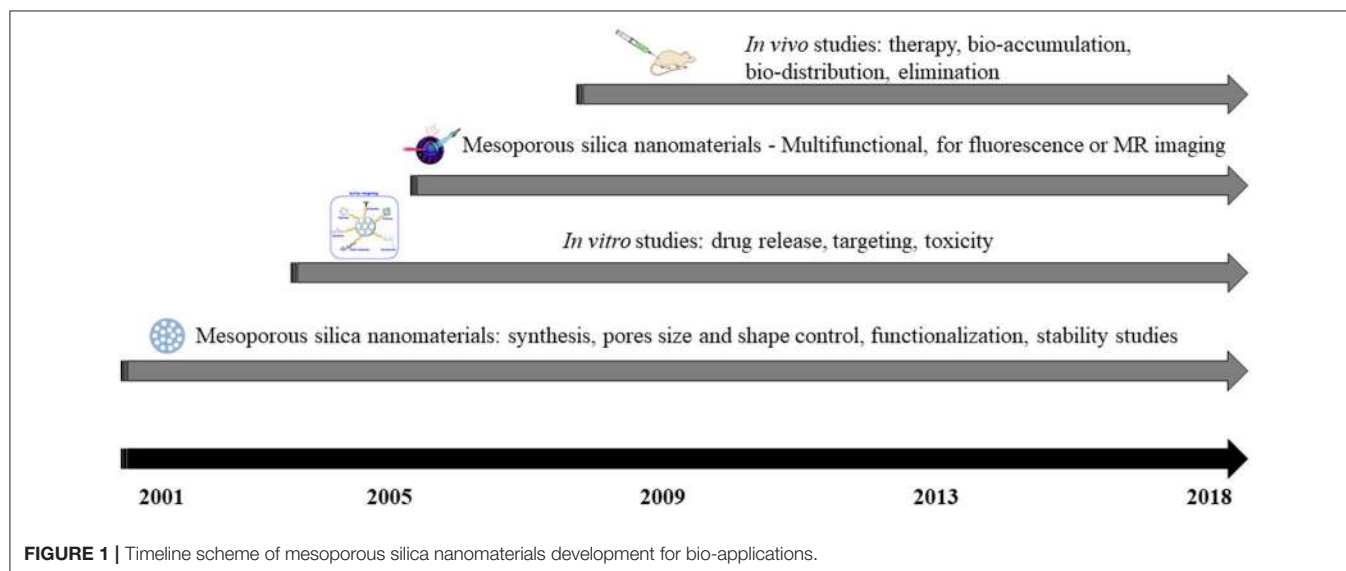
(Kim et al., 2008; Lin et al., 2012), toxicity (Huang et al., 2011; Meng et al., 2011), and therapeutic effect (Kim et al., 2008; Meng et al., 2011).

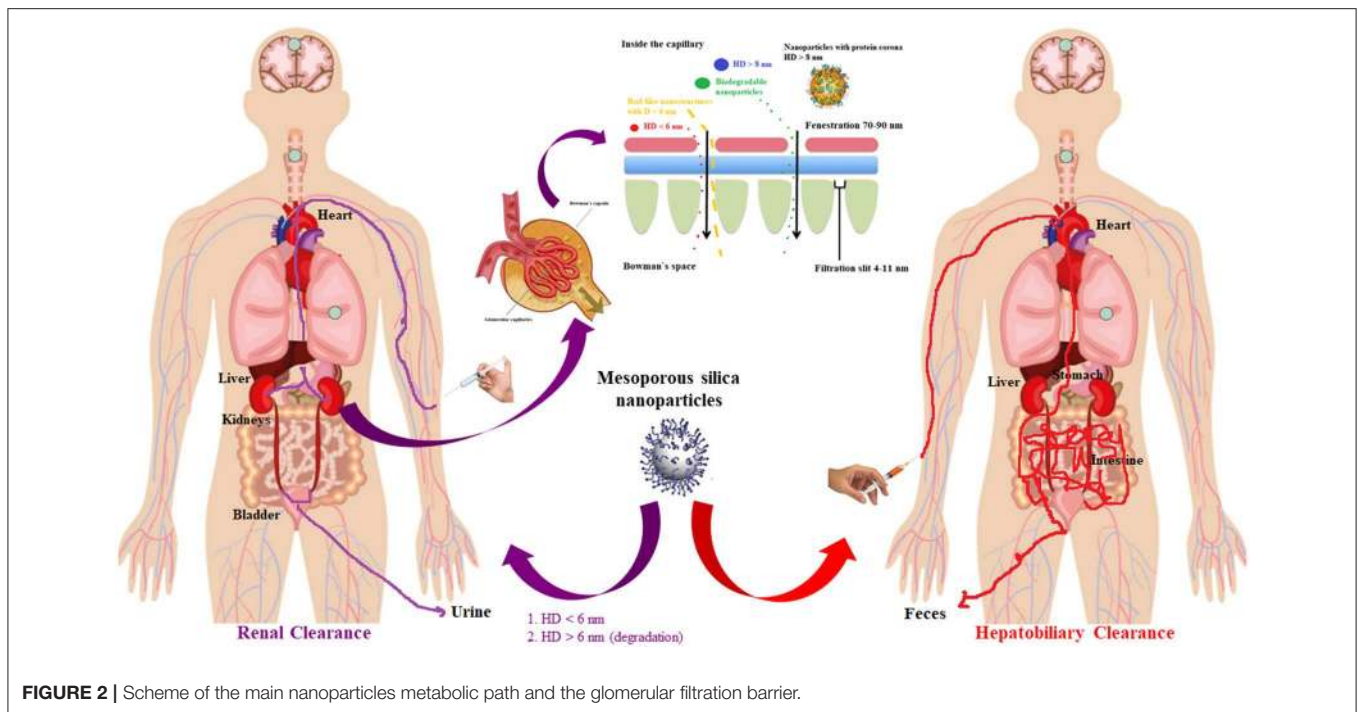
Although these nanomaterials have gain an increased interest and proved their compatibility for bio-applications in the last 10 years, various aspects must be taken into consideration prior to be clinically used (Lin et al., 2012). For instance, if they are intravenous injected, the biodistribution depends on the particles diameters and surface properties, therefore, the concern must be targeted in the size and stability control under the biological environment (37°C, highly salted or serum-containing media) before injection (He et al., 2010; Lin et al., 2012). Another aspect that must be taken into consideration is the toxicity of mesoporous silica nanomaterials, the adverse effects being carefully examined.

Various studies concentrated on *in vitro* drug delivery, controlled release, or toxicity of mesoporous silica materials (Rosenholm et al., 2010; He and Shi, 2011; Lin et al., 2011; Xu et al., 2012). This review will mainly emphasize advancement in the domain, underlining the emergent synthesis methods, strategies to improve mesoporous silica stability and biodegradability.

Nowadays, the chemotherapeutics delivery evolved, resulting nano-encapsulated drug formulations which can improve the pharmacological profile of the free drugs. However, mesoporous silica materials are gradually receiving interest due to their unique properties, such as well-established drug delivery properties (Vallet-Regi et al., 2007) and versatility for creating high-performing hybrid materials. Besides mesoporous silica, other multifunctional devices based on various nano-platforms were discovered (Soenen et al., 2011; Monnier et al., 2014; Chauhan et al., 2018; Hameed et al., 2018).

It is well-known that bulk silica is intensively used in food or cosmetic industry, indicating that it has low toxicity. FDA (US Food and Drug Administration) cataloged silica compound





as safe (ID Code: 14808-60-7)<sup>1</sup>. However, when a chemical compound is conceived like a nanomaterial, new limitations or safety risks arise, caused by their particles size (Lin et al., 2012). As an example, the interaction that appears between the nanoparticles and the cells, allowing their assimilation by the tumor cells, could result in unpredicted side effects in the healthy cells (Buzea et al., 2007).

For the mesoporous silica utilization in bio-approaches (Santos et al., 2015), the matrix degradation should be considered for the elucidation of the release kinetics, although for functionalized silica the parameter is harder to manage (Allen and Cullis, 2013; Sercombe et al., 2015).

The parameters and effects that must be monitored include, beside the degradability and the possibility to be eliminated (Figure 2), the size (Shang et al., 2014), shape (Huang et al., 2010; Li et al., 2015), pore volume (Li et al., 2018), and surface functionalization. Mesoporous silica with 100–200 nm nanoparticles dimensions are considered the optimal choice, preventing fast release (Li et al., 2012; Lin et al., 2012) and acute toxic effect (Napierska et al., 2009; Nishimori et al., 2009; Abbaraju, 2017), without aggregating on physiological fluids, blood capillaries and alveoli (McCarthy et al., 2012; Abbaraju, 2017).

Furthermore, the rod-like particles are considered more satisfactory than the spherical particles, as a consequence to easily achieve polyvalent interactions with the membranes (Huang et al., 2010; Meng et al., 2011; Lin et al., 2012).

The interest on mesoporous silica for drug delivery depends on various factors the most important being the scale of the silica nanoparticles interaction with living systems. Before reaching the market, all nanomedicines must be industrially transferred, obviously, after clinical translation. Regarding the first step, the industrial technology is related to the scaling up process, involving also the reproducibility and the total costs, resulting in the ordinary barriers for commercialization. For example, the mesoporous silica nanoparticles are obtained in the lab from milligrams to grams of product, but the large-scale batches production under Good Manufacturing Practices (GMP) conditions is a roadblock to their commercialization. Furthermore, reproducibility on their synthesis at small scale is relatively easy, but at the industrial scale is difficult. In this respect, the mesoporous silica clinical translation has been delayed, being blocked in the first milestone, whether or not the nanoparticles are reproducible and scalable, in terms of stability and high loading capacity. So far, researchers have not overlapped this milestone, although some advances were made. The next milestone to consider must be related to their potential toxicity and immunogenicity, which has been found to strongly depend on the surface functionalization. It has been demonstrated that mesoporous silica was perfectly biocompatible, in different animal models, in which toxicity has been discarded. However, until now, the mesoporous silica nanomaterials were not evaluated into any clinical trial, this being a delicate step, since many nanodrugs failed the clinical translation even before the clinical trials because of reiterative pitfalls.

Taking into account all the above-mentioned drawbacks and limitations, the integration of various features in a single entity could be considered a mirage. This review will highlight

<sup>1</sup><https://www.drugs.com/inactive/silicon-dioxide-colloidal-200.html> (accessed July 28, 2019).

also the evolution of hybrid inorganic-silica nanomaterials with various bio-applications.

Taking into account all aspects, to currently categorize the mesoporous silica nanomaterials as appropriate tools for bio-applications, they must act in accordance with modification requirements with respect of morphology and surface, resulting in the minimization of the immune reply and enhance tissue/cell recognition—targeting.

## SYNTHESIS OF MESOPOROUS SILICA NANOMATERIALS

At the beginning, scientists focused on improving the synthesis of mesoporous silica nanomaterials, trying to control their pore structure, size, and stability. **Table 1** summarizes some typical synthesis methods for the mesoporous silica nanomaterials.

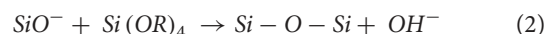
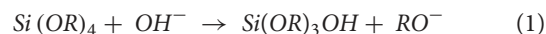
Typical scanning and transmission electron microscopy (SEM and TEM) images of mesoporous silica prepared by our group are presented in mesoporous **Figure 3** (Miricioiu et al., 2019).

Mesoporous silica nanoparticles can be used as host materials for transporting therapeutics medicaments or encapsulation of molecules due to their biocompatibility, high loading capacity, the capability to attach target ligands for specific cellular recognition, or the design of well-defined and tuneable porosity (Tang et al., 2012; Hao et al., 2016; Vazquez et al., 2017). In order to achieve these, the morphology of the silica must be considered as one of the most important factors. One common synthesis method for mesoporous silica is the use of structure directing agents (neutral or charged surfactants) (Yuan et al., 2011; Vazquez et al., 2017). Generally, mesoporous silica are obtained from a silica precursor (or sodium silicate tetraethylorthosilicate-TEOS) by incorporating a surfactant, in an alcoholic solution under basic conditions (Pang and Tang, 2005; Hodali et al., 2016). Some studies focused on the mechanism of silica nanospheres and nanorods formation, by modifying the surfactant concentration (Lelong et al., 2008; Wang et al., 2013) and sol-gel dilution (Chen and Wang, 2012). The interaction between the Si–O–Si/species and the surfactant was monitored, and the pore diameters, shape, order, and morphology were correlated with the surfactant properties (size, length, etc.) (Vazquez et al., 2017). Also, the mesoporous silica obtaining was studied in non-alcoholic medium (Lelong et al., 2008; Chen and Wang, 2012; Vazquez et al., 2017), but the spherical particles formation was restricted by the surfactant amount (under 1 wt.%). The specific surface area of the mesoporous silica materials was around 1,030–1,070 m<sup>2</sup>/g, with a pore volume of 0.81–0.85 cm<sup>3</sup>/g. The use of EtOH was considered, maintaining a fixed amount of CTAB (4.1 wt.%) and ordered spherical and rod-like particles was obtained (Wang et al., 2013). The mesoporous silica material presented a specific surface area of 1,500 m<sup>2</sup>/g and a pore volume of 0.86 cm<sup>3</sup>/g. As it can be noticed, the dilution of the sol-gel results in the modification of the specific surface area and in the transformations of the particles morphology (from spherical to rod-like), highlighting that silica mesoporosity and morphology are related to the micelles formation and ordering.

A general synthetic route follows some typical steps: a silica source (tetraethyl orthosilicate-TEOS or sodium orthosilicate-Na<sub>2</sub>SiO<sub>6</sub>) is mixed with a surfactant, then, a hydroxide (NH<sub>4</sub>OH or NaOH) is added, allowing that the silicate is hydrolyzed, surrounding the spherical micelles; finally, in order to silicate micelles self-assemble into cylinders, the mixture must be subjected to hydrothermal treatment (Lin et al., 2012). Surfactant can be removed by calcination, solvent extraction, or dialysis. First mesoporous silica with nanoparticles adequate for bio-application were obtained in 2001 (Fowler et al., 2001; Lin et al., 2012). Afterwards, many investigations adopted the introduction of a co-solvent or another surfactant (Lin et al., 2012) for particles growth suppression, in order to get mesoporous silica nanomaterials with controlled size—**Table 1** (Cai et al., 2001; Fowler et al., 2001; Lin and Tsai, 2003; Han and Ying, 2005; Berggren and Palmqvist, 2008; Sutewong et al., 2011).

The addition of surfactant during the synthesis generates a structure with many small pores (mesoporous structure) between 2 and 50 nm, according to IUPAC notation (Assefa et al., 2016). Recently, templates as chitosan were used to inherent amino and hydroxyl functional groups, intermediating future functionalization of the mesoporous silica (Lalchhinguipui et al., 2017).

In order to produce silica nanomaterials with size suitable for bio-applications, a catalyzed sol–gel process has been employed. This process uses the organo-silane precursors which, by hydrolysis (1) and condensation (2), generating a new state (sol) (Brinker and Scherer, 1990; Mai and Meng, 2013):

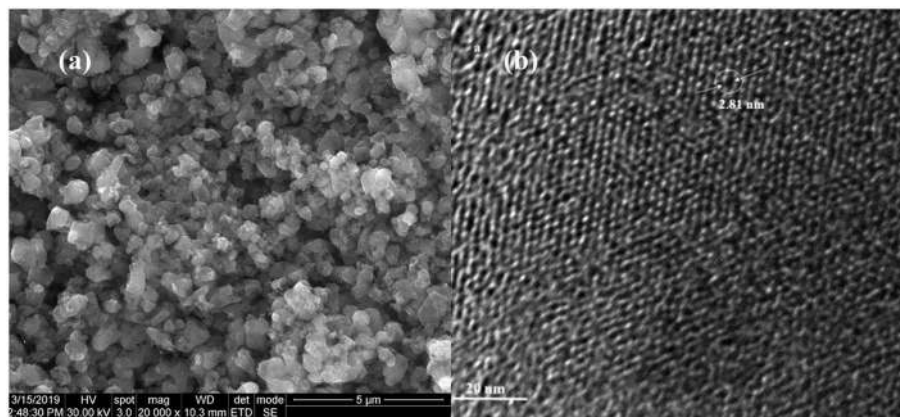


For example, monodispersed nanosilica with particles size between 50 and 2,000 nm was obtained by Stober process, using the hydrolysis of tetraethylorthosilicate, catalyzed by ammonia, in an aqueous alcohol solution (Stober et al., 1968; Yanagisawa et al., 1990). The first *sanvicens* mesoporous silica nanomaterials were synthesized for catalytic applications (Yanagisawa et al., 1990; Kresge et al., 1992). Later, sub-micrometer-scaled MCM-41 particles were prepared by a modified Stober process (Grun et al., 1997) and MCM-41 with 100 nm was synthesized by means of a diluted surfactant solution (Cai et al., 2001). Nano-silica with particle diameter under 50 nm were synthesized by applying two surfactants or dialysis (Suzuki et al., 2004; Li et al., 2012).

MCM-41 silica was typically obtained via a surfactant (hexadecyltrimethylammonium bromide) dispersed in ultrapure water; the mixture is stirred for several hours in ambient conditions; then the silica source, for example sodium silicate is added, stirring continuously the mixture. After that, the mineralizer, tetramethyl ammonium hydroxide is added, stirring the mixture another 30 min (Oshima et al., 2006). Then, the pH is adjusted to 10.5, checking it after 15 min. The mixture is agitated for 24 h and then it is subjected to hydrothermal treatment, by introduction into an autoclave 3–5 days, at 100–120°C. The resulting mixture is filtered under vacuum, washed with water and dried (Miricioiu et al., 2019). After aging,

**TABLE 1** | An overview of some synthesis methods for mesoporous silica nanomaterials.

Surfactant	Silica source	Size control method	Particle size (nm)	Pore structure	Surfactant removal	References
Hexadecyltrimethylmonium bromide	Tetraethyl orthosilicate	Water dilution and neutralization	60–100	Ordered 2D hexagonal	Calcination	Fowler et al., 2001
Hexadecyltrimethylmonium bromide	Tetraethyl orthosilicate	Dilution	100–2,500	Ordered 2D hexagonal	Calcination	Cai et al., 2001
C <sub>n</sub> TAMX alkyltrimethyl ammonium halide (n = 14–18; X = Br or Cl)	Sodium silicate	Low concentration of surfactant-silica source	30–70	Disordered	Calcination	Lin and Tsai, 2003
Pluronic P65, P123, F108, F127	Tetraethyl orthosilicate	Surfactant suppresses particles growth	100–300	Ordered 3D cubic	Calcination	Han and Ying, 2005
Pluronic P123	Tetraethyl orthosilicate	Water and salt addition	50–300	Ordered 2D hexagonal	Calcination	Berggren and Palmqvist, 2008
Hexadecyltrimethylmonium bromide	Tetraethyl orthosilicate and (3-aminopropyl) triethoxysilane	Dye incorporation and pore expander addition	100–220	Ordered 3D cubic	Ethanollic acid extraction	Sutewong et al., 2011

**FIGURE 3** | Typical scanning electron (a) and transmission electron (b) microscopy for MCM-41 mesoporous nanosilica.

the resulting nanoparticles are calcined at 550–600°C in order to eliminate the excess of hexadecyltrimethylmonium bromide and to weaken the interactions between the surfactant and the formed silica (Li et al., 2012). Scanning and transmission electron microscopy certified the hexagonal arrangement after the hexadecyltrimethylmonium bromide removal (Figure 3; Miricioiu et al., 2019).

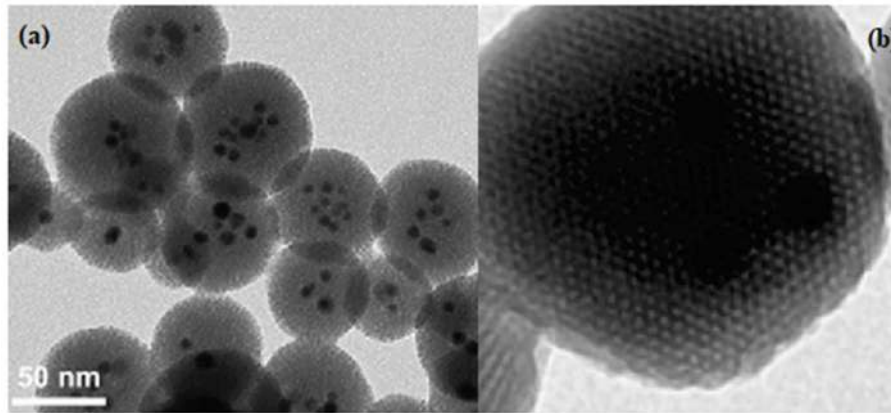
## FUNCTIONALIZATION OF THE MESOPOROUS SILICA NANOMATERIALS

For the silica nanomaterials extension in the bio-domain, physical and chemical surface modifications have been applied. In this manner, the biocompatibility can be enhanced, the non-specific adsorption can be prevented and functional groups for further biomolecule conjugation purposes can be provided. The

most common surface modification includes layer by layer self-assembly (LSA) and chemical surface functionalization (Jafari et al., 2019).

The mesoporous silica nanomaterials can be functionalized by incorporation during the synthesis of metal or metal oxide nanocrystals (Figures 4a,b).

A heterogeneous mixture formed by the surfactant-coated metal nanocrystals in an organic solvent must be added to a solution of a surfactant (such as hexadecyltrimethylmonium bromide), in order to obtain a metal-functionalized silica (Li et al., 2012). Then, a silicate source is added to the mixture to promote the condensation reaction, thus, gold, silver and iron oxide being embedded into the mesoporous silica (Coti et al., 2009; Thomas et al., 2010). This functionalized systems can possess various bio-activities, for example antimicrobial, assured by the dissolved metallic ions, plasmonic, or magnetic characteristics (Li et al., 2012).



**FIGURE 4** | Typical TEM image for (a) mixed iron-oxide and silver mesoporous silica and (b) Zn embedded in mesoporous silica.

To evaluate the substantial effect of different functionalization methods, research have been achieved to design colloidal core-shell mesoporous silica with various types of linear PEG (polyethylene glycol) modifications (Cauda et al., 2010). The silica functionalization can decrease the degradation rate comparing with the un-functionalized ones, the explication being the existence of the PEG matrix on the nanomaterial surface. PEG is hydrophilic, preventing in this manner the proteins adsorption and it reduces unwanted interactions of the physiological environment with the nanosilica (Yang et al., 2019).

Other research highlighted the silica surface functionalization with hydroxyl, carboxyl and PEG groups (noted OH-SiNPs, COOH-SiNPs, and PEG-SiNPs) and their bio-distribution and urinary excretion were studied (Figures 5A,B; He et al., 2008).

*In vivo* optical data from the urinary bladder showed that the nanomaterials were partially eliminated through renal route, highlighting that these modifications are independent on the renal elimination (Figure 5C; Yang et al., 2019). Nevertheless, PEG derivate manifested longer blood circulation and lower liver uptake compared to the hydroxyl and carboxyl derivatives.

Various research investigated the SBA-15 silica functionalization. For studying the effect of surface functionalization upon deterioration behavior, Kim et al. explored the biodegradation of functionalized SBA-15, modified with hydroxyl, amine and carboxyl moieties on the surface (Choi et al., 2015; Yang et al., 2019). The carboxyl functionalized silica had the lowest degradation percentage. These studies indicated that the SBA-15 surface functionalization results in a reduction of the degradation rate then the neat silica, highlighting that the functionalization could affect the silica shell corrosion by connecting with the cations from the biological media for reducing the SBA-15 clearance rate (Choi et al., 2015; Yang et al., 2019).

A key factor that enables silica nanomaterials to be used in bio-applications is the capability to capture various loads in the pores channels, thus protecting the active compounds from enzymatic degradation (Li et al., 2012). The mesoporous silica nanoparticles are usually charged by immersion in the active compound solution, the therapeutic being assimilated through adsorption. When silica surface is functionalized,

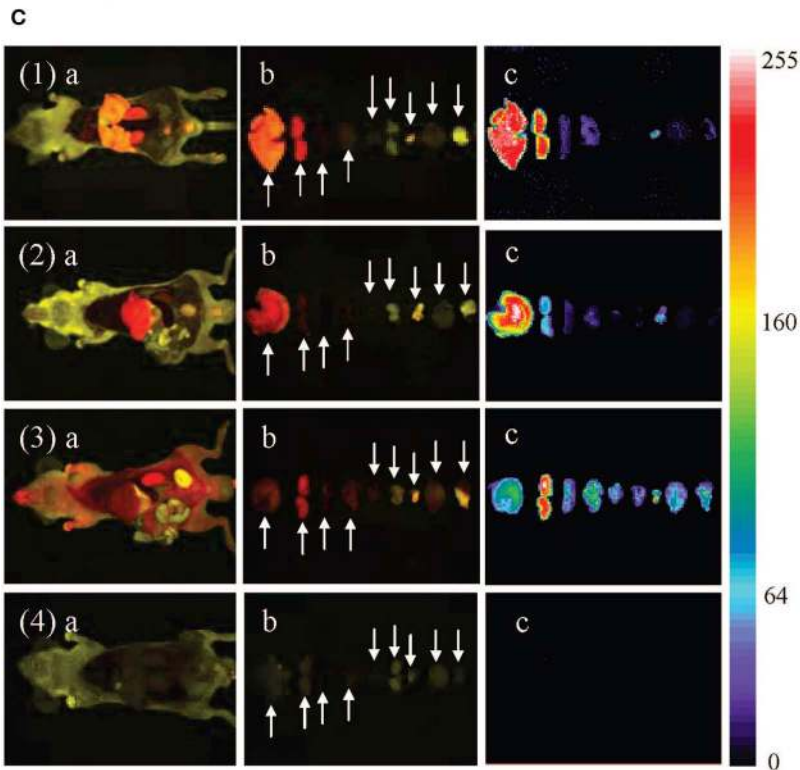
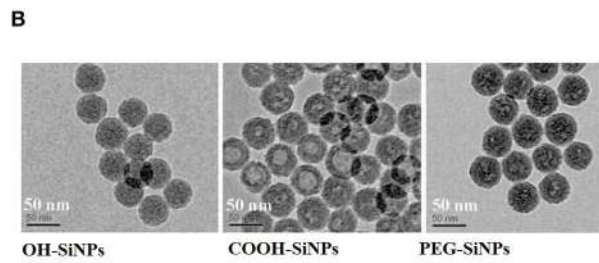
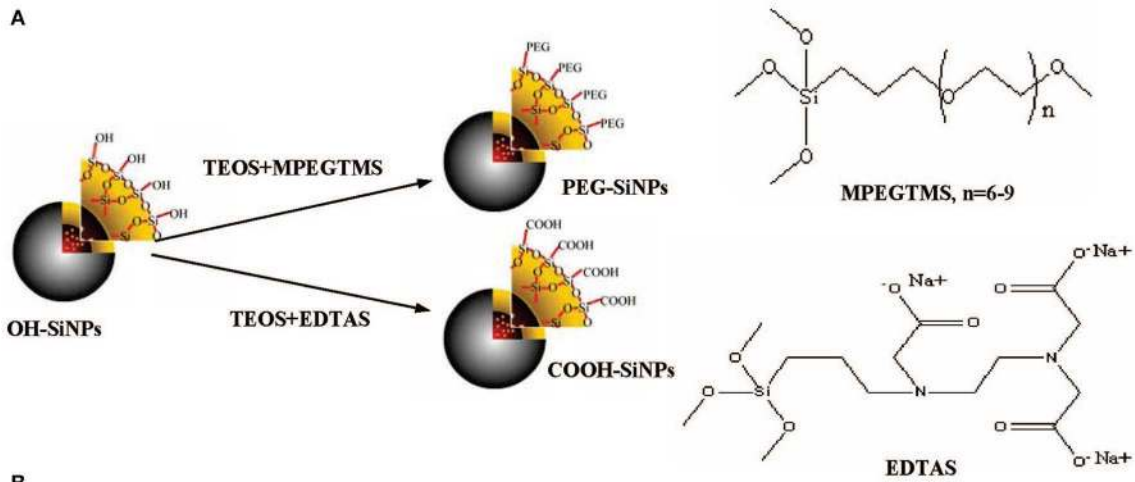
the cargo is able to be controllable released at the targeted damaged tissue, no premature release in the bloodstream being observed, reducing any secondary effect and increasing the therapeutic efficiency (Li et al., 2012). For example, Niculescu et al. reported SBA-15 mesoporous silica functionalized with amino groups from organic amines (aminopropyl triethoxysilane) for bio-active coordinative complex delivery (Niculescu et al., 2018). It was observed a linkage between the functional groups from the coordination compound and the amino groups from the silica surface, resulting an improvement of the hydrophobic interaction with the hydrophobic active principle (Niculescu et al., 2018). Once the degree of silylation is decreased by amination, the drug release rate will be improved.

## BIOCOMPATIBILITY

In the context of bio-applications, mesoporous silica nanomaterials are generally considered biocompatible, with minimal non-specific or adverse effects. However, there are several factors that affect the silica biocompatibility, such as individual size, shape, and surface chemistry, until this moment the mesoporous silica biocompatibility remaining inconclusive (Hudson et al., 2008; Tang et al., 2012). This review take into account the current advances on how particles shape, size and surface properties influence the interaction with living cells (Jafari et al., 2019).

The biocompatibility, bio-distribution and clearance are influenced by the mesoporous silica nanomaterials morphology. For example, short-rod mesoporous silica is distributed predominantly at the liver level, whereas long-rod silica is caught in the spleen and manifest a reduced elimination rate (Huang et al., 2011; Jafari et al., 2019). The particles shape also influences cellular uptake, *in vitro* research reporting that the shape is independent of the endocytosis rates and dependent on endocytotic rate (Trewyn et al., 2008; Jafari et al., 2019).

Particles dimensions can influence the biological parameters (distribution, duration of blood circulation, or elimination rate) (Jafari et al., 2019). When the nanoparticles are intravenously delivered, they are predominantly directed to the liver and



**FIGURE 5** | Illustration **(A)** and TEM images **(B)** of three silica surface functionalized nanomaterials. **(C)** *Ex vivo* imaging of mice after intravenous injection, with various organs throughout necropsy after 4.5 h, for treated mice (1) OH-SiNPs, (2) COOH-SiNPs; (3) PEG-SiNPs and untreated mice (4). Arrows represent from left to right: liver, kidney, spleen, lung, heart, spermary, bladder, brain, and muscle. Reproduced with permission He et al. (2008) Copyright 2008, American Chemical Society.

spleen (Maleki and Hamidi, 2016). The silica nanoparticles with smaller size have a longer blood circulation lifetime (He et al., 2011). The mesoporous silica nanoparticles elimination by urine increases with the particles size, affecting the degradation rate and the biocompatibility. *In vitro* studies showed some toxicity for spherical 1,220 nm nanoparticles at concentration levels higher than 25 mg/mL (He et al., 2009).

Furthermore, the mesoporous silica nanomaterials biocompatibility may be influenced by the surface properties. Cationic charges on the surface may produce considerable immune reaction and cytotoxicity in contrast with the neutral and anion counterparts (Nel et al., 2009; Verma and Stellacci, 2010; Jafari et al., 2019), but they are favorable for trans-vascular transport in tumors. A negative zeta potential is considered related to the serum opsonin. The mesoporous silica biocompatibility is affected by the silanol groups at the outer layer, they negatively interacting with the biological molecules and destroying their structure (Slowing et al., 2009). Therefore, surface functionalization is essential for altering surface reactivity, in order to enhance the biocompatibility.

## BIO-APPLICATIONS

### Drug Delivery

Mesoporous silica nanomaterials present unique properties that qualify them as ideal nano-carriers for hosting, protecting and transporting drugs to the target site. The incorporation of targeting agents at the mesoporous silica surface is feasible for conducting them to the damaged tissue, growing the specificity and reducing unwanted secondary effects (Lin et al., 2012). Furthermore, multifunctional mesoporous silica nanomaterials can be design so that they possess synergistic therapeutic effects against diseased tissues. Most of the investigations on the mesoporous silica for drug delivery has been dedicated to cancer therapy.

The first study on silica type-MCM-41 for ibuprofen controlled release was achieved by the group of Vallet-Regi et al. (2001). The ibuprofen liberation profile highlighted a divergent behavior, which depends on the way that the active substance is loaded in the silica, but it is independent on the pore size. The *in vitro* experiments were achieved within constant state and the mixture was not stirred while the drug was released, limiting the diffusion at the particles surface (Wang, 2009). Later on, other study focused on the effect of pores size from the MCM-41 on the ibuprofen release rate, revealing that, in a simulating body fluid (SBF) solution, it is decreasing direct proportional with the pores size decreasing in the domain of 2.5–3.6 nm (Horcajada et al., 2004).

Another important mesoporous material for therapeutics delivery systems is MCM-48 silica, recently attracting interest due to its matrix containing unique penetrating bi-continuous channels, which can be used when easy molecule accessibility and rapid transport is required. MCM-48 was investigated as carrier for ibuprofen and erythromycin (Izquierdo-Barba et al., 2005), the therapeutics release rate decreasing with the pores diameters and the surface chemical modification (Izquierdo-Barba et al., 2005).

Several investigations have been reported for drug delivery based on organic modified mesoporous materials. It is generally accepted that the functionalization influences the adsorption and delivery. MCM-41-based materials were modified with organic aminopropyl groups for the control of the ibuprofen release, the functionalization being decisive for the active compound adsorption and release (Munoz et al., 2003; Zeng et al., 2005).

From the same class of mesoporous silica, SBA-15 with large and controlled pore size has a high ordered hexagonal matrix (Zhao et al., 1998). The SBA-15 has pores with an average diameter around 6 nm, larger than the MCM-41 pores diameter, which is around 3 nm (Niculescu et al., 2011). Due to this characteristic, it is generally assumed that SBA-15 will present less limitation for the release of bulk molecules. Calcined SBA-15 was tested for the antibiotic amoxicillin delivery (Vallet-Regi et al., 2004), proven that the drug quantity incorporated within the silica network depends on the solvent, pH, and amoxicillin concentration (Zhang et al., 2018). In the pure SBA-15, the Si-OH groups exist only at the surface, forming weak hydrogen bonds with the active compound; this is the reason why silica is not strong enough to retain the drug and allow it to be delivered in a sustained manner (Hashemikia et al., 2015; Zhang et al., 2018). In order to surpass this milestone, functional groups were introduced on the surface of SBA-15 (Doadrio et al., 2006).

SBA-15 nanomaterials were post- and one-pot reaction modified with amino groups for ibuprofen (IBU) and bovine serum albumin (BSA) delivery (Song et al., 2005). Results showed that the drugs assimilation and delivery were extremely influenced by the SBA-15 silica surface properties. The ibuprofen delivery from the post-synthesis functionalized SBA-15 was efficiently controlled, because of the ionic interaction established between the ibuprofen carboxylic groups and the amino groups from silica surface. Recently, SBA-16 mesoporous silica was used for immobilization and release of two antiseptic organic complexes with Zn was tested in deionized water, not in a simulated body fluid (Zelenak et al., 2005). The complexes were liberated after 10 h. Nevertheless, traces of the active compounds were found in the silica after 80 h, as a consequence of the vigorous immobilization in the silica matrix.

MSU-type mesoporous silica has also been studied for drug delivery, such as penta-peptide drug, which is instantaneously delivered after the solid was washed with dimethylformamide (DMF) (Tourne-Peteilh et al., 2003; Wang, 2009). Ibuprofen and antipyrine can be delivered by carbonized mesoporous silicon microparticles, but no release profile was reported (Lehto et al., 2005).

### Cell Imaging and Photosensitizer Carrier

The silica nanoparticles can be used in imaging, dye-doped materials being synthesized by Stöber or reverse micro-emulsion method. Monodispersed solid nanosilica with particle diameter between 50 nm and 2  $\mu$ m was obtained by Stöber method, which is a simple and efficient approach. The first well-dispersed colloidal silica spheres including fluorophores or dyes were



synthesized by Vanblaaderen and Vrij (1992) and Abbaraju (2017). This study was extended for obtaining fluorescent core-shell nanosilica particles (C dots), which are water-soluble and non-toxic and having particle diameters between 20 and 30 nm (Ow et al., 2005; Abbaraju, 2017). These dots constitute biological exploration devices with increased bio-stability, dye quantum effectiveness and diminished energy transfer reaction, caused by the limited rotational motility of the dye captured in the C dots nucleus, assuring the preservation against a dissolution medium effect or molecular quenchers (Burns et al., 2009; Abbaraju, 2017). FDA approved the use of the C dots in human clinical trial in 2011, the study showing that the nanoparticles were harmless in human use, without any traces after renal elimination (Abbaraju, 2017).

The reverse micro-emulsion method for obtaining dye-doped nanosilica particles involves the use of water, surfactant and oil (Jin et al., 2011). The silica precursor's hydrolysis, condensation, and the formation of dye trapped nanoparticles occur at the surfactant-oil interface, to form fluorescent nanoparticles. By using this method, monodispersed silica nanoparticles with the diameters of 30–60 nm were obtained (Santra et al., 2001a,b; Bagwe et al., 2004; Sanvicens and Marco, 2008; Yoo and Pak, 2013). In 2004, a modified micro-emulsion method was reported for the incorporation of organic dye into silica nanoparticles (Zhao et al., 2004). The same approach was applied for obtaining hybrid silica nanoparticles doped with Pb-Se quantum dots for cell imaging, their toxicity being lowered by individual or multiple covering of the silica (Tan et al., 2007; Abbaraju, 2017).

Moreover, hollow nanosilica containing vast cavity and mesopores were used for optical magnetic resonance imaging, positron emission tomography (PET) (Suschek et al., 2002; Abbaraju, 2017) and ultrasound imaging (Shi et al., 2013).

Photodynamic therapy is a photosensitizer-based tumor ablative treatment, followed by the tumor local radiation at a specific wavelength in order to activate the photosensitizer (Suschek et al., 2002; Abbaraju, 2017). After activation, it shifts the energy to molecular oxygen, producing reactive oxygen entities with cytotoxic effect, which are able to oxidize the target cellular macromolecule, resulting in the tumor cell removal (Figure 6; Lucky et al., 2015).

Mesoporous silica nanomaterials have also been employed as vehicles for fluorescent agents, being optically transparent due to their nanoscale particle size, not disturbing the emission of fluorescent agents. Taking into account that quantum dots can be easily oxidized, exhibiting fluorescence, PEGylated liposome-coated quantum dots-mesoporous silica were developed the oxidation prevention and the dispersion stability improvement (Pan et al., 2011; Wang et al., 2015). For example, the *in vitro* study of cadmium ions as quantum dots highlighted that the liposome-modified mesoporous silica prevented the quantum dots degradation (Pan et al., 2011).

An effective biomedical tool is considered the magnetic resonance imaging (MRI), providing the capacity to non-invasively get anatomic and functional data with high resolution (Wang et al., 2015). Mesoporous silica nanomaterials-based magnetic resonance contrast agents exhibit an increased sensitivity due to their high specific surface, providing increased payloads of the active magnetic centers (Wartenberg et al., 2013; Cha and Kim, 2019). Moreover, silica mesoporous structure provides easy access into the magnetic center. Mesoporous silica nanomaterials functionalized with targeted ligands may be efficiently conducted to damaged tissue for diagnostic goals, the accumulation of these nanomaterials-based magnetic resonance contrast agents at the selected site conferring an augmented imaging susceptibility (Wang et al., 2015).

Mesoporous silica nanoparticles are also used for application in photodynamic therapy, being vectors due to their flexible synthesis, porosity and the matrix capacity to absorb the light (Abbaraju, 2017). For example, there were prepared organically modified nanosilica particles for the retention of 2-devinyl-2-(1-hexyloxyethyl)-pyropheophorbide (HPPH), which is a photosensitizer used in phase I/II of clinical trials for treating esophageal cancer (Roy et al., 2003; Abbaraju, 2017). The entrapment of the photosensitizer into mesoporous silica nanoparticles can conduct to the discharge from the nanocarrier, inducing reduced efficiency. Some mesoporous silica nanomaterials were obtained for combined photodynamic and photothermal therapy, by using the release of carboxy aluminum phthalocyanine with small Pb nanosheets (Zhao et al., 2014; Abbaraju, 2017). The mesoporous silica nanomaterials covalently bond the photosensitizer, while the Pb electrostatically covered

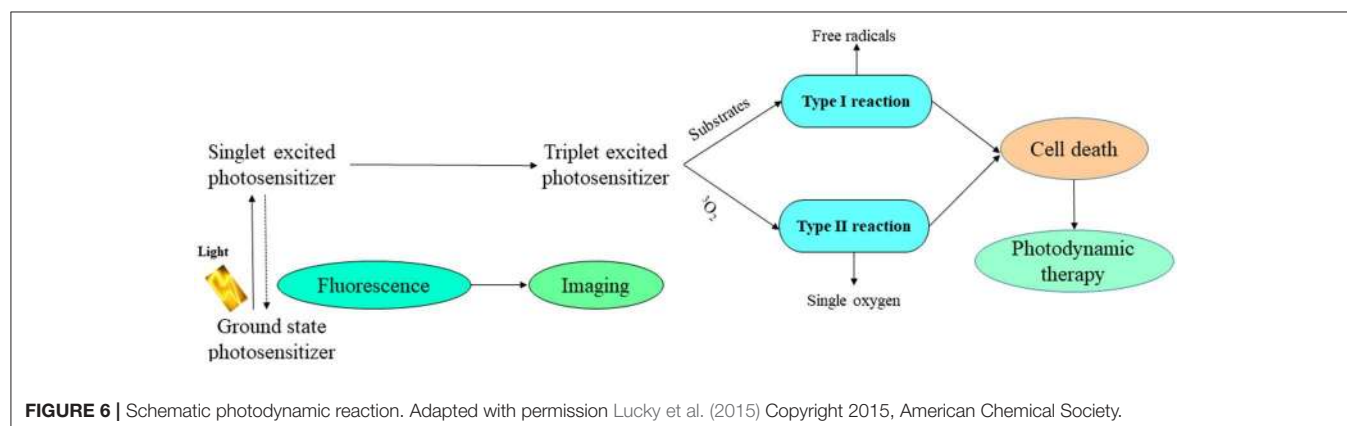


FIGURE 6 | Schematic photodynamic reaction. Adapted with permission Lucky et al. (2015) Copyright 2015, American Chemical Society.

the silica surface. The HeLa-type cervical cancer cells viability decreased with 65% after the administration of functional nanocomposites, the effect being significant than the individual treatment (Abbaraju, 2017).

## Mesoporous Silica Nanomaterials in Vaccines

The actual challenge in vaccines includes the induction of strong and safely immune-protective response in the host at low cost. Mesoporous silica nanomaterials can be used as an antigen carrier due to antigen preservation and its delivery to presenting cells (Kapczynski et al., 2012; Abbaraju, 2017).

For example, SBA-15-type nanomaterial possesses enhanced immunogenicity and immune reaction than  $\text{Al}(\text{OH})_3$ , *in vitro* macrophages studies showing that silica manifested increased phagocyte intake and minimal interaction with the cells (Carvalho et al., 2010; Abbaraju, 2017). Furthermore, the highest concentration of SBA-15 also conducted to a significant increase of the cells number, creating interleukin(IL)-4 and interleukin(IL)-13 and, generating a heterogeneous reaction of both Th1-type and Th2-type cytokines (Abbaraju, 2017).

Mesoporous silica rods were tested in adjusting the immune cells and potential application as a vaccine matrix to induce adaptive immune reaction (Kim et al., 2015; Abbaraju, 2017). *In vivo* tests showed that mice immunized with full mesoporous silica rods vaccine manifested important growth of  $\text{Thy 1.2}^+$  leukemic cells, inducing increased expression of the Peripheral blood  $\text{CD4}^+$   $\text{CXCR5}^+$  T helper cell clonal and T follicular helper cells differentiation (Kim et al., 2015). The silica surface modification effect upon immune cell activation was studied (Abbaraju, 2017). The mesoporous silica nanomaterials were modified with poly(ethylene glycol) (PEG) and poly(ethylene glycol) (PEG)/arginine-glycine-aspartic (RGD) and they were investigated in the immune cell adhesion and infiltration, the PEG derivate inducing higher CD86 expression than the RGD derivate (Abbaraju, 2017). Also, the PEG-RGD derivate exhibited lower inflammatory effect than the PEG-one.

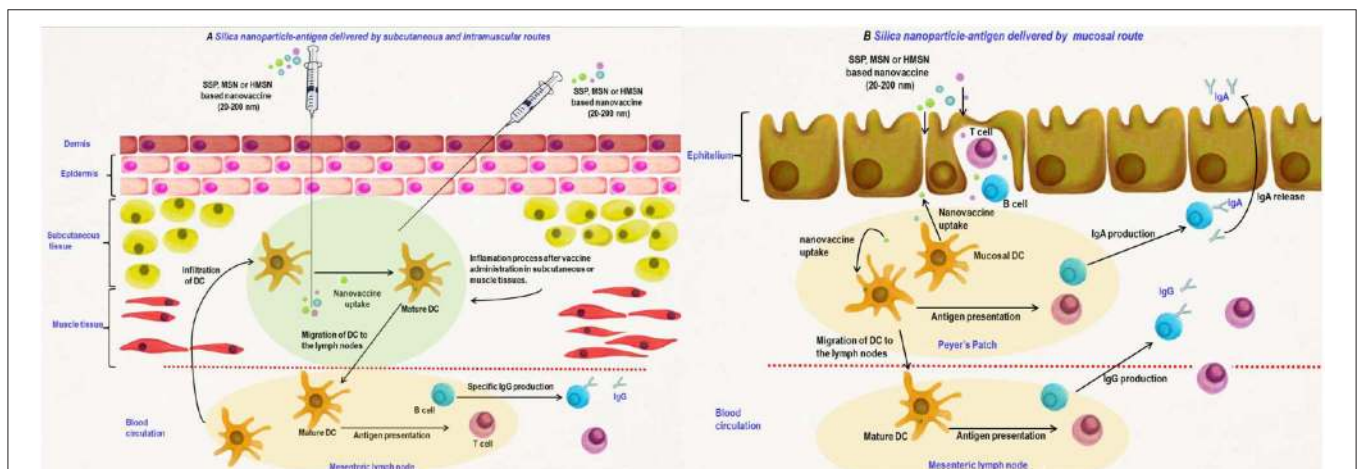
However, the impact of all the crucial factors in adjusting the immune reaction was not completely elucidated. The effect of nanomaterials pores and particles size on immunological properties was studied by orally administration to mice, using Bovine serum albumin as model adjuvant (Wang et al., 2012). Three types of nanosilica particles with various particles diameters {S1, [S2 and 1-2(SBA-15)]} were applied, the Immunoglobulin G antibody from the plasma after oral administration of bovine serum albumin-loaded S1, S2, SBA-15 being in the sequence  $\text{SBA-15} < \text{S2} < \text{S1}$  (Abbaraju, 2017).

Also, the influence of particle size on targeting dendritic cells was studied, demonstrating that the particles smaller than 20–30 nm in diameter can straight get to dendritic cell. **Figure 7** presents the silica nanoparticles delivery into lymph nodes. Nevertheless, particles with diameters higher than 20 nm can be phagocytosed and the dendritic cells uptake is also presented (Navarro-Tovar et al., 2016).

On the other hand, silica nanomaterials were also used for DNA vaccines delivery, relying on the transitory manner of the intended antigen in the host cells (Navarro-Tovar et al., 2016). Silica nanomaterials-DNA exhibited a clear enhancement in the immunogenicity, in contrast with DNA at a reduced magnitude as against the conventional vaccine. Silica-based vaccine also manifested increased proliferative responses, suggesting that silica nanomaterials can be considered as good delivery systems for the DNA vaccines, stimulating cellular and humoral reactions. This perspective for the distribution by mucosal routes constitutes an important target, due to the advantages of mucosal immunization such as easy administration and immune profiles.

## CONCLUSIONS

Various types of nanosystems for cancer-targeted imaging and therapy were developed in the last decade. Among them, silica-based nanomaterials have been extensively synthesized, due to their non-toxic nature and facile chemistry for surface functionalization. The state-of-the-art reflected that



**FIGURE 7** | Silica nanomaterials-based vaccines delivery by parenteral (A) and mucosal (B) routes. Adapted with permission Navarro-Tovar et al. (2016) Copyright 2016, Taylor & Francis.

materials based on nanosilica constitute fascinating media for new vaccines design, insuring the antigen conjugation (Cassano et al., 2017) and cellular adaptive immune responses. Mesoporous silica nanoparticles have been used in clinical trials for diagnostic purposes and drug delivery. The toxicity of these nanomaterials should be further investigated and evaluated at the clinical and pre-clinical levels. Concluding, the utilization of silica nanoparticles is significantly influencing the medicine domain, by obtaining new compounds to fight epidemiologic diseases.

This review drew special attention the main progress in drug delivery and bio-applications (Wang et al., 2015) of mesoporous silica nanomaterials. Mesoporous silica nanomaterials have attractive characteristics, such as a large specific surface, uniform and tuneable pores, increased pore volume, and decreased mass density (Kumar et al., 2018). They were intensively studied for drug delivery since 2000, to provide the improvement of the drug loading capacity and *in vivo* targeting efficiency, decreasing the unwanted effects on healthy organs. Due to their versatile mesoporous structure and porosity, they possess important advantages, for example, as drug delivery system, the release of the cargo is well controlled. Also, magnetic and luminescent mesoporous silica nanomaterials provide the simultaneous bioimaging and drug delivery.

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## AUTHOR CONTRIBUTIONS

V-CN conceived and designed the study, contributed to the collection of data, performed the data interpretation, and the manuscript writing.

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**Conflict of Interest:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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