Mesoporous Silica Nanoparticles for the Treatment of Complex Bone Diseases: Bone Cancer, Bone Infection and Osteoporosis

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Abstract: Bone diseases, such as bone cancer, bone infection and osteoporosis, constitute a major issue for modern societies as a consequence of their progressive ageing. Even though these pathologies can be currently treated in the clinic, some of those treatments present drawbacks that may lead to severe complications. For instance, chemotherapy lacks of great tumor tissue selectivity, affecting healthy and diseased tissues. In addition, the inappropriate use of antimicrobials is leading to the appearance of drug-resistance bacteria and persistent biofilms, rendering current antibiotics useless. Furthermore, current antiosteoporotic treatments present many side effects as a consequence of their poor bioavailability and the need to use higher doses. In view of the exposed evidences, the encapsulation and selective delivery to the diseased tissues of the different therapeutic compounds seem highly convenient. In this sense, silica-based mesoporous nanoparticles offer great loading capacity within their pores, the possibility of modifying the surface to target the particles to the malignant areas and great biocompatibility. This manuscript is intended to be a comprehensive review of the available literature on complex bone diseases treated with silica-based mesoporous nanoparticles, whose further development and eventual translation into the clinic could bring significant benefits for our future society.

1. Introduction

In the last decades, nanotechnology has been applied to a variety of fields, ranging from novel electronic devices to the study of biological processes [1–4]. In particular, the application of nanotechnology to medicine, the so-called nanomedicine, has attracted the attention of many researchers, and it is expected to revolutionize the pharmaceutical and biotechnological fields in the near future [5–7].

The first developments in the field of nanomedicine were reported in the early 60's when liposomes were first proposed as carriers [8,9]. Since then, scientists have engineered many different nanocarriers to address effective delivery of therapeutics. Those nanoparticles can be classified as either organic or inorganic. Examples of organic nanocarriers include liposomes, which are amphiphilic lipids that rearrange in water to yield vesicles with an inner aqueous compartment surrounded by lipid bilayers [10]; polymeric nanoparticles produced from polymer chains showing

different functionalities [11] or polymeric micelles composed by amphiphilic block copolymers able to rearrange in aqueous media [12]. Examples of inorganic nanocarriers include metal nanoparticles synthesized from noble metals, such as gold or silver [13]; carbon nanoparticles such as carbon nanotubes, fullerenes or mesoporous carbon nanoparticles [14] or silica-based mesoporous nanoparticles, which have been extensively studied owing to their capacity to load large amounts of therapeutic molecules [15]. The main advantages of silica-based mesoporous nanoparticles over other types of particles include the robustness of the silica framework, that allows the use of harsh reaction conditions for their modification, and their excellent textural properties. In fact, conventional polymeric nanoparticles usually present low drug capacity, usually less than 5% of total weight, whereas these silica-based mesoporous nanoparticles offer greater values [16,17]. The main disadvantage over other formulations would be the fact that the translation of these type of particles remains challenging. However, it should be mentioned that silica is "generally recognized as safe" by the US FDA, and it is often used as excipient in drug formulations and as dietary supplement [18,19]. In this sense, the administration of fenofibrate-loaded ordered mesoporous silica materials in men was found to be safe, and the doses were well tolerated by the patients [20]. In addition, small silica nanoparticles (c-dots, 7 nm) for imaging purposes were approved by FDA for a human clinical trial, demonstrating that they were well tolerated by the patients and accumulated in the tumor site [21]. In consequence, silica-based nanoparticles constitute a powerful and promising tool that might be promptly translated into the clinic.

This review will cover the application of silica-based mesoporous nanoparticles for the treatment of complex bone diseases, such as bone cancer, bone infection and osteoporosis. These pathologies are predominantly found in elderly people, who will constitute a quarter of the European population by 2020 [22]. Then, bone diseases will definitely entail a significant impact on the health care systems and, consequently, bone-targeted nanomedicines, *i.e.*, nanomedicines able to specifically reach bone diseases, could bring significant benefits for our future society.

2. Mesoporous Silica Materials

2.1. The Beginning of a New Era: Ordered Mesoporous Silica Materials

Ordered mesoporous silica materials were first reported in the early 90's by Mobil Oil Corporation researchers [23] and scientists from Waseda university [24]. These bulk mesoporous materials have attracted great attention because they present (1) tunable and narrow pore size distributions (2-30 nm); (2) adjustable porous structures; (3) high specific surface areas (up to 1500 cm^2/g); (4) high pore volumes (*ca*. 1 cm^3/g) and (5) high silanol density on the surface that allows further modifications [25,26]. Owing to their exquisite physico-chemical properties, mesoporous silica materials have been broadly applied in a number fields, including heavy metal adsorption [27,28], catalysis [29,30] or energy storage [31,32], among others.

In addition, these materials find broad application within the field of biomaterials, owing to their ability to adsorb molecules within their pores and release them in a sustained fashion. In fact, these materials have been widely studied since Prof. Vallet-Regí and coworkers first reported their suitability as drug delivery systems back in 2001 [33].

In light of their great properties and their potential biomedical application, researchers focused their efforts on translating those excellent features of bulk materials to the nanoscale dimension. As a result, mesoporous silica nanoparticles (MSNs) were developed soon after, opening the gates to multiple biomedical applications, such as controlled drug delivery [34,35], efficient gene transfection [36–38], antibacterial treatment [39,40] or bone tissue regeneration [41,42], among others.

2.2. Synthesis and Functionalization of Mesoporous Silica Nanoparticles

The synthesis of MSNs is based on a modification of the Stöber method, which initially yielded micron-sized monodispersed and non-porous silica spheres [43]. In this sense, the addition of surfactants as structure-directing agents results in silica nanoparticles with excellent physico-chemical properties and showing porosity. This methodology allows to obtain homogenous

94 nanoparticles within the range 50-300 nm [25]. The morphology and dimensions of these surfactant-
95 templated mesoporous silicas can be tailored by controlling the reaction conditions (*e.g.*, pH,
96 temperature, surfactant concentration or silica precursor) [44]. As an example, a synthetic protocol
97 for the synthesis of MCM-41 (*Mobil Composition of Matter*) MSNs is depicted in Figure 1.

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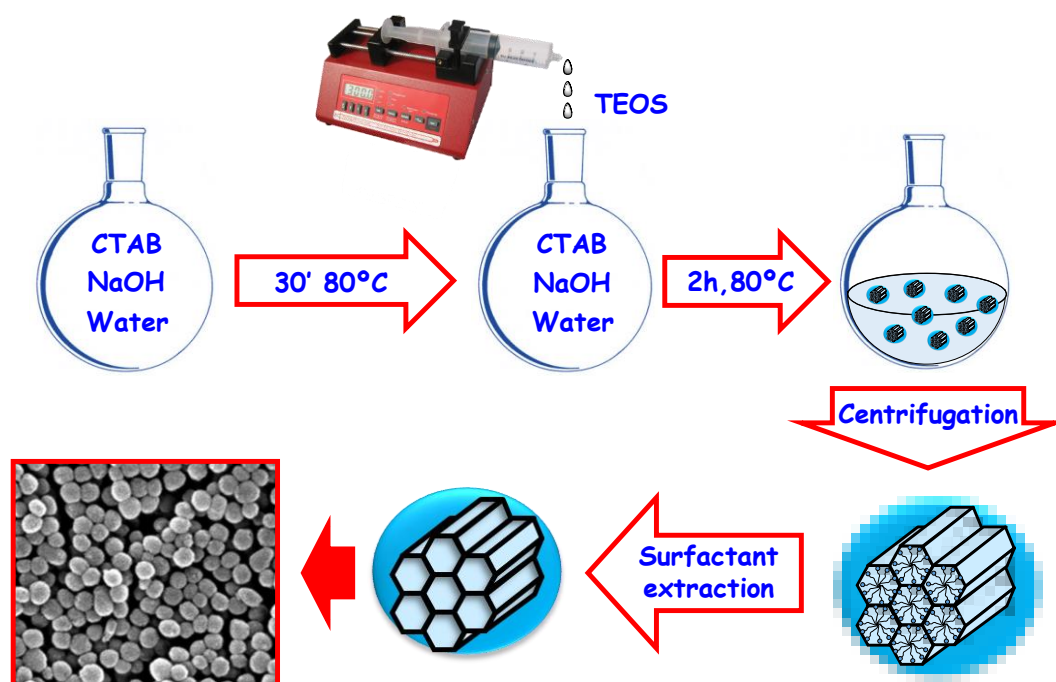
99 **Figure 1.** Synthesis of MCM-41 MSNs using a modification of the Stöber method. The surfactant
100 molecules self-assemble forming rod-like micelles around which the silica precursors polymerize,
101 leading to the formation of a silica backbone with hexagonally ordered mesopores. TEOS: Tetraethyl
102 ortosilicate; CTAB: Cetyltrimethylammonium bromide.

103 The positively charged polar heads of the surfactant molecules interact with the negatively
104 charged silica precursors, leading to the formation of the silica framework by means of the hydrolysis
105 and condensation of the silica precursor onto the self-assembled rod-like surfactant micelles. Then,
106 the organic template is removed using a solvent extraction method, yielding MSNs with empty pores
107 ready to be filled with therapeutic molecules. This method is usually preferred over calcination, since
108 the latter may cause irreversible aggregation of the particles and cytotoxic byproducts, limiting their
109 potential application [45,46].
110 One of the most remarkable features of MSNs is their high density of silanol groups on the
111 surface. These chemical groups allow the easy functionalization of the nanoparticles surface, usually
112 using organosilanes bearing different functionalities (amine, carboxylic acid, thiol…), to increase the
113 versatility of the produced nanocarriers. The particular organosilane employed allows to tune the
114 interactions between the payload and the silica matrix, which might be beneficial for particular
115 diseases [47,48]. The functionalization can be accomplished through two different approximations:
116 post-synthesis or co-condensation. The post-synthesis method involves the modification of the
117 surface after the synthesis. This approximation can lead to different groups inside and outside the
118 pores, depending on whether the process is performed before or after removing the template. The co-
119 condensation approach consists in the simultaneous addition of the silica precursor and the
120 functional organosilane during the formation of the particles. This approximation can yield
121 nanoparticles bearing various functional groups homogenously distributed throughout the silica
122 backbone or biodegradable periodic nanoparticles with labile bonds within the silica framework [25].

123 *2.3. Mesoporous Silica Nanoparticles as Smart Drug Delivery Systems*

124   Aside from being biocompatible, any nanoparticle intended to be employed as drug delivery
125 system should fulfill some basic requirements, such us maximizing the amount of therapeutics
126 loaded, minimizing premature release, reaching the target area and releasing the cargo on-demand
127 only where needed. In this sense, the extraordinary textural properties of MSNs endow them with
128 great loading capacities, being able to load huge amounts of therapeutic molecules within their pores,
129 as demonstrated by Scanning Transmission Electron Microscopy [49]. In addition to serving as drug
130 reservoir, the silica matrix provides a protective shell for the molecules against potential pH- or
131 enzymatic-mediated drug degradation in the organism.
132   The loading of therapeutic molecules within MSNs can be easily accomplished as consequence
133 of their open porous structure. However, this also means that the cargo molecules might easily diffuse
134 out of the pores before reaching the target area. This premature release can be minimized using the
135 so-called stimuli-responsive gatekeepers, which are structures able to open and close the pore
136 entrances on-demand in response to certain stimuli [50–53]. In this manner, premature and
137 nonspecific drug release would be minimized and the release would only take place upon application
138 of a convenient stimulus at the diseased area (Figure 2).
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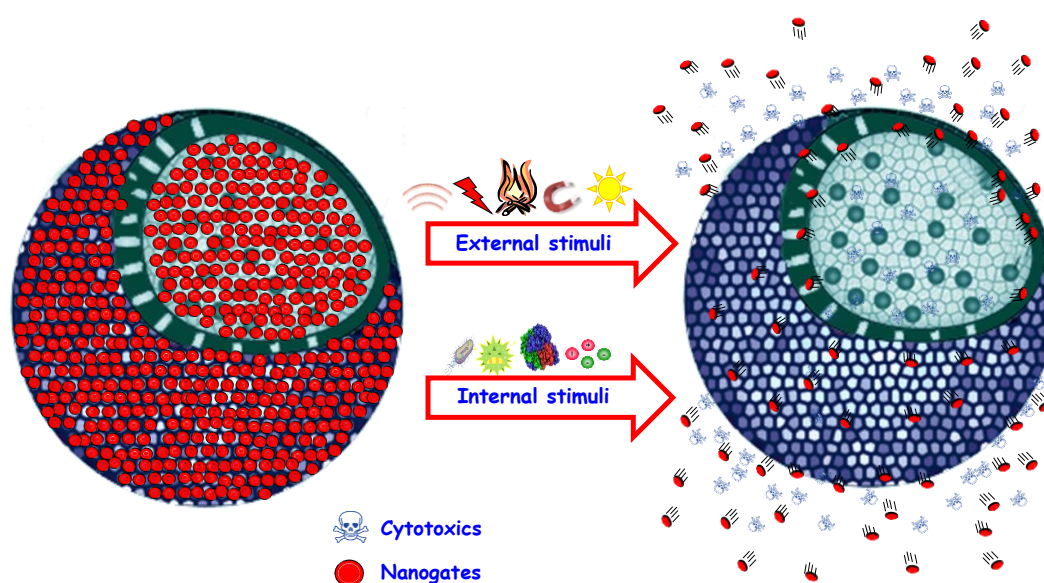
141 **Figure 2**. Schematic representation of stimuli-responsive MSNs. In response to the stimulus, the
142 gatekeeper opens the pore entrances, triggering the drug release. The origin of the stimulus can be
143 internal (pH, enzymes, redox species, etc) or external (magnetic fields, light, ultrasounds, etc).

144   Stimuli can be applied from inside or outside the organism. The use of internal stimuli is
145 interesting because of the significant variations of various relevant biomarkers that can be found in
146 some diseases. For instance, the pH of some subcellular organelles and that of the tumoral matrix are
147 more acidic compared to the physiological value [54], and analogous behavior is observed in bacterial
148 infections [55]. These pH variations have been employed to trigger the release from pH-responsive
149 smart MSNs [56–59]. In addition, some enzymes, which have been observed to be overexpressed in
150 osteoporotic [60] or tumoral scenarios [61,62], have the ability to cleave very specific peptidic
151 sequences. In this sense, it is possible to use those peptides to close the pore entrances of MSNs and
152 trigger the drug release only in those situations, where the enzymes are overexpressed [63–65].
153 Another relevant example of internal stimulus is the overexpression of redox species in the cytoplasm
154 of tumoral cells compared to the extracellular fluids [66,67], which has been employed to initiate the
155 drug release from different redox-responsive MSNs [68–70].
156   External stimuli, which should be innocuous to the organism, have also attracted great attention.
157 Their main advantage is that they would allow the application of the stimulus directly by the
158 clinician, thereby providing a much higher control of the release kinetics. For instance, the generation

159 of heat through the application of alternating magnetic fields has been employed trigger the drug
160 release from MSNs and generate hyperthermia-mediated cell death [71–73]. The use of light
161 (ultraviolet, visible, near-infrared) has also attracted the attention of many researchers, and
162 constitutes a non-invasive method to trigger the release from MSNs [74–76]. Another relevant
163 example of non-invasive and innocuous stimulus are ultrasounds, which have been successfully
164 employed to externally trigger the payload release from MSNs [77–79].

2.4. Biodistribution and Biodegradation of Mesoporous Silica Nanoparticles

166   The most common routes of administration of the above-mentioned smart nanoparticles are
167 intravenous, subcutaneous or localized injections in the target area. In particular, the intravenous
168 administration leads to the rapid delivery and distribution of the particles throughout the organism,
169 albeit it entails challenging issues. For instance, the particles administration leads to the formation of
170 a protein corona around them that defines their biological entity. This protein coating might limit the
171 functionality of the nanoparticles and enables their recognition by the organism, triggering their
172 removal by the mononuclear phagocyte system and decreasing the efficiency of the treatments [80].
173 An effective approximation to overcome that issue would be the modification of the nanoparticles
174 with hydrophilic polymers, such as poly(ethylene glycol), which might help reduce the amount of
175 proteins adsorbed onto the nanoparticles by creating a hydrophilic layer, enhancing their colloidal
176 stability and increasing their circulating half-life [81–83]. In this sense, it has been shown in murine
177 models that non-PEGylated MSNs rapidly accumulate in the lung, liver and spleen while their
178 PEGylated counterparts show increased circulating half-life [84,85].
179   Besides the effect of PEGylation on the particles biodistribution, there are other relevant
180 parameters that influence the final fate of MSNs. For instance, it has been shown *in vivo* that the larger
181 the nanoparticles the faster their excretion [85]. In addition, it has been observed that, unlike spherical
182 particles, those presenting elongated or cylindrical shapes undergo faster clearance from the
183 bloodstream [86]. Finally, the surface charge is a key parameter since it determines the interaction of
184 the particles with the surrounding media. In this sense, it has been shown that positively charged
185 nanoparticles are more prone to undergo opsonization and subsequent clearance than their slightly
186 negative or neutral counterparts [87,88].
187   Aside from achieving effective accumulation at the diseased area, it would be desirable that the
188 MSNs degrade somehow to facilitate their excretion after exerting their therapeutic activity. In this
189 sense, the dissolution rate of the silica backbone is a key factor for their elimination. Silica-based
190 mesoporous nanoparticles are composed of polycondensed silica tetrahedrons (SiO_4) interconnected
191 by siloxane bonds (-Si-O-Si-) and presenting silanol groups (-Si-OH) on the surface. The silica
192 dissolution is consequence of the nucleophilic attack of water to the siloxane and silanol groups,
193 generating biocompatible silicic acid as by-product that can be excreted through the urine [89]. The
194 dissolution rate depends on the particular characteristics of the particles and can be tuned through
195 the introduction of organic modifications on the surface. Those modifications have been shown not
196 to affect the biodistribution and biocompatibility of the MSNs [86].

3. Mesoporous Silica Nanoparticles for the Treatment of Bone Cancer

3.1. General Concepts on Bone Cancer and Bone Metastasis

199   Cancer is the term given to a group of diseases sharing an unstoppable cell division and with
200 potential to spread in other organs and tissues. It is a leading cause of mortality worldwide and its
201 prevalence is progressively increasing, with 1.7 million of estimated new cases and 600,000 cases of
202 estimated deaths only in the United States in 2019 [90].
203   Bone-related tumors fall into primary bone tumors and metastatic bone tumors. They are
204 considered to be highly deadly even though chemotherapy has improved the patient survival for
205 sarcomas [91]. The most common malignant primary bone tumors are osteosarcoma,
206 chondrosarcoma and Ewing sarcoma, which account for 70% of such malignancies. They originate in
207 the bone, where mesenchymal stem cells behave both as ontogenic progenitor tumor cells and

208 stromal cells that contribute to tumor development. The stroma of these tumors comprises
209 osteoblasts, osteoclasts, endothelial and immune cells and mesenchymal stem cells. In particular,
210 osteoclast have grabbed great attention because their activity (bone destruction) can be metabolically
211 enhanced directly by tumor cells and, reversibly, the presence of osteoclasts boosts the aggressiveness
212 of cancer cells [92].

213 Metastasis is the spread of cancer cells from a primary tumor to distant sites to create secondary
214 tumors. It is a stage of the disease usually considered to be incurable and whose treatments are mainly
215 palliative [93]. Its origin is the pre-metastatic niche, which is an environment in a secondary organ
216 induced by the primary cancer cells that provides favorable conditions for the growth of tumoral cells
217 [94]. The exact mechanism of that metastatic organotropism remains unclear but it is thought to be
218 related with tumor-derived exosomes. Exosomes are nanometric membrane-bound vesicles secreted
219 by tumors cells that contain functional biomolecules, such as proteins, RNA, DNA and lipids [95]. In
220 this sense, it has been reported that tumor exosome integrins can determine organotropic metastasis
221 by fusing with organ-specific resident cells to stablish the pre-metastatic niche. Once uptaken, they
222 induce cellular changes in the target organ (through the activation of Scr phosphorylation and pro-
223 inflammatory S100), thus promoting cancer cell colonization and organ-specific metastasis [96].

224 A characteristic feature of this disease is that some types of cancer cells preferentially migrate
225 and induce metastasis to specific organs [95]. In this sense, breast and prostate tumors normally lead
226 to bone metastases, which are secondary tumors formed when primary tumor cells home to the
227 skeleton [97,98]. Cancer cells can leave the primary tumor site owing to the poor adhesion among
228 each other in the tumoral matrix [99]. Once colonized the bone, tumor cells secrete proteins that
229 interact with resident cells in the bone marrow to induce the differentiation, recruitment and
230 activation of osteoblasts and osteoclasts. Then, during the bone resorption the calcium ions and the
231 growth factors secreted from the mineralized bone matrix promote tumor cell growth, leading to
232 vicious cycle that supports tumor growth in bone and subsequent fatal outcome [94].

233 It is believed that, when primary tumor cells migrate, the interaction of these disseminated cells
234 with the new microenvironment determines whether they will proliferate to form a secondary tumor
235 or undergo growth arrest and subsequent dormancy. Dormant cells are cells that stop dividing but
236 still survive in a quiescent state, waiting for the appropriate environmental conditions to re-enter the
237 cell cycle again [100]. These cells are clinically undetectable and, consequently, constitute a major
238 issue for future tumor recurrence and metastases [101]. Current pharmacological approximations are
239 aimed at maintaining cancer cells in the dormant state; reactivating dormant cells to increase their
240 susceptibility to drugs; and eliminating cancer cells. Those strategies rely on the modulation of certain
241 factors present on or secreted by the dormant cells in such a way that their overexpression of
242 inhibition affects the fate of those dormant cells [102]. In this sense, the use of mesoporous silica
243 nanoparticles might be interesting to enhance those treatments, as they could be employed to load
244 therapeutic agents able to modulate the expression of those factors. In addition, they could be
245 employed to co-load those agents with antitumoral drugs, consequently enhancing the efficacy of the
246 treatments and minimizing tumor recurrence.

247 *3.2. Nanotechnology for Cancer Treatment*

248 Current anticancer treatments mainly rely on chemotherapy, radiotherapy and/or surgery [103–
249 105]. Those treatments, yet effective in many cases, present several drawbacks. In particular,
250 chemotherapy lacks of a great tumor tissue selectivity, leading to nonspecific drug distribution and
251 side effects. In this sense, nanoparticles have emerged as a powerful tool to encapsulate drugs and
252 reduce side effects [106–108].

253 The rationale behind the use of nanoparticles in cancer treatment relies on the Enhanced
254 Permeability and Retention effect (EPR effect), which is the basis of some commercialized
255 nanomedicines [109]. The EPR effect, first reported by Maeda and coworkers [110], promotes the
256 passive accumulation of nanoparticles in solid tumors as a result of the hypervasculature, the
257 enhanced permeability and the poor lymphatic drainage found in many tumors (Figure 3).
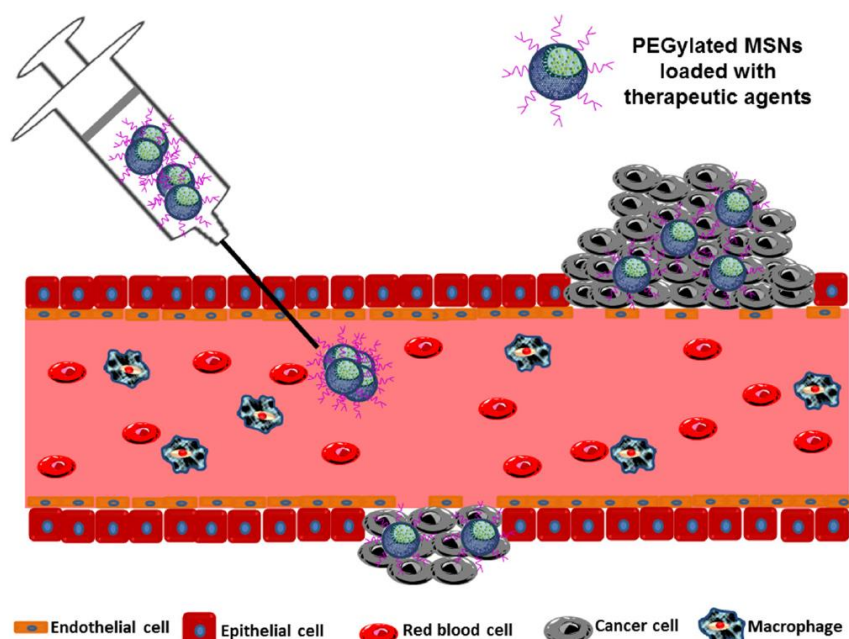
Figure 3. EPR effect. Nanoparticles passively accumulate in the tumor owing to the presence of fenestration in the tumor blood vessels. Once there, the particles remain in the tissue for long periods of time as a consequence of the poor lymphatic drainage. Reproduced from Ref [111] with permission of MDPI.

Owing to the uncontrolled angiogenesis, the newly formed vessels present an abnormal architecture, including wide fenestrations (200-2000 nm endothelial cell-cell gaps), irregular vascular alignment or lack of smooth muscle layer, among others. As a result, molecules larger than 40 kDa leak out from them and accumulate in the extravascular tumoral tissues. On the contrary, healthy tissues do not show this abnormal development and no accumulation is observed, thus creating a differential selectivity for cancer tissues [112]. In addition, unlike normal tissues where the extracellular fluid is constantly removed, tumors present defective lymphatic drainage and the accumulated macromolecules tend to remain in the tumoral mass for longer periods of time [113].

The magnitude of the EPR effect in humans highly depends on the particularities of the patient and the tumor [114] although some alternative strategies, such as tumor-homing peptides or some types of cells, are currently being explored to overcome the lack of EPR effect.

These alternative approximations have successfully been evaluated using *in* vivo tumor models, demonstrating the suitability of using MSNs for tumor drug delivery. In this sense, tumor-homing peptides (e.g., iRGD, iNGR) not only induce spontaneous accumulation of nanoparticles in the tumor tissues, but also enhance their diffusion into the tumoral mass [115,116]. In addition, there are certain types of cells with migratory properties that can transport nanoparticles directly to tumors tissues. For instance, nanoparticles can be attached to hypoxic bacteria that migrate to the hypoxic areas of tumors [117,118]. In addition, mesenchymal stem cells have been shown to migrate to tumors in response to the secretion of various signaling molecules. Then, a smart strategy is to induce the internalization of drug-loaded nanoparticles within these cells to then delivering them specifically to tumor tissues [119–122].

Besides delivering the nanoparticles to malignant tissues, the carriers can be engineered so that they preferentially recognize cancer cells over healthy cells. This targeting strategy relies on the overexpression of some receptors only on the membrane of tumoral cells. Examples of this approach include the functionalization of the particles with antibodies [123,124], proteins [70,125], small molecules [126–130] or peptides [131–133], among others.

3.3. Targeting Bone-Localized Tumors with Mesoporous Silica Nanoparticles

290   Addressing nanoparticles to bone metastases is challenging, as small metastases are poorly
291 vascularized and, consequently, the magnitude of the EPR effect is low compared to big solid tumors
292 [134]. A smart approximation would be the modification of the particles with targeting molecules
293 with high affinity towards calcium phosphate surfaces (bone tissue), such as bisphosphonates [135],
294 to complement the EPR effect. In this sense, the surface modification with the bisphosphonate
295 zoledronate has been proved to be effective in delivering MSNs to bone metastases originated from
296 lung [136] and breast cancer [137].
297   Besides targeting the particles to bone tissue, it would be desirable for the nanomedicines to be
298 subsequently internalized only by the tumoral cells. In this sense, our group recently reported a smart
299 approximation for the sequential targeting of bone tumors or bone metastases that could be easily
300 implemented into any nanomedicine (Figure 4) [138].

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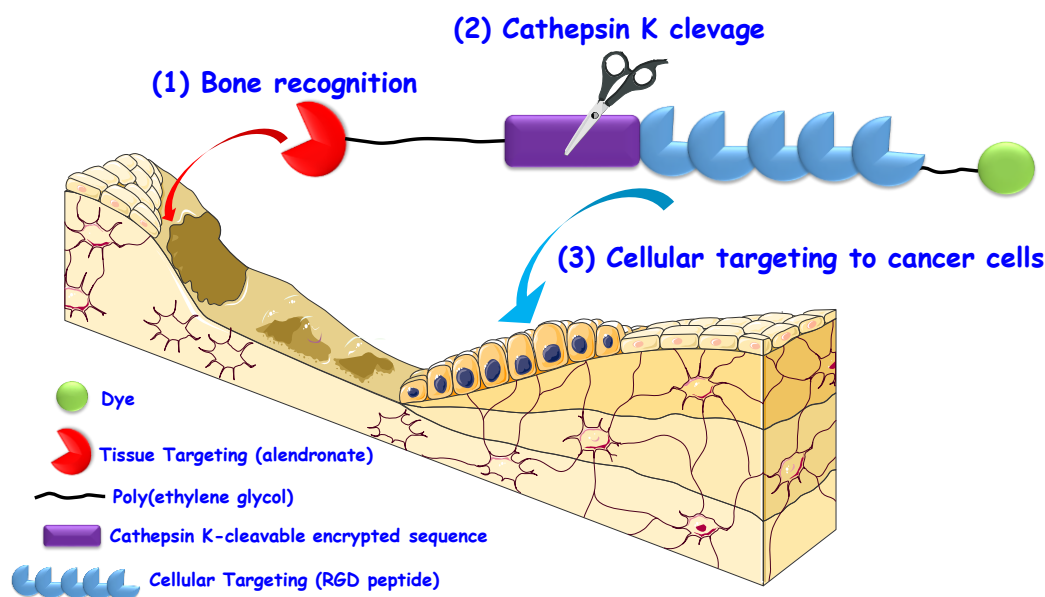
Figure 4. Encrypted approach for the sequential targeting of bone cancer tissue and cancer cells. (1)
The presence of a bone targeting agent (alendronate) would help accumulate the nanomedicines in
the bone tumor tissue; (2) Once there, the overexpressed cathepsin K would cleave a specific peptidic
sequence, (3) exposing the RGD (arginine-glycine-aspartic) motif, which is able to promote the
selective uptake of nanomedicine by sarcoma tumoral cells.

307   As observed in Figure 4, the system is composed of two targeting agents and employs PEG
308 chains to mimic a nanocarrier. The first one is the bisphosphonate alendronate, which can bind bone
309 tissue. Then, there is a peptidic fragment containing a cathepsin K-cleavable sequence followed by
310 the RGD motif, which is able to promote the selective internalization in osteosarcoma cells thanks to
311 the overexpression of $\alpha\beta$ integrins. In this manner, the alendronate molecule would help the EPR
312 effect to accumulate the nanomedicines in the bone tumor tissue. Once there, cathepsin K, which is
313 overexpressed in bone tumors and bone metastases, would cleave the encrypting sequence, thereby
314 exposing the RGD motif and triggering the preferential uptake of the nanomedicines.
315   As it happens with many other cancer cells, bone tumoral cells overexpress specific receptors
316 that can be targeted using conveniently engineered MSNs. Aside from targeting MSNs to
317 osteosarcoma [139], the RGD motif can also be employed to recognize endothelial cells, which can
318 help MSNs target the tumor endothelium of fibrosarcoma to then eliminate the cancerous cells using
319 multimodal therapy [140]. In this sense, folic acid can be employed to target overexpressed folate
320 receptors in fibrosarcoma [141] and osteosarcoma cells [142]. In addition, the modification of MSNs
321 with a glucose analog enhances their accumulation in bone tumor cells, as a consequence of their
322 great glucose consumption due to the high metabolic demand of tumors [143]. Some surface
323 receptors, such as the CD11c, can also be targeted using specific antibodies, which are able to trigger
324 the selective internalization of MSNs in osteosarcoma [144].

325   The decoration of MSNs with proteins can also increase their cellular uptake. For instance, the
326 lectin concanavalin A binds overexpressed sialic acid residues to promote the cellular uptake of pH-
327 responsive MSNs in osteosarcoma cells [145]. Transferrin receptors are overexpressed in
328 fibrosarcoma cells and, consequently, the protein transferrin can be employed to enhance the uptake
329 of MSNs in those bone tumoral cells [146].

330   Besides employing active targeting moieties, MSNs can be internalized *via* electrostatic
331 interactions with the negatively charged cell membrane. The positively charged surface can be
332 shielded using PEG, which can be detached using a cleavable bond. The charge is exposed again
333 upon application of ultrasounds, which triggers the nanoparticles uptake after the accumulation in
334 the solid bone tumor *via* EPR effect [147].

335 *3.4. Controlled Release of Therapeutics in Bone Tumors with Mesoporous Silica Nanoparticles*

336   There are various examples of the suitability of using silica-based mesoporous nanomatrices for
337 the delivery of antitumoral [148–152] or imaging agents [139,153,154] to bone cancer cells. Moreover,
338 researchers have taken advantage of the features of the bone tumoral environment to design stimuli-
339 responsive MSNs for the treatment of sarcomas. Among the internal stimuli, the acidic environment
340 of the lysosomes can be employed to trigger the drug release from pH-responsive polymer-coated
341 MSNs [145] or pulsatile on-off MSNs whose pore entrances are sealed with pH-responsive
342 nanovalves [155]. In addition, it is possible to load immunotherapy agents within the pores of pH-
343 responsive lipid-coated MSNs for synergistic chemo-immunotherapy [156]. In addition to pH
344 variations, the enzyme alkaline phosphatase, which is characteristic bone-related tumors, can be
345 employed to degrade the gatekeepers of silica-based mesoporous glasses [157]. Moreover, the
346 esterase enzymes can also be employed to cleave the nanocaps of MSNs [142].

347   There are some examples of the use of light to trigger the drug release from MSNs in bone tumor
348 scenarios. For instance, ultraviolet light can be employed to cleave light-responsive bonds connected
349 to transferrin, which acts as both gatekeeper and targeting agent, triggering the drug release [146]. In
350 addition, porphyrins can be engineered as gatekeepers using a linker cleavable in the presence of
351 singlet oxygen, which are self-produced by the porphyrin caps upon application of visible light [158].

352   Aside from delivering small therapeutic molecules, MSNs allow the effective delivery of
353 proteins [159] or DNA strands [160] into bone cancer cells. There is a type of nucleic acids, small
354 interfering RNA (siRNA), that triggers the knockdown of specific and relevant proteins, which makes
355 them useful for the treatment of various diseases [161]. Unfortunately, siRNAs have short half-life,
356 poor penetration through cell membranes and easily degrade upon RNase action in the organism
357 [162]. For that reason, the use of MSNs as protective shell for these nucleic acids have been widely
358 explored. In this sense, the polo-like kinase 1, which is an essential gene for the correct execution of
359 cell division [163], is overexpressed in bone tumors and has been targeted with great efficacy using
360 siRNA-loaded MSNs [164–167].

361   A summary of all the nanocarriers here described for bone tumors is summarized in Table 1.

362

pharmaceutics

MDPI

Table 1. Summary of the different silica-based nanocarriers applied for the treatment of bone tumors

Cell line	Description	Reference
Osteosarcoma		
MG-63	MSNs loaded with ammonia borate as negative computed tomography contrast agents for the diagnosis of osteosarcoma	[154]
	Silica-based mesoporous glass nanospheres for the delivery of alendronate against osteosarcoma cells and osteoclasts	[150]
	Silica-based mesoporous glasses with osteogenic properties for the release of alendronate against osteosarcoma cells	[149]
	Eu-doped silica-based mesoporous glass nanospheres with osteogenic properties for the release of doxorubicin	[148]
	Influence of the different functionalizations of MSNs on their uptake by osteosarcoma cells	[144]
KHOS	Poly-L-lysine-coated MSNs for the delivery of siRNA to knockdown polo-like kinase 1	[165]
	MSNs with large mesopores for the delivery of siRNA to knockdown polo-like kinase 1	[164]
	Co-loading of topotecan and siRNA to knockdown polo-like kinase 1 in dendrimer-like MSNs	[166]
	PEI-coated MSNs for the delivery of siRNA to knockdown polo-like kinase 1	[167]
HOS	Stimuli-responsive silica-based mesoporous glasses responsive to alkaline phosphatase overexpressed in bone tumors	[157]
	Dendrimer-coated MSNs for the delivery of non-viral oligonucleotides	[160]
	MSNs functionalized with singlet oxygen-sensitive porphyrin caps for release of topotecan	[168]
	MSNs engineered for ultrasound-induced cellular uptake through the detachment of a shielding PEG layer	[147]
	Concanavalin A-targeted and pH-responsive MSNs for the delivery of doxorubicin	[169]
HTB-85	Silica-based mesoporous glass nanospheres with osteogenic properties for the release of doxorubicin	[151]
U2Os	Folic acid-targeted MSNs for enzyme-responsive release of camptothecin	[142]
UMR-106	RGD-targeted and Bi-doped MSNs for chemo-photothermal therapy and imaging	[139]
Fibrosarcoma		
L-929	Ultrasound, pH and magnetically-responsive on-off gated MSNs for the delivery of doxorubicin	[155]
	Gd-doped MSNs for magnetic resonance imagining of fibrosarcoma	[153]
	pH-responsive MSNs for the intracellular delivery of proteins	[159]
	pH-responsive MSNs for combined chemo-immunotherapy	[156]
HT-1080	Influence of MSNs size on the doxorubicin release and the uptake of the particles by fibrosarcoma cells	[152]
	MSNs decorated through an ultraviolet light-responsive linker with transferrin acting as gatekeeper and targeting agent	[125]
	RGD-targeted MSNs for multimodal treatment of fibrosarcoma in a chicken embryo model	[140]

364

365   **4. Mesoporous Silica Nanoparticles for the Treatment of Bone Infection**

366   *4.1. General Concepts on Bacterial Bone Infections*

367   Bone infection is a major issue for health care systems and entails important socioeconomic
368   implications [170]. The appearance of bone infections is directly related with the progressive ageing
369   of current society and, consequently, the increased use of implantable medical devices and their
370   potential bacterial contamination. These infections are mainly caused by *Staphylococcus epidermis*,
371   *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* [40]. Regular bacteria can be
372   relatively easy eliminated using antibiotics. However, the inappropriate use of those antimicrobials
373   is progressively leading to more cases of drug-resistant bacteria, which are expected to cause more
374   than 10 million deaths by 2050 [171]. This antimicrobial resistance induces uncontrolled bacterial
375   growth and formation of persistent biofilms. Biofilms are communities of microorganisms embedded
376   in a self-produced polysaccharide matrix [172]. This protective matrix endows them with resistance
377   to antibiotics and host immune systems that, otherwise, would eliminate bacteria in their planktonic
378   state (free-floating bacteria) [173]. The biofilm—related antimicrobial resistance relies, not only on
379   the physical hindrance of the matrix, but also on (1) the presence of bacterial and host DNA and
380   proteins that may increase the shielding capacity of the matrix [174]; (2) the presence of bacteria with
381   different acquired resistances and antibiotic sensitivies [175]; (3) the development of efflux pumps
382   [176]; (4) the presence of enzymes able to degrade antimicrobials [177] and (5) the establishment of
383   quorum sensing (bacteria-bacteria communication) [178]. The process of biofilm formation is
384   depicted in Figure 3.
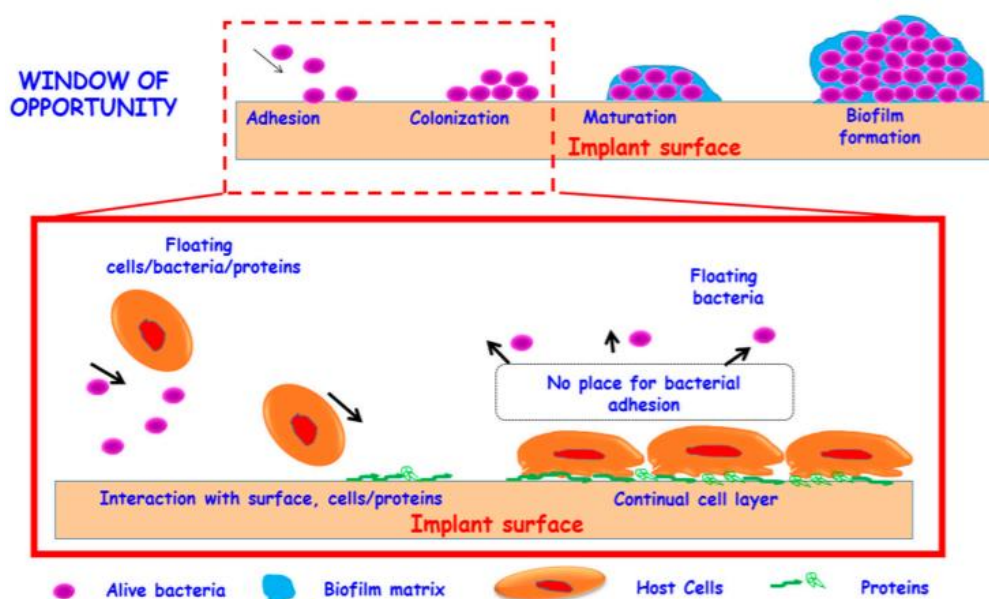
385

386   **Figure 3**. Schematic representation of biofilm formation on an implant surface. The process involves
387   4 steps: (1) bacterial adhesion, (2) bacterial growth, (3) maturation and (4) biofilm formation. In
388   addition, bacteria may leak out from the matrix and lead to bacterial dispersion. The first stages
389   constitute a *window of opportunity*, in which it is still possible to prevent biofilm formation.
390   Reproduced from Ref [40] with permission of MDPI.

391   The formation of the biofilm comprises 4 steps: (1) adhesion of bacteria to the implant surface;
392   (2) bacterial growth in multiple bacterial layers; (3) maturation and (4) final biofilm formation. In
393   addition, bacteria detach from the biofilm to then colonize other areas and induce further infections
394   [179]. As observed in Figure 3, during the first phases of biofilm formation the individual
395   microorganisms are floating on the implant, reversibly interacting with the surface. In consequence,

396 these stages constitute a *window of opportunity* that clinicians should take advantage of to prevent
397 irreversible biofilm formation and subsequent resistance [40].

398 *4.2. Preventing Protein and Bacterial Adhesion and Biofilm Formation: Zwitterionic Mesoporous Silica*
399 *Nanoparticles.*

400   In view of the evidences exposed in the previous subsection, avoiding bacterial contamination
401 of implants constitutes a major concern. In this sense, the development of the so-called *zwitterionic*
402 materials has fueled the design of antifouling nanostructured materials able to prevent protein
403 adsorption, bacterial adhesion and biofilm formation (Figure 4).
404
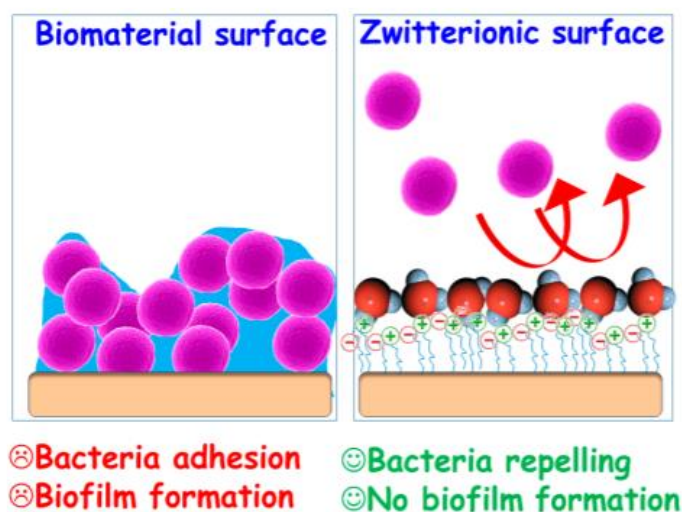
405

406 Figure 4. Schematic representation of bacterial colonization in standard surfaces *vs.* *zwitterionic*
407 surfaces. Unlike in unmodified surfaces, *zwitterionic* materials create a hydration layer that prevents
408 bacterial adhesion and biofilm formation. Reproduced from Ref [40] with permission of MDPI.

409   *Zwitterionic* surfaces are characterized by an equal number of negative and positive charges, so
410 the net charge is expected to be neutral. This neutrality leads to the formation of a hydration layer
411 onto the surface that physically hampers adhesion and biofilm formation [180]. In fact, owing to the
412 reduced protein adsorption, *zwitterionic* functionalizations have also been postulated as substitutes
413 for PEGylation [181], which might be beneficial to overcome the growing appearance of anti-PEG
414 antibodies [182].
415   The first example of mesoporous silica materials with *zwitterionic* behavior was reported by our
416 group back in 2010, using SBA-15 mesoporous materials modified with randomly distributed amino
417 and carboxylic acid short chains on the surface that resulted in significantly lower protein adhesion
418 [183]. A similar approach using amino and phosphonate groups was recently reported, yielding
419 MSNs with extremely low protein adsorption and excellent antibacterial properties. In addition, the
420 nanoparticles showed great biocompatibility with preosteoblasts, assuring their biocompatibility for
421 the treatment of bone infection [184]. Interestingly, this *zwitterionic* approach using two small
422 molecules can be employed to design pH-responsive gatekeepers by taking advantage of the
423 interaction between both short chains, which interact at physiological pH and experience repulsion
424 forces at acid pH [185].
425   Aside from merging molecules with opposite charges, there are molecules that are *zwitterionic*
426 in nature. In this sense, the modification of MSNs with phosphorylcholine groups yields
427 nanoparticles showing reduced protein adsorption and able to provide sustained drug release in
428 response to changes in pH [186]. An analogous approximation is the modification of MSNs with
429 sulfobetaine groups to prevent protein adhesion [187]. Moreover, it is possible to polymerize this
430 kind of *zwitterionic* molecules to yield polymer-coated nanoparticles with low protein binding affinity
431 [188]. In addition, there are some amino acids that are useful for the design of this kind of surfaces.
432 For instance, the amino acid lysine presents this behavior owing to the $-NH_3^+$/COO^- pairs and has

433 been grafted to MSNs [189] and silica-based mesoporous bioactive glasses [190], leading to reduced
434 bacterial adhesion and biofilm formation. A similar approach consists in using the amino acid
435 cysteine to obtain neutral surfaces, yielding MSNs with high stability in human serum [191].

4.3. Addressing Bone Infections with Mesoporous Silica Nanoparticles

437 Besides preventing biofilm formation, it is still necessary the elimination of the infection. In this
438 sense, it is possible to engineer multifunctional mesoporous silica nanomatrices able to prevent
439 bacterial adhesion and biofilm formation and to release antimicrobials in a controlled manner only
440 in infected bone tissues [192,193]. In addition, there are examples of stimuli-responsive mesoporous
441 bioactive silica-based nanomatrices able to trigger the release only in the presence of proteolytic
442 enzymes characteristics of infected bone tissue scenarios [157,194].
443 In an effort to increase the efficiency of the delivery and, consequently, a reduction of the dose,
444 the research efforts have been headed towards the development of bacteria-targeted MSNs. In this
445 sense, the presence of positive charges on the surface of the particles increases their affinity to the
446 negatively charged biofilm and bacteria wall. In this manner, it is easier for the particles to diffuse
447 into the biofilm to then interact with bacteria and exert their therapeutic effect. Examples of this
448 approach include the use of short positively charged alkoxysilanes [195] or third-generation
449 dendrimers, whose great number of positive charges is able to permeate the bacteria wall and induce
450 the MSNs internalization [196]. Besides using positively charged MSNs, lectins have been shown to
451 be effective in targeting and promoting internalization of MSNs into the biofilm, as a consequence of
452 the presence of glycan-type polysaccharides in this protective matrix. In fact, the lectin concanavalin
453 A is able to trigger this internalization and exert antibacterial effect by itself, which is even more
454 emphasized when loading an antibiotic in the mesopores [197].
455 A smart approximation to enhance the possibilities that mesoporous silica materials may offer
456 against bone infection is the incorporation of the particles within scaffolds. In the context of bone
457 diseases, scaffolds are materials that are intended to mimic bone tissue and contribute to its
458 regeneration. The advantages over using bare scaffolds are increased antibiotic loading capacity or
459 controlled drug release, among others [198]. Examples of this approximation are the incorporation of
460 silica-based mesoporous glasses in PLGA (poly-(L-lactic-co-glycolic acid)) [199] or MSNs in porous
461 collagen gelatin [200] for the controlled release of vancomycin against bone infection. In addition,
462 MSNs-loaded scaffolds allow the co-delivery of therapeutic compounds. In this sense, it is possible
463 to load cephalexin within the mesopores and vascular endothelial growth factors in the scaffold
464 structure to achieve bacteria elimination and bone reconstruction [201].
465 A summary of different materials for the treatment of bone infection can be found in Table 2.
466
467

468

Table 2. Summary of mesoporous silica-based materials against bone infection

Bacteria	Description	Reference
E.coli	Pronase-responsive gatekeepers for levofloxacin-loaded silica-based mesoporous glasses	[202]
	Levofloxacin-loaded *Zwitterionic* MSNs with reduced protein adhesion	[184]
	Lysine-coated MSNs to inhibit *e.coli* adhesion	[189]
	Acid phosphatase-responsive gatekeepers for levofloxacin-loaded silica-based mesoporous glasses	[203]
	Positively charge MSNs target the bacteria wall of *e.coli*	[195]
	Levofloxacin-loaded MSNs coated with polycationic dendrimers destroys biofilm and internalize in bacteria	[204]
	Levofloxacin-loaded MSNs decorated with concanavalin A targets and internalize the biofilm	[197]
S.aureus	Levofloxacin-loaded *Zwitterionic* MSNs with reduced protein adhesion	[184]
	Lysine-coated *zwitterionic* MSNs to inhibit *s.aureus* adhesion and *s.aureus* biofilm formation	[189]
	Lysine-coated *zwitterionic* silica-based mesoporous glasses to prevent *s.aureus* adhesion	[190]
	Levofloxacin-loaded and positively charged MSNs targets and destroy *s.aureus* biofilm and bacteria	[195]
	MSNs-loaded scaffolds for the co-delivery of cephalexin and vascular endothelial growth factor	[201]
	Vancomycin-loaded silica-based mesoporous glasses contained in PLGA scaffolds	[199]
	Vancomycin-loaded MSNs contained in collagen gelatin scaffolds	[200]

469

5. Mesoporous Silica Nanoparticles for the Treatment of Osteoporosis

5.1. General Concepts on Osteoporosis

Osteoporosis is the most frequent metabolic disease affecting bone tissue. It is characterized by reduced bone mass and microarchitectural deterioration and results in more than 9 million fractures annually worldwide (one osteoporotic fracture every 3 seconds) [205], with special incidence in aged women [206]. Its origin relies on the alteration of the bone remodeling process, which consists in the removal of old bone (osteoclast) to then create new one (osteoblasts). The imbalance of this process leads to reduced bone mass and, consequently, osteoporosis.

Current osteoporosis treatments, which are not fully satisfactory, are limited to anti-resorptive drugs and anabolic agents [207,208]. Anti-resorptive drugs decrease the excess of bone resorption by targeting osteoclast activity. Examples of these compounds include bisphosphonates [209], raloxifene [210] or denosumab [211]. The excess of bone resorption can be counteracted using anabolic agents, which are compounds able to stimulate bone formation. Examples of these drugs are human parathyroid hormone [212], growth factors or siRNA [213].

Unfortunately, current treatments present some drawbacks. For instance, bisphosphonates are known to induce gastric side effects or fractures after long use. Raloxifene may cause venous thromboembolism. Moreover, cases of hypocalcemia, anaphylaxis or atrial fibrillation have been associated to denosumab. In addition, anabolic agents, such as siRNA, might be easily degraded by the harsh environment present in the organism [212]. These issues might be addressed by delivering the antiosteoporotic agents specifically to the diseased bone tissues and, consequently, the use of nanoparticles seems highly appealing.

### 5.2. Addressing Osteoporosis with Mesoporous Silica Nanoparticles

The first example of mesoporous silica materials applied for the controlled release of anti-resorptive molecules was reported by our group back in 2006, when MCM-41 and SBA-15 materials were employed for the loading and controlled release of alendronate [214]. In this sense, the introduction of phosphorous groups in SBA-15 mesoporous silica nanomatrices enhanced the loading of alendronate and induced the formation of apatite, a component of bone, making these materials promising candidates for the treatment of osteoporosis [215]. Additional examples of anti-resorptive molecules loaded in mesoporous silica-based nanoparticles are ipriflavone [216], salmon calcitonin [217] or zolendronic acid [218], showing all of them promising results in terms of anti-osteoclast activity and osteogenesis.

A great feature of MSNs is that they allow the loading of hydrophobic compounds, consequently enhancing their bioavailability. In this sense, they allow the incorporation within their mesopores of sparingly soluble anabolic agents able to induce bone formation. Examples are the loading of dexamethasone, which induces bone regeneration through the stimulation of bone mesenchymal stems cells [219], or estradiol, which enhances the biological functions of osteoblast and inhibits the proliferation of osteoclasts [220].

Osteostain, a C-terminal peptide from a parathyroid hormone-related protein, induces strong bone anabolism through a great stimulation of osteoblastogenesis [221]. It has been shown that osteostatin-loaded SBA-15 greatly stimulate osteoblastic growth *in vitro* [222]. Furthermore, these osteostatin-loaded mesoporous materials have been proved to be effective in regenerating bone defects *in vivo* [212,223]. In addition to osteostatin, the bone morphogenic protein-2 (BMP-2) is considered to be one of the most effective growth factors to induce osteoblast differentiation and boost bone regeneration. In this sense, MSNs are useful for the co-delivery of dexamethasone and BMP-2 to achieve great bone regeneration *in vivo* [224]. Moreover, the residues 73-92 of BMP-2 not only promote osteogenesis and bone regeneration but also increase the internalization of bone mesenchymal stem cells of MSNs decorated with this peptidic fragment. [225].

517   Aside from being useful for bone cancer treatment, siRNA molecules also find application in the
518 treatment of osteoporosis. In this sense, the localized release of siRNA able to knockdown RANK
519 from silica-based mesoporous bioactive glasses has been to shown to be highly effective in
520 suppressing osteoclastogenesis and, consequently, osteoporosis [226]. A similar approach against
521 osteoporosis was recently reported by our group using an *in vivo* model of ovariectomized mice
522 (Figure 5).

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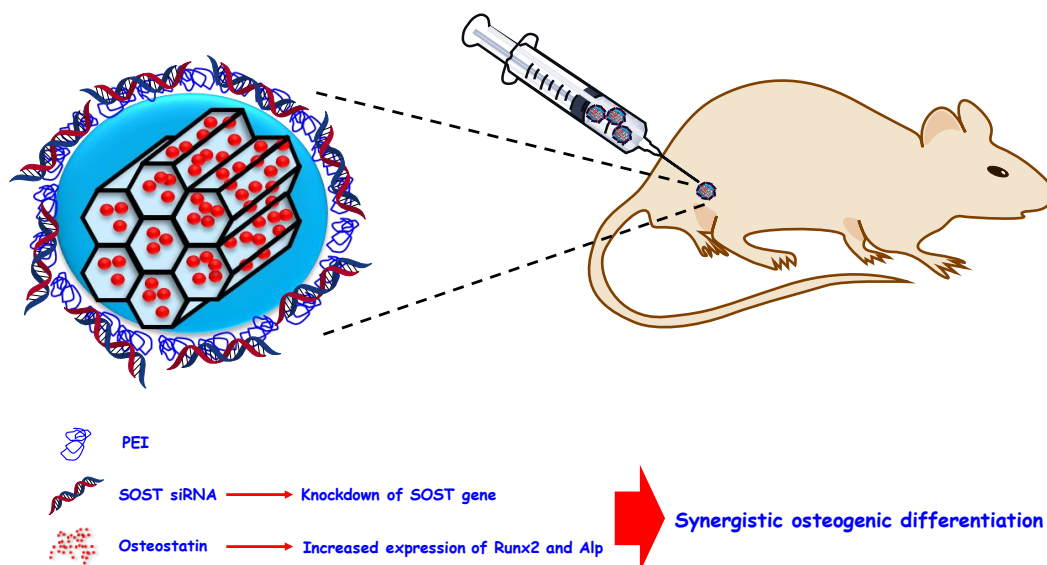
524   Figure 5. PEI-coated MSNs as anti-osteoporotic nanocarrier. Osteostatin was loaded in the mesopores
525   and a siRNA able to knockdown SOST gene was introduced within the polymeric mesh. The co-
526   delivery of both therapeutic agents resulted in synergistic osteogenesis in ovariectomized mice. PEI:
527   Polyethyleneimine.

528   MSNs can load therapeutic compounds not only in their mesopores but also within polymeric
529 coatings through electrostatic interaction. In this sense, Figure 5 shows MSNs carrying the anabolic
530 agent osteostatin in the pores and a specific siRNA able to knockdown SOST gene interacting with a
531 PEI coating. This gene encodes the protein sclerostin, which can inhibit the Wnt/β-catenin pathway,
532 a major signaling carrier that regulates bone development and remodeling. Based on this, the siRNA
533 and osteostatin-loaded nanoparticles were administered to osteoporotic ovariectomized mice,
534 showing synergistic effects on all the bone regeneration biomarkers studied [227].
535   There are some metal ion species known to induce osteogenesis. For instance, copper ions
536 enhance bone density by inhibiting bone resorption, and their incorporation in mesoporous silica
537 nanospheres has been proved to be effective in stimulating the differentiation of bone mesenchymal
538 stem cells into the osteogenic lineage [228]. Moreover, impregnating silica-based mesoporous
539 bioactive glasses with Ga (III) leads to the formation of apatite together with the disruption of
540 osteoclastogenesis and early differentiation of pre-osteoblast towards osteoblastic phenotype [229].
541 In addition, the osteogenic ability of Zn^{2+} ions is enhanced when the ions are co-delivered with
542 osteostatin from silica-based mesoporous bioactive glasses [230]. Furthermore, there are
543 nanoparticles able to stimulate bone regeneration *per se*. Examples of these kind of behavior are Au
544 nanoparticles supported on MSNs that increase the osteogenic capability of preosteoblastic cells [231]
545 or silica-based mesoporous bioactive glasses that are capable of reducing the bone-resorbing
546 capability of osteoclasts [232].
547   A summary of all the above-described materials for the treatment of osteoporosis can be found
548 in Table 3.

549

pharmaceutics

MDPI

Table 3. Summary of silica-based mesoporous materials for the treatment of osteoporosis

Therapeutic agent	Description	Reference
Anti-resorptive treatment		
Alendronate	First example of controlled release of bisphosphonates from mesoporous silica materials (MCM-41 and SBA-15)	[214]
	Phosphorus-containing SBA-15 mesoporous silica materials for bone regeneration and release of alendronate	[215]
Ipriflavone	Silica-based mesoporous nanospheres for the release of ipriflavone without affecting osteoblast viability	[216]
Zolendronic acid	Zolendronic acid-loaded MSNs/hydroxyapatite coatings on implants with enhanced inhibition of osteoclasts activity	[218]
Salmon calcitonin	MSNs for the release of salmon calcitonin with significant therapeutic effects *in vivo*	[217]
siRNA (RANK)	Silica-based mesoporous glass nanospheres to deliver of siRNA to knockdown RANK and inhibit osteoclastogenesis	[226]
Ions	Mesoporous silica-based nanospheres for the delivery of Cu ions able to inhibit osteoclastogenesis	[228]
	Silica-based mesoporous glasses for the release of Ga ions able to disturb osteoclastogenesis	[229]
Particle	Silica-based mesoporous glasses reduce the bone-resorbing capability of osteoclasts *per se*	[232]
	Au nanoparticles supported on MSNs increases the osteogenic capability of pre-osteoblastic cells	[231]
Anabolic treatment		
Dexamethasone	Alendronate-targeted MSNs for the delivery of dexamethasone to bone tissue	[219]
Estradiol	Multilayered-coated MSNs for the delivery of estradiol from titanium substrates	[220]
Osteostatin	Osteostatin-loaded SBA-15 mesoporous silica materials stimulates the growth and differentiations of osteoblasts	[222]
	Osteostatin-loaded SBA-15 mesoporous materials regenerates bone in a rabbit femur cavity defect	[212]
	Osteostatin-loaded SBA-15 mesoporous silica materials increase the early repair response in bone after local injury	[233]
BMP-2 and dexamethasone	pH-responsive co-delivery of dexamethasone and BMP-2 protein for synergistic osteogenic effect	[224]
	BMP-2 derived peptide-decorated MSNs for enhanced uptake in bone mesenchymal stem cells and synergistic effect of the peptidic fragment and dexamethasone	[225]
Osteostatin and siRNA (SOST)	Enhanced osteogenic expression through MSNs co-delivering osteostatin and siRNA able to knockdown SOST gene	[227]
Zn ions and osteostatin	Co-delivery of osteogenic Zn ions and osteostatin from mesoporous silica-based glasses induces high osteogenic response	[230]

6. Conclusions

Complex bone diseases, such as bone cancer, bone infection and osteoporosis, constitute a major concern for our progressively aged modern societies. Most of the current treatments present several drawbacks, leading to the deterioration of the patient health and the subsequent socioeconomic impact. In this sense, the use of nanoparticles, in particular mesoporous silica-based nanoparticles, has emerged as a powerful approximation to reduce the different side effects. This type of nanoparticles present high loading capacities, biocompatibility and can be engineered to prevent premature drug release and address the particles to the affected tissues. The different nanosystems here presented constitute reliable approximations for the treatment of bone diseases and, consequently, current research should be headed towards the effective translation of these nanomaterials into the clinic.

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Conflicts of Interest: The authors declare no conflict of interest.

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