



# Tuning mesoporous silica dissolution in physiological environments: a review

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## ABSTRACT

Matrix degradation has a major impact on the release kinetics of drug delivery systems. Regarding ordered mesoporous silica materials for biomedical applications, their dissolution is an important parameter that should be taken into consideration. In this paper, we review the main factors that govern the mesoporous silica dissolution in physiological environments. We also provide the necessary knowledge to researchers in the area for tuning the dissolution rate of those matrices, so the degradation could be controlled and the material behaviour optimised.

## Introduction

Ordered mesoporous silica materials (OMS) have received great attention by the biomedical scientific community since they were proposed for the first time as drug delivery systems by the research group headed by Vallet-Regí et al. [1]. Their unique structural and textural properties, such as tuneable pore structure, large surface area and pore volume, controllable pore diameter and morphology, and functionalisable surface, make OMS excellent candidates to be applied as drug delivery devices in different biomedical applications [2–5].

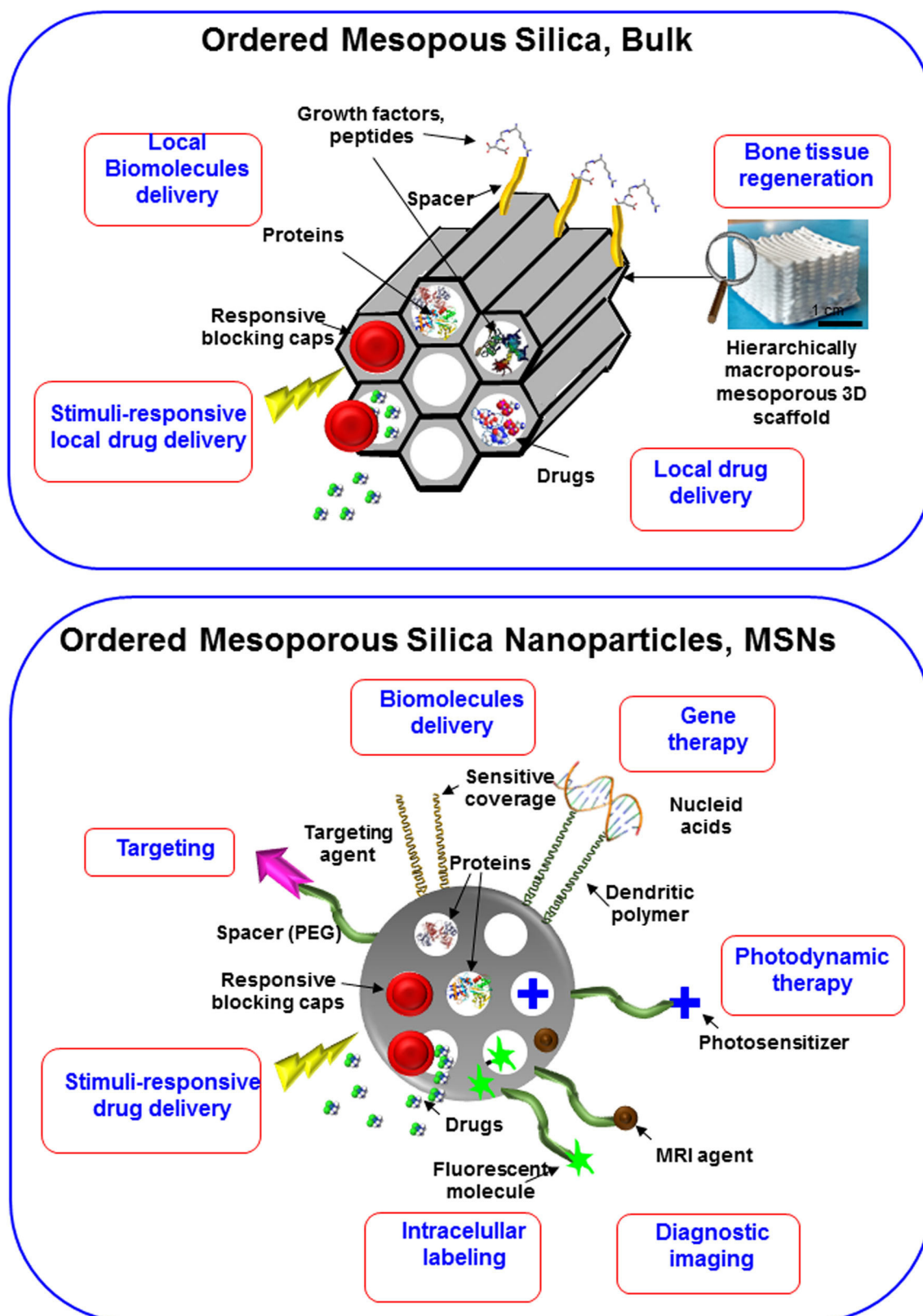
Initially, OMS were purposed as bioceramics for local drug delivery and bone tissue regenerations due to their surface characteristics, such as biocompatibility and bioactivity, and their capability to load and release in a controlled fashion different therapeutic

cargoes for the treatment of diverse pathologies (Fig. 1, top) [6–8]. The most widely employed OMS explored for such applications were MCM-41, SBA-15 and MCM-48.

OMS can be prepared with different morphologies, such as bulk [9, 10], fibres [11, 12], rods [13, 14], films [15, 16], monoliths [17, 18], spheres [19]. Among them, mesoporous silica nanoparticles (MSNs), with sizes in the 20–300 nm range, have found many applications in nanomedicine (Fig. 1, bottom), underlining their systemic administration as nanocarriers for diagnosis and treatment of complex diseases such as cancer [20–25].

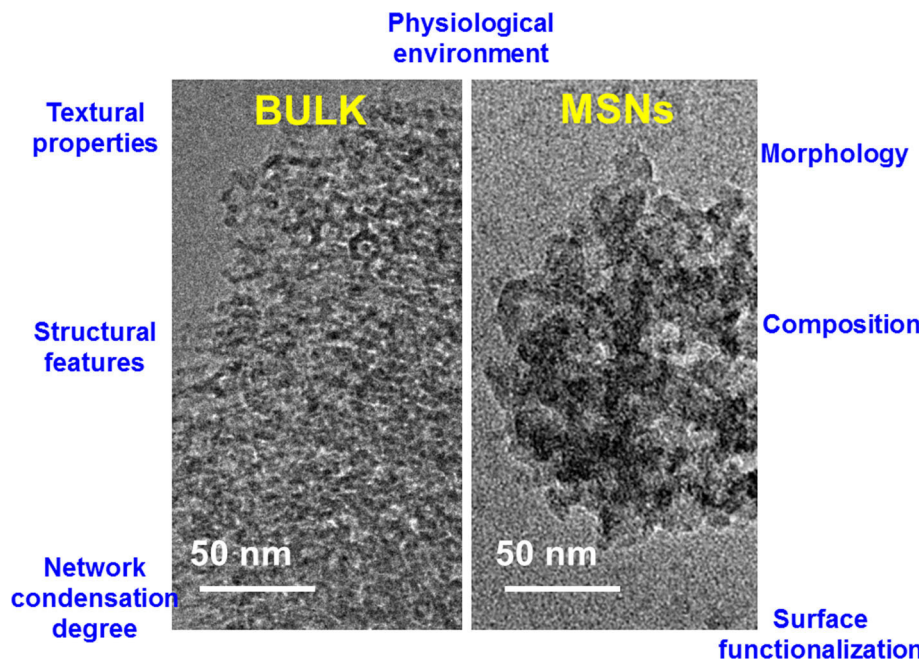
The degradability of different drug delivery devices is a key parameter for their successful translation to a clinical scenario. In this sense, dissolution has profound implications in the mechanical properties of materials used for bone filling. Most importantly,

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**Figure 1** Schematic depiction of the most relevant applications of OMS: in bulk, highlighting local drug delivery and bone tissue regeneration purposes (*top*); and as MSNs incorporating different moieties according to the foreseen use (*bottom*).

**Figure 2** Main factors that govern silica dissolution in physiological fluids from OMS both in bulk and as MSNs.



the degradation of the drug delivery matrix will modify its drug release kinetics, as well as it can be deeply important for its toxicity [26]. Despite all of the extensive research that has been carried out on OMS for biomedical applications, the degradation of these materials has been much less studied. In fact, in most of the recent research articles regarding OMS for biomedical application, little or no attention has been paid to the stability of those materials in the biological environment in which they would carry out their function. This review intends to provide some insight into the main design characteristics that researchers should take into account to modulate OMS stability for specific biomedical applications. Some of the main factors that govern the dissolution rate of mesoporous silica and that will be addressed in this review can be found in Fig. 2.

## Degradation of ordered mesoporous silica

OMS are composed of polycondensed silica tetrahedrons ( $\text{SiO}_4$ ) interconnected by siloxane bonds ( $-\text{Si}-\text{O}-\text{Si}-$ ) exhibiting different condensation degree and therefore displaying reactive silanol groups ( $-\text{SiOH}$ ) on the surface. This silica network is characterised by an amorphous structure at atomic level in a similar way to conventional sol-gel glasses [27]. OMS are structurally unique, exhibiting order at the mesoscopic scale (2–50 nm) and disorder at the atomic

scale. Thus, the pore channels formed within the materials are separated by amorphous silica walls and arranged periodically on lattices [28].

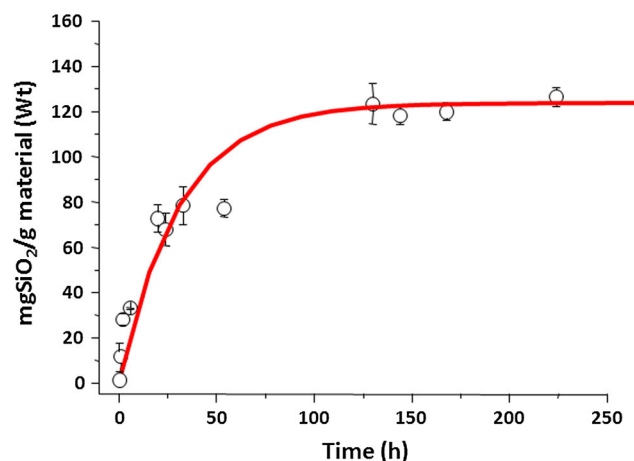
Several authors have dedicated a great effort to investigate the dissolution of sol-gel derived silica matrices in physiological fluids [29–34]. It was found that the dissolution of these sol-gel silica matrices exhibits several steps, mainly characterised by an initial surface burst erosion followed by a slow bulk degradation. It is postulated that the rates of bulk degradation depend on the physical-chemical characteristics of the condensed silica network [35].

As a representative example of silica dissolution profile, that of SBA-15 material under physiological conditions is displayed in Fig. 3. In this particular case, the curve is characterised by a relatively fast dissolution rate up to ca. 5 days followed by plateau in which the amount of silica released to the medium is minimal.

## Key factors that govern silica degradation from ordered mesoporous materials in bulk

OMS in bulk have been mainly proposed for bone tissue repair applications due to their biocompatible and bioactive behaviour in physiological environment and above all owing their capability to act as local drug delivery devices. For this reason, it becomes essential to investigate the degradation process of these matrices in physiological media. For





**Figure 3** Silica dissolution profile from SBA-15 under physiological conditions (phosphate buffer saline, PBS) showing an initial surface burst release followed by a slow matrix degradation.

a better understanding of the evolution of the surface of OMS in bulk during the degradation process, an exhaustive study by high-resolution transmission electron microscopy (TEM) has been reported elsewhere using SBA-15 (Fig. 4) [33]. The obtained results reveal that during the initial burst effect up to 5 days there is a decrease in the mesopore wall thickness; meanwhile, the 2D-hexagonal structure with  $p6mm$  plane group is preserved, as it can be observed in the periodicity of the crystal lattice fringes in the direction perpendicular to the mesopores. However, after longer time periods, a total loss of the mesoporous structure occurs.

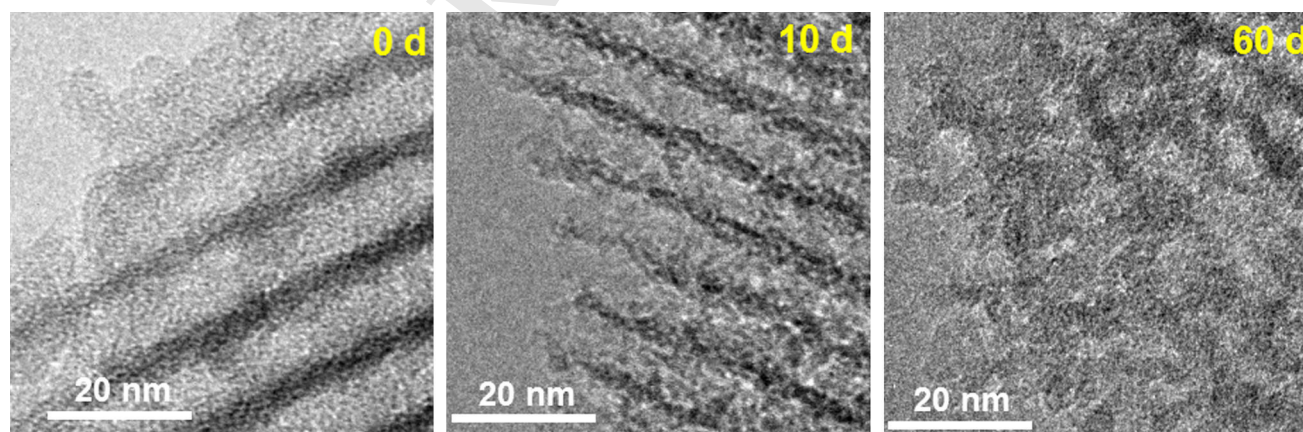
In fact,  $^{29}\text{Si}$  solid-state nuclear magnetic resonance (NMR) studies carried out using MCM-41 and SBA-

15 materials in bulk show a remarkable initial increase in  $\text{Q}^2$  ( $(\text{OH})_2\text{Si}=\text{}$ ) and  $\text{Q}^3$  ( $(\text{OH})-\text{Si}\equiv$ ) species after 7 days of assay in aqueous medium [36]. This phenomenon can be ascribed to the water penetration within the mesopores, which provokes an increase in the number of silanol groups ( $-\text{SiOH}$ ) due to the hydrolysis of siloxane ( $-\text{O}-\text{Si}-\text{O}-$ ) bonds. This is in agreement with the decrease in the wall thickness observed from the TEM studies previously described for SBA-15 (Fig. 4). For longer periods of assay (21 days), there is an increment of  $\text{Q}^4$  species ( $\text{SiO}_4$ ), pointing to the repolymerisation of the silanol groups to produce siloxane bonds [36]. These findings agree with the silica release profile described in Fig. 3, where the initial silica burst release effect is followed by a plateau where the silica dissolution evolves slowly.

There are several factors that influence silica degradation from OMS in bulk: (1) textural and structural properties; (2) network condensation degree; (3) chemical composition; (4) surface functionalisation; and (5) physiological medium.

#### Textural and structural properties

Undoubtedly, the textural properties such as pore diameter, surface area and pore volume directly affect silica dissolution process from OMS in bulk. However, the number of published studies on this topic is scarce and there is great deal of controversy since it is difficult to separate the influence of these factors from the silica network condensation degree, which are frequently tightly related [34]. As an



**Figure 4** High-resolution TEM images showing the degradation process of SBA-15-type mesoporous material in physiological conditions (PBS) at different time periods (10 and 60 days). After

10 days, the wall thickness decreases while keeping the 2D-hexagonal structure. However, long-term assay (60 days) demonstrates the total loss of the ordered mesoporous structure.

example, the effect of pore diameter increase on silica dissolution when comparing the behaviour of MCM-41 (~2.5 nm) and SBA-15 (~8 nm) in aqueous medium has been reported [37]. This study revealed that the larger the pore diameter, the faster the diffusion of the fluids through the mesochannels, and therefore higher the reactivity [38].

Regarding the structural features of OMS in bulk, 3D cubic mesostructures such as MCM-48 are expected to exhibit faster silica dissolution rates than 2D hexagonal mesostructures such as that of MCM-41 or SBA-15 [39]. Nonetheless, there are not concluding research works that avail this observation in physiological media.

### Network condensation degree

Since the silica dissolution in aqueous media involves the nucleophilic attack of water molecules with the siloxane ( $-\text{Si}-\text{O}-\text{Si}-$ ) and silanol ( $-\text{SiOH}$ ) groups of the mesoporous material, the network condensation degree plays a pivotal role into this process. Thus, the lower the silica condensation degree, the higher the silica dissolution rate. Therefore, several scientific reports have shown that different parameters involved in the synthesis of OMS, such as silica source, pH, temperature, surfactant removal procedure (calcination or solvent extraction), strongly influence the silica degradation rate in physiological media [40].

### Chemical composition

The degradation rate of OMS is strongly related to the chemical composition. Different strategies have been reported in the literature that aimed at tailoring the silica dissolution from these matrices by incorporating heteroatoms into the silica network. Among the most relevant herein, we focus on calcium- and phosphorous-doped OMS for their direct implication in bone tissue regeneration processes, where new bone formation and release of biological agents are aimed.

In this sense, it has been reported that doping OMS with different calcium oxide amounts helps to obtain an adaptable degradation performance [41–44]. In addition, the presence of CaO as network modifier is also a very important factor for the bioactivity process, i.e. the formation of a hydroxycarbonate apatite (HCA) layer on the surface of bioactive materials

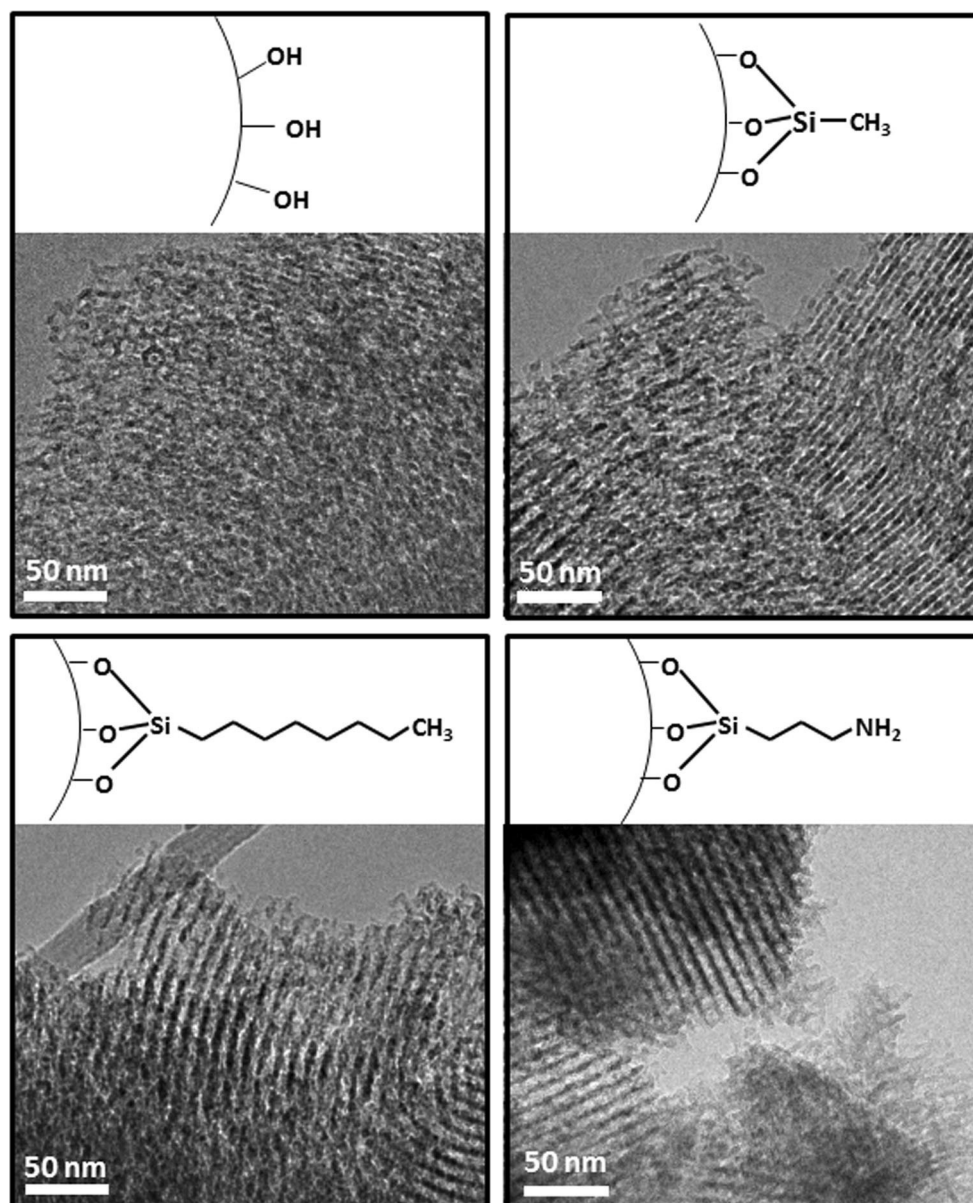
[45, 46]. The presence of CaO units into the  $\text{SiO}_2$  network induces a decrease in the silica network condensation degree and consequently higher silica dissolution. This is in agreement with results derived from different investigations carried out on bioactive glasses in the  $\text{SiO}_2$ –CaO– $\text{P}_2\text{O}_5$  system prepared by traditional melt-quench, sol-gel or evaporation-induced self-assembly (EISA) methods [47–49].

Phosphorous incorporation into OMS has also been reported for SBA-15 and MCM-41 materials. These articles have revealed that the incorporation of  $\text{PO}_4$  units in the mesoporous materials results in materials with reduced silica leaching in aqueous medium as well as an increased bioactivity and biocompatibility [50, 51]. These results could be explained by the increase in the cross-linking degree together with an increase in the acidity of the mesoporous silica network by Si substitutions by P atoms (formation of Si–O–P linkages). The creation of active centres Si–O–P would favour the bioactive process. In the case of multicomponent materials ( $\text{SiO}_2$ –CaO– $\text{P}_2\text{O}_5$  systems), such as certain mesoporous bioactive glasses, independently of the presence of calcium phosphate clusters, the sole existence of orthophosphate ions restricts the amount of  $\text{Ca}^{2+}$  ions available for modifying the silica network [35]. This is because  $\text{PO}_4^{3-}$  ions consume a significant fraction of  $\text{Ca}^{2+}$  modifiers for preserving charge balance, which leads to a reduction in the level of silicate network depolymerisation and therefore decreases matrix solubility.

### Surface functionalisation

The functionalisation of silica surface with organic moieties has been demonstrated to play a key role in modulating the reactivity of OMS. Moreover, the incorporation of diverse functionalities on the surface of OMS has been proven to be able to tune the silica leaching by creating a protecting barrier towards water molecules from physiological environments. This has been ascribed to an increase in the hydrophobic character of OMS. Figure 5 shows the degradation process in PBS, studied by TEM, after 60 days of incubation of pure silica SBA-15 and SBA-15 functionalised by the post-synthesis grafting of different organosilanes containing methyl, octyl or aminopropyl groups [33]. TEM images clearly reveal the protective effect of organosilanes on structural features of SBA-15, showing that the well-ordered 2D-hexagonal structure is maintained during the long-

**Figure 5** TEM images showing the degradation process in physiological conditions (PBS) after 60 days of pure silica SBA-15 and SBA-15 functionalised by post-synthesis with different alkoxy silanes. Pure silica SBA-15 undergoes a total loss of mesostructural order, whereas SBA-15 functionalised with methyl groups shows small ordered domains of 2D-hexagonal structure. SBA-15 functionalised with octyl chains or aminopropyl groups exhibit a well-ordered 2D-hexagonal structure, which is preserved after the long-term assay.



term assay for SBA-15 functionalised with octyl chains or aminopropyl groups, which are the organic moieties exhibiting the highest relative hydrophobicity.

### Physiological environment

The influence of physiological medium on the degradation rate of OMS has been scarcely studied. In this sense, in vitro degradation tests using unmodified SBA-15 and SBA-15 functionalised with different organosilanes have been carried out in three different media, such as PBS, simulated body fluid (SBF) and Dulbecco's modified Eagle's medium (DMEM). The obtained results showed that the

complexity of the aqueous medium regarding the ionic composition and the presence or absence of proteins did not significantly affect the silica lixiviation for unmodified SBA-15.

### Key factors that govern silica degradation from mesoporous silica nanoparticles

OMS as MSNs are under extensive evaluation as carriers of drugs for biomedical application. The number of publications focused on controlling the cargo release by capping the pores is growing exponentially in the last years. However, there are not many studies evaluating the eventual dissolution of



the nanoparticles after cargo release, which is a desirable feature of a drug delivery nanosystem. In fact, it is well known that silica normally decomposes into free silicon species in the form of harmless monosilicic acid by-products that after entering the bloodstream or lymph would be excreted by the urine. This is why MSNs present fewer challenges for long-term use than other nanocarriers that are not metabolised [52]. For this reason, a thorough understanding of its solubility and biodegradability is of outmost importance to ensure its biocompatibility and efficacy for different pathological conditions. Figure 6 shows micrographs of 200 nm MSNs dispersed in PBS for different periods of time. Nanoparticle degradation can be clearly observed after a few days in aqueous suspension.

Braun et al. [53] have recently evaluated the dissolution of MSNs of different sizes (80, 200 and 1500 nm). The dissolution profile of the nanoparticles was similar independently of the size of the particles. They found a much slower dissolution for non-porous silica, although that was the only sample without thermal treatment post-synthesis (all mesoporous materials were calcined). Yamada et al. [54] also evaluated the degradation process of MSNs of different sizes (20–80 nm), and they also found that the degradation process was independent of the particle size.

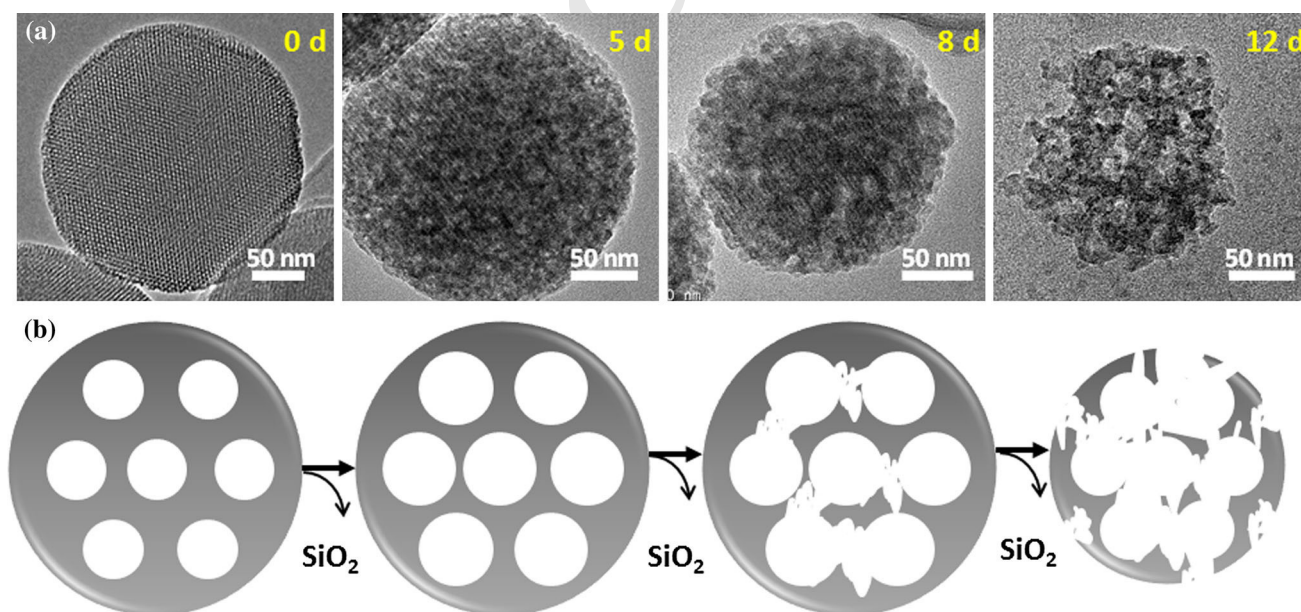
In a similar way to OMS in bulk, MSN solubility in aqueous media has also been observed to depend on several factors, such as morphology, surface area and functionalisation.

### Nanoparticle morphology

Hao et al. [55] evaluated the influence of the nanoparticle morphology on its degradability. They studied nanoparticles with different aspect ratios (AR), from spheres (AR = 1) to rods (AR = 2 and AR = 4). They found that nanospheres were more rapidly dissolved than nanorods. The authors suggest that sphere-shaped MSNs underwent faster dissolution due to their relative larger outer surface area compared to rod-shaped MSNs.

### Surface area

The surface area of the MSNs is also expected to play a key role in the dissolution kinetics of the nanoparticles. In this sense, the higher is the surface area the greater contact with the physiological fluid at the interfaces, which leads to higher dissolution rates. This trend was observed by Townley and co-workers, who evaluated the solubility of two types of MSNs: blackberry-like MSNs (surface area of 303 m<sup>2</sup>/g) and chrysanthemum-like MSNs (surface area of 934 m<sup>2</sup>/g).



**Figure 6** TEM micrographs of MSNs after suspension in PBS for different periods of time (from left to right): 0, 5, 8, 12 days (a), schematic representation of the dissolution process of MSNs in aqueous medium (b).

g) under a phosphate-buffered saline solution [52]. After incubation at 37 °C, the samples were periodically removed for TEM imaging, observing that nanoparticles with the lowest surface area were the least degraded, as expected.

### Chemical composition

The effect in nanoparticle degradability of different chemical modifications of MSNs has also been studied by different authors. Shi et al. [56] reported that Ca-doped MSNs have a faster degradation rate than undoped MSNs. Fontecave et al. [57] reported that mesoporous mixed silica–zirconia oxides followed slower dissolution kinetics than pure mesoporous silica. In the case of calcium-doped systems, the decrease in the connectivity of the silica network, because of the increase in non-bridging oxygens, leads to a faster dissolution rate [56]. However, for silica–zirconia systems, dissolved silica in the medium cannot reach the saturation level due to the recondensation of silica on local zirconium centres in the mesoporous matrix [57].

Some work has been done to ease the degradation of nanoparticles once they have performed their function. Maggini et al. [58] recently reported breakable MSNs by introducing redox-cleavable disulphide bonds inside the silica network that induced the loss of particle structure when exposed to a reducing environment (like the intracellular medium). This particle self-destruction would then facilitate the degradation and excretion of the resulting smaller particles.

### Surface functionalisation

Cauda et al. [59] evaluated the dissolution of colloidal MSNs in SBF up to 1 month. In that work, the authors evaluated non-functionalised silica as well as phenyl-, chloropropyl-, aminopropyl-functionalised nanoparticles and PEG-coated nanoparticles. They found that the fastest-degrading material was phenyl-functionalised mesoporous silica, while PEG coating significantly reduced the dissolution rate as well as it decreased the formation of hydroxyapatite-like material on the nanoparticle surface. They also observed that, during the dissolution process, there was an increase in pore size and a decrease in porosity and surface area of the nanoparticles. Hao et al. [55] also studied the effect of PEG on MSN degradation

and found a slower degradation of PEGylated nanoparticles and also a change in the dissolution process itself. While naked MSNs were dissolved from the external surface towards the inside, PEGylated nanoparticles started dissolving from the inside of the nanoparticle, advancing then towards the external surface. Cauda et al. [60] also evaluated the influence in the dissolution process of MSNs with covalently grafted PEG of different molecular weights (550 and 5000 Da). They found that denser and longer polymer chains slowed down the dissolution of the silica in a more efficient manner. Recently, our research group has reported similar results regarding degradation of polymer-coated MSNs, with a significantly slower silica dissolution when functionalised with a copolymer [61].

### Physiological environment

The liquid medium in which the MSNs are dispersed is another key parameter regarding silica stability. Braun et al. [52] evaluated MSN degradation in simulated lung fluid (SLF), SBF, simulated gastric fluid (SGF) and PBS. They found the fastest dissolution rate in SLF, with similar behaviour in PBS or SBF and the slowest degradation in SGF. Hao et al. [55] also evaluated the effect of foetal bovine serum on nanoparticle stability. They showed that proteins from the serum accelerated the dissolution process, decreasing nanoparticle stability. This factor is of foremost importance when regarding the biomedical application of these nanoparticles, since they will be in contact with a very wide variety of proteins in the biological environment.

### In vivo dissolution

He et al. [62] evaluated the biodistribution, biodegradation and excretion of MSNs with different sizes (80–360 nm) and with or without PEG coating. They evaluated the concentration of products of silica degradation in urine, at different time points after tail vein injection of the MSNs. They found that the excreted amount of degradation products decreased with time for all of the materials tested. They observed a significantly lower amount of degradation products for smaller nanoparticles, and for a given size, a slower degradation was seen for PEGylated MSNs. The authors attributed that behaviour to an easier capture by liver and spleen of MSNs with



larger particle size, while PEGylation would diminish their accumulation in those organs and increase their circulation time.

## Conclusions

From the data presented in the literature regarding ordered mesoporous silica dissolution in physiological environments, it can be concluded that OMS materials for drug delivery will suffer degradation, as observed both in bulk and in nanoparticles. However, nanoparticle degradation will take place faster than in bulk. The rate at which that dissolution takes place can be tuned by carefully designing the material characteristics, from textural and morphological properties of the materials to post-synthesis modifications directed to control silica dissolution. Furthermore, the specific physiological environment will also modify the dissolution behaviour. This implies that each particular material should be designed taking into account the environment at which it will be exposed (either in a local implant or to be systemically administered) in order to optimise the degradation behaviour of the material to allow the correct development of its desired function.

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## Compliance with ethical standards

**Conflict of interest** Authors declare no conflict of interest.

## References

- [1] Vallet-Regí M, Rámila A, del Real RP, Pérez-Pariente J (2001) A new property of MCM-41: drug delivery system. *Chem Mater* 13:308–311
- [2] Vallet-Regí M, Balas F, Arcos D (2007) Mesoporous materials for drug delivery. *Angew Chem Int Ed* 46:7548–7558
- [3] Wang S (2009) Ordered mesoporous materials for drug delivery. *Microporous Mesoporous Mater* 117:1–9
- [4] Manzano M, Colilla M, Vallet-Regí M (2009) Drug delivery from ordered mesoporous matrices. *Expert Opin Drug Deliv* 6:1–18
- [5] Yang P, Gai S, Lin J (2012) Functionalized mesoporous silica materials for controlled drug delivery. *Chem Soc Rev* 41:3679–3698
- [6] Vallet-Regí M, Ruiz-González L, Izquierdo-Barba I, González-Calbet JM (2006) Revisiting silica-based ordered mesoporous materials: medical applications. *J Mater Chem* 16:26–31
- [7] Vallet-Regí M, Colilla M, Izquierdo-Barba I (2008) Bioactive mesoporous silicas as controlled delivery systems: application in bone tissue regeneration. *J Biomed Nanotechnol* 4:1–15
- [8] Vallet-Regí M, Colilla M, González B (2011) Medical applications of organic–inorganic hybrid materials within the field of silica-based bioceramics. *Chem Soc Rev* 40:596–607
- [9] Kresge CT, Leonowicz ME, Roth WJ, Vartuli JC, Beck JS (1992) Ordered mesoporous molecular sieves synthesized by a liquid–crystal template mechanism. *Nature* 359:710–712
- [10] Zhao DY, Feng JL, Huo QS, Melosh N, Fredrickson GH, Chmelka BF, Stucky GD (1998) Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 angstrom pores. *Science* 279:548–552
- [11] Che S, Liu Z, Ohsuna T, Sakamoto K, Terasaki O, Tatsum T (2004) Synthesis and characterization of chiral mesoporous silica. *Nature* 429:281–284
- [12] Yamauchi Y, Suzuki N, Kimura T (2009) Formation of mesoporous oxide fibers in polycarbonate confined spaces. *Chem Commun* 38:5689–5691
- [13] Yu CZ, Fan J, Tian BZ, Zhao D, Stucky GD (2002) High-yield synthesis of periodic mesoporous silica rods and their replication to mesoporous carbon rods. *Adv Mater* 14:1742–1745
- [14] Kosuge K, Sato T, Kikukawa N, Takemori M (2004) Morphological control of rod- and fiberlike SBA-15 type mesoporous silica using water-soluble sodium silicate. *Chem Mater* 16:899–905
- [15] Soler-Illia GJAA, Innocenzi P (2006) Mesoporous hybrid thin films: the physics and chemistry beneath. *Chem Eur J* 12:4478–4494
- [16] Sanchez C, Boissiere C, Grosso D, Laberty C, Nicole L (2008) Design, synthesis, and properties of inorganic and hybrid thin films having periodically organized nanoporosity. *Chem Mater* 20:682–737

- [17] Melosh NA, Davidson P, Chmelka BF (2000) Monolithic mesophase silica with large ordering domains. *J Am Chem Soc* 122:823–829
- [18] Naik SP, Fan W, Yokoi T, Okubo T (2006) Synthesis of a three-dimensional cubic mesoporous silica monolith employing an organic additive through an evaporation-induced self-assembly process. *Langmuir* 22:6391–6397
- [19] Schacht S, Huo Q, Voigt-Martin IG, Stucky GD, Schüth F (1996) Oil-water interface templating of mesoporous macroscale structures. *Science* 273:768–771
- [20] Lai C-Y, Trewyn BG, Jęstinija DM, Jęstinija K, Xu S, Jęstinija S, Lin VS-Y (2003) A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules. *J Am Chem Soc* 125:4451–4459
- [21] Vallet-Regí M, Ruiz-Hernández E (2011) Bioceramics: from bone regeneration to cancer nanomedicine. *Adv Mater* 23:5177–5218
- [22] Wu KC-W, Yamauchi Y (2012) Controlling physical features of mesoporous silica nanoparticles (MSN) for emerging applications. *J Mater Chem* 22:1251–1256
- [23] Colilla M, González B, Vallet-Regí M (2013) Mesoporous silica nanoparticles for the design of smart delivery nanodevices. *Biomater Sci* 1:114–134
- [24] Baeza A, Colilla M, Vallet-Regí M (2015) Advances in mesoporous silica nanoparticles for targeted stimuli-responsive drug delivery. *Expert Opin Drug Deliv* 12:319–337
- [25] Castillo RR, Colilla M, Vallet-Regí M (2016) Advances in mesoporous silica-based nanocarriers for co-delivery and combination therapy against cancer. *Expert Opin Drug Deliv*. doi:10.1080/17425247.2016.1211637
- [26] Studer AM, Limbach LK, Van Duc L, Krumeich F, Athanassiou EK, Gerber LC, Moch H, Stark WJ (2010) Nanoparticle cytotoxicity depends on intracellular solubility: comparison of stabilized copper metal and degradable copper oxide nanoparticles. *Toxicol Lett* 197(3):169–174
- [27] Vallet-Regí M (2014) Bio-ceramics with clinical applications. Wiley, Chichester
- [28] Terasaki O, Ohsuna T, Liu Z, Sakamoto Y, Garcia-Bennett AE (2004) Structural study of mesoporous materials by electron microscopy. *Stud Surf Sci Catal* 148:261–288
- [29] Czuryżkiewicz T, Ahvenlammi J, Korteso P, Ahola M, Kleitz F, Jokinen M, Lindén M, Rosenholm JB (2002) Drug release from biodegradable silica fibers. *J Non Cryst Solids* 306:1–10
- [30] Viitala R, Jokinen M, Tuusa S, Rosenholm JB, Jalonen HJ (2005) Adjustably bioresorbable sol-gel derived SiO<sub>2</sub> matrices for release of large biologically active molecules. *Sol Gel Sci Technol* 36:147–156
- [31] Korteso P, Ahola M, Kangas M, Kangasniemi I, Yli-Urpo A, Kiesvaara J (2000) In vitro evaluation of sol-gel processed spraydried silica gel microspheres as carrier in controlled drugdelivery. *Int J Pharm* 200:223–229
- [32] Jokinen M, Peltola T, Veittola S, Rahiala H, Rosenholm JB (2000) Adjustable biodegradation for ceramic fibres derived from silica sols. *J Eur Ceram Soc* 20:1739–1748
- [33] Izquierdo-Barba I, Colilla M, Manzano M, Vallet-Regí M (2010) In vitro stability of SBA-15 under physiological conditions. *Microporous Mesoporous Mater* 132:442–452
- [34] He Q, Shi J, Zhu M, Chen Y, Chen F (2010) The three-stage in vitro degradation behavior of mesoporous silica in simulated body fluid. *Microporous Mesoporous Mater* 131:314–320
- [35] Gunawidjaja PN, Mathew R, Lo AYH, Izquierdo-Barba I, García A, Arcos D, Vallet-Regí M, Edén M (2012) Local structures of mesoporous bioactive glasses and their surface alterations in vitro: inferences from solid-state NMR. *Phil Trans R Soc A* 370:1376–1399
- [36] Choi Y, Lee JE, Lee JH, Jeong JH, Kim J (2015) A biodegradation study of SBA-15 microparticles in simulated body fluid and in vivo. *Langmuir* 31:6457–6462
- [37] Gouze B, Cambedouzou J, Parrès-Maynadié S, Rébiscoul D (2014) How hexagonal mesoporous silica evolves in water on short and long term: role of pore size and silica wall porosity. *Microporous Mesoporous Mater* 183:168–176
- [38] Izquierdo-Barba I, Ruiz-González L, Doadrio JC, González-Calbet JM, Vallet-Regí M (2005) Tissue regeneration: a new property of mesoporous materials. *Solid State Sci* 7:983–989
- [39] Sakamoto Y, Kim T-W, Ryoo R, Terasaki O (2004) Three-dimensional structure of large-pore mesoporous cubic Ia-3d imaged silica with complementary pores and its carbon replica by electron crystallography. *Angew Chem Int Ed* 43:5231–5234
- [40] Bass JD, Grosso D, Boissiere C, Belamie E, Coradin T, Sanchez C (2007) Stability of mesoporous oxide and mixed metal oxide materials under biologically relevant conditions. *Chem Mater* 19:4349–4356
- [41] Li X, Zhang L, Dong X, Liang J, Shi J (2007) Preparation of mesoporous calcium doped silica spheres with narrow size dispersion and their drug loading and degradation behavior. *Microporous Mesoporous Mater* 102:151–158
- [42] Yan XX, Deng HX, Huang XH, Lu GQ, Qiao SZ, Zhao DY, Yu CZ (2005) Mesoporous bioactive glasses. I. Synthesis and structural characterization. *J Non Cryst Solids* 351:3209–3217
- [43] Xia W, Chang J (2006) Well-ordered mesoporous bioactive glasses (MBG): a promising bioactive drug delivery system. *J Control Release* 110:522–530

- [44] Diaz A, Lopez T, Manjarrez J, Basaldella E, Martinez-Blanes JM, Odriozola JA (2006) Growth of hydroxyapatite in a biocompatible mesoporous ordered silica. *Acta Biomater* 2:173–179
- [45] Maçon ALB, Kim TB, Valliant EM, Goetschius K, Brow RK, Day DE, Hoppe A, Boccaccini AR, Kim IY, Ohtsuki C, Kokubo T, Osaka A, Vallet-Regí M, Arcos D, Fraile L, Salinas AJ, Teixeira Vueva Y, Almeida Miola M, Vitale-Brovarone C, Verné E, Höland E, Jones JR (2015) A unified in vitro evaluation for apatite-forming ability of bioactive glasses and their variants. *J Mater Sci Mater Med* 26:1–10
- [46] Turdean-Ionescu C, Svensson B, Grins J, Izquierdo-Barba I, García A, Arcos D, Vallet-Regí M, Edén M (2015) Composition-dependent in vitro apatite formation at mesoporous bioactive glass-surfaces quantified by solid-state NMR and powder XRD. *RSC Adv* 5:86061–86071
- [47] Arcos D, Greenspan DC, Vallet-Regí M (2003) A new quantitative method to evaluate the in vitro bioactivity of melt and sol–gel-derived silicate glasses. *J Biomed Mater Res A* 65:344–351
- [48] Gunawidjaja PN, Izquierdo-Barba I, Mathew R, Jansson K, García A, Grins J, Arcos D, Vallet-Regí M, Edén M (2012) *J Mater Chem* 22:7214–7223
- [49] Hench LL, Polak JM (2002) Third-generation biomedical materials. *Science* 295:1014–1017
- [50] García A, Colilla M, Izquierdo-Barba I, Vallet-Regí M (2009) Incorporation of phosphorus into mesostructured silicas: a novel approach to reduce the SiO<sub>2</sub> leaching in water. *Chem Mater* 21:4135–4145
- [51] Vallet-Regí M, Izquierdo-Barba I, Rámila A, Pérez-Pariente J, Babonneau F, González-Calbet JM (2004) Phosphorous-doped MCM-41 as bioactive material. *Solid State Sci* 7:233–237
- [52] Huang X, Young NP, Townley HE (2014) Characterization and comparison of mesoporous silica particles for optimized drug delivery. *Nanomater Nanotechnol* 4:1–15
- [53] Braun K, Pochert A, Beck M, Fiedler R, Gruber J, Lindén M (2016) Dissolution kinetics of mesoporous silica nanoparticles in different simulated body fluids. *J Sol Gel Sci Technol* 79(2):319–327
- [54] Yamada H, Urata C, Aoyama Y, Osada S, Yamauchi Y, Kuroda K (2012) Preparation of colloidal mesoporous silica nanoparticles with different diameters and their unique degradation behavior in static aqueous systems. *Chem Mater* 24(8):1462–1471
- [55] Hao N, Liu H, Li L, Chen D, Li L, Tang F (2012) In vitro degradation behavior of silica nanoparticles under physiological conditions. *J Nanosci Nanotechnol* 12(8):6346–6354
- [56] Li X, Zhang L, Dong X, Liang J, Shi J (2007) Preparation of mesoporous calcium doped silica spheres with narrow size dispersion and their drug loading and degradation behavior. *Microporous Mesoporous Mater* 102(1–3):151–158
- [57] Fontecave T, Sanchez C, Azaïs T, Boissière C (2012) Chemical modification as a versatile tool for tuning stability of silica based mesoporous carriers in biologically relevant conditions. *Chem Mater* 24(22):4326–4336
- [58] Maggini L, Cabrera I, Ruiz-Carretero A, Prasetyanto EA, Robinet E, De Cola L (2016) *Nanoscale* 8(13):7240–7247
- [59] Cauda V, Schlossbauer A, Bein T (2010) Bio-degradation study of colloidal mesoporous silica nanoparticles: effect of surface functionalization with organo-silanes and poly(ethylene glycol). *Microporous Mesoporous Mater* 132(1–2):60–71
- [60] Cauda V, Argyo C, Bein T (2010) Impact of different PEGylation patterns on the long-term bio-stability of colloidal mesoporous silica nanoparticles. *J Mater Chem* 20(39):8693
- [61] Paris JL, Cabañas MV, Manzano M, Vallet-Regí M (2015) Polymer-grafted mesoporous silica nanoparticles as ultrasound-responsive drug carriers. *ACS Nano* 9(11):11023–11033
- [62] He Q, Zhang Z, Gao F, Li Y, Shi J (2011) In vivo Biodistribution and Urinary Excretion of Mesoporous Silica Nanoparticles: effects of Particle Size and PEGylation. *Small* 7(2):271–280

