Silica-Based Stimuli-Responsive Systems

Subjects: Materials Science, Biomaterials

Contributor: Pablo Botella Asuncion

Silica nanoparticles are safe vehicles for antitumor molecules due to their stability in physiological medium, high surface area and easy functionalization, and good biocompatibility. Silica surface can be engineered with specific organic moieties for the development of stimuli-responsive systems (SRSs), that is, delivery nanostructures that release their cargo under the action of a specific stimulus. When used as drug carriers, these stimuli-responsive nanoparticles are good candidates for strong therapeutic activity with no toxicity effects.

silica nanoparticles drug delivery stimuli-responsive controlled release cancer therapy camptothecin docetaxel doxorubicin

1. Introduction

In recent years, nanoparticles have emerged as key players in modern medicine, with applications ranging from contrast agents in medical imaging to gene delivery carriers in individual cells. An increasing number of nanotherapeutic drugs have already been commercialized or reached the clinical stage [1]. In the case of oncologic applications, and compared to simple molecule therapies, currently most FDA-approved nanoparticle-based drug delivery systems (DDSs) are being designed for the re-formulation of combinations of chemotherapeutic drugs, looking for enhanced pharmacokinetics (PK), biocompatibility, tumor-targeting, and stability, while simultaneously minimizing systemic toxicity and overcoming drug resistance [2]. Furthermore, the possibility of introducing tracking moieties to promote medical imaging leads to the development of efficient theranostic systems, which are able to carry out diagnostic and therapy in one go [3].

In this context, the use of silica nanoparticles (SNPs), and especially of mesoporous silica nanoparticles (MSNs), in drug delivery was formerly based on their physical and textural properties, with empty mesoporous channels to absorb relatively large amounts of bioactive molecules. Different groups have systematically studied the influence of pore diameter, pore structure, surface area, and pore volume on drug loading and release rate [4][5]. It has been shown that the decrease in pore diameter leads to a decrease in drug-loading quantity and release rate. At the same time, the pore structure type in terms of pore connectivity may condition the diffusion process and, in this sense, a one-dimensional pore structure with cage-like pores is the most promising pore geometry for providing high drug-loading amount and slow drug release. Additionally, both pore volume and surface area favor the incorporation of drug molecules within the mesoporous structure.

The incorporation of drugs in SNPs can take place through non-covalent interactions, such as hydrogen bonding, physical adsorption, electrostatic interaction, and π–π stacking [6][7]. Unfortunately, in most cases, these kinds of interactions are very weak, and some or total premature release of the cargo may occur before reaching the destination. The premature release problem not only limits the use of a DDS for effective therapy, but also plays a major challenge on possible side effects that can be related to the activity of the active principle outside the targeted cells or tissue. In this sense, surface functionalization of SNPs with appropriate organic groups allows for the incorporation of the therapeutic molecules by more stable interacting forces, such as ionic bond and covalent bond. These functionalized mesoporous SNPs are highly stable DDSs, able to deliver the drug with no leakage before reaching the designated site of cells or tissue.

Furthermore, silica surface can be engineered with specific organic moieties for the development of stimuli-responsive systems (SRSs), that is, delivery nanostructures that release their cargo under the action of a specific stimulus [8]. When used as drug carriers, these stimuli-responsive nanoparticles are good candidates for strong therapeutic activity with no toxicity effects. A wide range of different SRSs can be classified as endogenous or exogenous, depending on the nature of the stimulus (internal or external) used to release the therapeutic agent at the specific site without premature release. However, these “smart” systems can be tailored to respond selectively to (i) internal stimuli such as pH, redox, enzyme, or temperature; and (ii) external stimuli such as magnetic field, light, and ultrasound [9][10][11]. It is important to note that charge release, in both cases, occurs via a different pathway. While SRSs that respond to internal stimuli take advantage of the differences between cancerous and normal tissue environments, SRSs that are sensitive to external stimuli modify their characteristics or properties in the presence of a physical event. One of the main advantages of these “smart systems” is that, by controlling the release of the drug in a specific area of the tissue, they allow, on the one hand, side effects to be minimized and, on the other hand, efficacy of the treatment to be improved [10].

At this point, selective cancer therapy needs to develop methodologies to target malignant cells and minimize the impact on healthy tissue. For this purpose, different components have been used as targeting moieties, as small molecules, peptide sequences, polysaccharides, aptamers, and antibodies. Actually, recent studies have been focused on cancer therapy with targeting molecules, such as aptamers and monoclonal antibodies [12][13]. The use of monoclonal antibodies for tumor targeting of drug delivery platforms is an important tool for clinical applications, due to their high affinity, specificity, and versatility. The term ‘affinity’ refers to the strength of the interaction between a single region of the monoclonal antibody and a single antigen. In this strategy, antibodies bind specifically to the corresponding antigens overexpressed on the surface on cancer cells, which can lead to selective drug accumulation at the tumor site [14]. The main benefit of this strategy is the reduction in adverse effects by selective interactions between antibody and cell-surface receptors [15].

2. Stimuli-Responsive Systems Based in Endogenous Activity

These nanodevices can be tailored by introducing breakable bonds or gatekeepers into the nanoparticle structure as pore blockers, which can degrade in response to an internal feature of the organism, including pH, enzymes, redox environment, and temperature. Some of the most significant proposed endogenous or internal stimulus-response systems are presented in **Table 1**.

Table 1. Types of MSN-based internal stimuli-responsive systems for drug delivery.

Stimulus	Drug Loading	Release System	Release Mechanism	Ref.
pH	Doxorubicin	MSNs grafted with the pH sensitive linker ATU and coated with the acid degradable polymer PAA	Acid-cleavable acetal (ATU) linker	[16]
	Doxorubicin and pheophorbide a	Hollow MSNs decorated with chitosan as a capping layer and GPTMS as crosslinking and attaching agent	At acidic pH, the CS/GPTMS layer swells, leaving the pores free.	[17]
	Doxorubicin	MSNs conjugated with supramolecular switches forming by hydrazone bond, azobenzene and α-cyclodextrin	Hydrolyzation of acid-sensitive hydrazine bonds	[18]
	Sulforhodamine B	MSNs with functionalized pore walls and grafted with a pH-responsive cross-linked polymer pDAEM	Protonation/deprotonation of tertiary amines of polymer	[19]
Redox	Camptothecin (CPT)	Silica hybrid nanoparticles conjugated with pyridine-2-yldisulfanyl)alkyl carbonate derivatives of CPT	Disulfide reduction, intra-molecular cyclization, and dissociation of nanoparticles	[20] [21]
	Pyrene	Spherical PLGA nanoparticles containing	Disulfide bridge reduction and pore opening	[22]

Stimulus	Drug Loading	Release System	Release Mechanism	Ref.
		hydrophobic molecules covered by a thin layer of a redox-responsive amorphous organosilica shell		
	Hydroxycamptothecin (HCPT)	Disulfide-doped organosilica-micellar hybrid nanoparticles	Two stage rocket-mimetic redox responsive mechanism. First, detachment of disulfide-bond of PEG and second, degradation of disulfide-doped silsesquioxane framework	[23]
	Ribonuclease A (RNase A)	Diselenide-bridged mesoporous SNPs	Degradation of diselenide bridge in oxidative and reduction conditions	[24]
Enzyme	Doxorubicin	Hollow MSNs grafted with chitosan as a gatekeeper by an azo linkage	Degradation of azo bonds	[25]
	Doxorubicin	Hybrid nanospheres composed of an organic core (liposome) and an inorganic shell formed by ester fragments bonded covalently to silica units	Ester bond hydrolysis	[26]
	Camptothecin	Amorphous SNPs decorated with CPT	Ester bond hydrolysis	[27]
	Docetaxel (DTX)	MSNs conjugated with	Ester bond hydrolysis	[28]

Stimulus	Drug Loading	Release System	Release Mechanism	Ref.
		DTX and a PSMA antibody		
Temperature	Doxorubicin hydrochloride	Magnetic MSNs coated with polymer poly(N-isopropylacrylamide-co-acrylamide) as a gate-keeper	Conformational change in thermoresponsive polymer P(NIPAM-co-MAA)	[29]
	Rhodamine 6G	Solid core mesoporous shells and nonporous solid corer SNPs grafted with poly(N-isopropylacrylami-de) brushes	Conformational change in thermoresponsive polymer PNIPAM	[30]
	Doxorubicin	Hollow MSNs coated with poly(N-isopropylacrylamide) modified with metha acrylamide (Mam) and with Fe_3O_4 nanoparticles embedded in the polymer shell	Conformational change in thermoresponsive polymer P(NIPAM-Mam)	[31]

3. Stimuli-Responsive Systems Based in Exogenous Activity

Systems based on exogenous stimuli work like a switch. When activated by an external stimulus to the human body (light, magnetic field, and ultrasound), their physicochemical properties are modified, and the release of the therapeutic agent incorporated in the nanoparticles into the desired tissue or cells is controlled. However, the nanocarrier cannot carry out the release without the presence of this stimulus [32][33]. **Table 2** presents some of the most significant proposals for exogenous or external stimuli-responsive systems.

Table 2. Types of MSN-based external stimuli-responsive systems for drug delivery.

or

stems

herapy. Theranostics 2020, 10, 956–967.

4. Vallet-Regí, M.; Balas, F.; Arcos, D. Mesoporous Materials for Drug Delivery. Angew. Chem.-Int. Ed. 2007, 46, 7548–7558.
5. Rosenholm, J.M.; Linden, M. Towards Establishing Structure-Activity Relationships for Mesoporous Silica in Drug Delivery Applications. J. Control. Release 2008, 128, 157–164.
6. Tang, S.; Huang, X.; Chen, X.; Zheng, N. Hollow Mesoporous Zirconia Nanocapsules for Drug Delivery. Adv. Funct. Mater. 2010, 20, 2442–2447.
7. Popova, M.; Koseva, N.; Trendafilova, I.; Lazarova, H.; Mitova, V.; Mihály, J.; Momekova, D.; Konstantinov, S.; Koleva, I.Z.; Petkov, P.S.; et al. Design of PEG-Modified Magnetic Nanoporous Silica Based Miltefosine Delivery System: Experimental and Theoretical Approaches. Microporous Mesoporous Mater. 2021, 310, 110664.

Stimulus	Drug Loading	Release System	Release Mechanism	Ref.
Magnetic	Camptothecin	MSNs capped with monodispersed Fe_3O_4 nanoparticles through chemical bond	Chemical bond cleavage	[34]
	Doxorubicin	Monodispersed manganese and cobalt doped iron oxide nanoparticles with a silica shell conjugated with the 4,4′-azobis(4-cyanovaleric acid) as a gate-keeper	Cleavage of the gatekeeper	[35]
Light	Fluorescein disodium and Camptothecin	MSNs modified with an optimal molar ratio of spiropyran and perfluorodecyltriethoxysilane	Conformational conversion of spiropyran	[36]
	Camptothecin	Light-activated mesostructured silica (LAMSs) nanoparticles functionalized with azobenzene moieties	Trans-cis photoisomerization of azobenzene	[37]
	Camptothecin	Nanoimpellers functionalized with azobenzene moieties and a two-photon fluorophore F	Trans-cis photoisomerization of azobenzene	[38]
	Camptothecin	Gold nanoclusters with a homogeneous thin monolayer of amorphous silica ($Au@SiO_2$)	Diffusion (promoted by local hyperthermia)	[39]
Ultrasound	Topotecan hydrochloride	MSNs functionalized with poly(ethylene glycol) and 4,4′-azobis(4-cyanovaleric acid)	Cleavage of the azo moiety of the thermosensitive linker	[40]
	Gadopentetate dimeglumine $Gd(DTPA)^{2-}$	MSNs with pores capped with poly(ethylene glycol)	Poly(ethylene glycol) bond cleavage	[41]

Botella, P. Glutathione-Sensitive Nanoplatform for Monitored Intracellular Delivery and Controlled Release of Camptothecin. RSC Adv. 2013, 3, 15121–15131.

21. Botella, P.; Muniesa, C.; Vicente, V.; Cabrera-García, A. Effect of Drug Precursor in Cell Uptake and Cytotoxicity of Redox-Responsive Camptothecin Nanomedicines. Mater. Sci. Eng. C 2016,

58, 592–599.

4. Targeting Molecules

Specific diffusion to cancer cells is mandatory in order to achieve high efficacy in chemotherapy with minimum effects over healthy tissue [42]. Here, it must be considered that when nanoparticles reach the bloodstream, passive targeting to tumor is usually promoted by the partial degradation of endothelium during the angiogenesis process, which allows accumulation into tumor area (enhanced permeability and retention effect, EPR) [43]. However, molecular and biological recognition may improve the selectivity of the treatment, with specific interactions ligand–receptor driving particle endocytosis into the malign cells [44].

Targeting moieties are usually incorporated on nanoparticle surface by covalent linking, mostly ester bond, amide bond and maleimide–thiol coupling [45], and the success of molecular recognition depends on the overexpression of the targeted receptors and, specially, on the affinity between the complementary blocks. According to the molecular size and chemical nature, tumor targeting molecules can be classified into five categories: (i) small molecules; (ii) polysaccharides; (iii) peptides; (iv) aptamers; and (v) antibodies. We, here, present some of the most relevant examples of application in silica-based nanomedicines.

Probably the most used targeting component has been folic acid (FA), based in the overexpression of FOLH1 receptors in many cancer types. For instance, MSNs functionalized with FA and camptothecin (CPT) have been used for targeted therapy of human breast cancer xenografts in mice, showing a significant increase in the tumor suppressing effect [46]. These authors explain this unexpected result due to the high CPT dosage and the lack of folate receptor expression in MCF-7 cells. In a further study, these authors developed silica-based nanomedicines using the so-called nanovalve concept, and functionalized with FA. In vitro testing showed active internalization when FA was a part of the nanocarrier surface [47].

Polysaccharides are usually applied as biodegradable coatings to nanomedicines, but some of them have shown targeting properties to specific tumor cells. Hyaluronic acid (HA) interacts with overexpressed receptor in cancer cells cluster determinant 44 (CD44) and receptor for HA-mediated motility (RHAMM) [48]. Through interaction with receptors, HA allow enhanced targeting in cancer therapy. Here, HA has been incorporated over doxorubicin-loaded MSNs due to its specific affinity to CD44 receptors, overexpressed on human colon cancer cell line HCT-116. The resulting conjugated showed stronger cytotoxic activity to HCT-116 cell than the free drug and non-targeted nanoparticles, due to the enhanced cell internalization behavior of HA-MSNs [49].

Interestingly, some peptides have exhibited potential for tumor targeting and gene delivery, despite their low specificity for antigens and nanocarriers [44]. Recently, C.J. Brinker's group proposed a modular design of a protocell system, in which a peptide targeting specific cancer cells overexpressed protein receptors (e.g., IL-11Rα, GRP78, and EphA5) is conjugated to a core–shell material, with a lipid bilayer coating, and a silica nucleus containing the therapeutic cargo. Specific tumor therapies were proposed, by exchanging the targeting peptide and/or therapeutic cargo [50]. In addition, SNPs, MSNs, and hollow MSNs have been functionalized with epidermal growth factor receptor (EGFR), an anticancer drug target for a number of cancers, such as non-small cell lung cancer, resistance

22. Quesada, M.; Muniesa, C.; Botella, P. Hybrid PLGA-Organosilica Nanoparticles with Redox-Sensitive Molecular Gates. Chem. Mater. 2013, 25, 2597–2602.
23. Jin, X.; He, J.; Shen, L.; Chen, J.; Wei, Z.; Qin, X.; Niu, D.; Li, Y.; Shi, J. Gradient Redox-Responsive and Two-Stage Rocket-Mimetic Drug Delivery System for Improved Tumor Accumulation and Safe Chemotherapy. Nano Lett. 2019, 19, 8690–8700.
24. Shao, D.; Li, M.; Wang, Z.; Zheng, X.; Lao, Y.H.; Chang, Z.; Zhang, F.; Lu, M.; Yue, J.; Hu, H.; et al. Bioinspired Diselenide-Bridged Mesoporous Silica Nanoparticles for Dual-Responsive Protein Delivery. Adv. Mater. 2018, 30, 1801198.
25. Cai, D.; Han, C.; Liu, C.; Ma, X.; Qian, J.; Zhou, J.; Li, Y.; Sun, Y.; Zhang, C.; Zhu, W. Chitosan-Capped Enzyme-Responsive Hollow Mesoporous Silica Nanoplatforms for Colon-Specific Drug Delivery. Nanoscale Res. Lett. 2020, 15, 123.
26. Corma, A.; Díaz, U.; Arrica, M.; Fernández, E.; Ortega, Í. Organic-Inorganic Nanospheres with Responsive Molecular Gates for Drug Storage and Release. Angew. Chem.-Int. Ed. 2009, 48, 6247–6250.
27. Botella, P.; Abasolo, I.; Fernández, Y.; Muniesa, C.; Miranda, S.; Quesada, M.; Ruiz, J.; Schwartz, S.; Corma, A. Surface-Modified Silica Nanoparticles for Tumor-Targeted Delivery of Camptothecin and Its Biological Evaluation. J. Control. Release 2011, 156, 246–257.
28. Rivero-Buceta, E.; Vidaurre-Agut, C.; Vera-Donoso, C.D.; Benlloch, J.M.; Moreno-Manzano, V.; Botella, P. PSMA-Targeted Mesoporous Silica Nanoparticles for Selective Intracellular Delivery of Docetaxel in Prostate Cancer Cells. ACS Omega 2019, 4, 1281–1291.
29. Tian, Z.; Yu, X.; Ruan, Z.; Zhu, M.; Zhu, Y.; Hanagata, N. Magnetic Mesoporous Silica Nanoparticles Coated with Thermo-Responsive Copolymer for Potential Chemo- and Magnetic Hyperthermia Therapy. Microporous Mesoporous Mater. 2018, 256, 1–9.
30. Baliś, A.; Wolski, K.; Zapotoczny, S. Thermoresponsive Polymer Gating System on Mesoporous Shells of Silica Particles Serving as Smart Nanocontainers. Polymers 2020, 12, 888.
31. Asghar, K.; Qasim, M.; Dharmapuri, G.; Das, D. Thermoresponsive Polymer Gated and Superparamagnetic Nanoparticle Embedded Hollow Mesoporous Silica Nanoparticles as Smart Multifunctional Nanocarrier for Targeted and Controlled Delivery of Doxorubicin. Nanotechnology 2020, 31, 455604.
32. Raza, A.; Rasheed, T.; Nabeel, F.; Hayat, U.; Bilal, M.; Iqbal, H.M.N. Endogenous and Exogenous Stimuli-Responsive Drug Delivery Systems for Programmed Site-Specific Release. Molecules 2019, 24, 1117.

colorectal cancer, and hepatocellular carcinoma, obtaining cell growth inhibition from 64 to 85% over a range of chemo- and gene therapies [51][52][53][54].

Aptamers are single-stranded DNA or RNA with 20–100 nucleotides that specifically bind to antigens forming three-dimensional structures. As protein antibodies, aptamers bind to cell membrane receptors and mediate conjugated nanoparticles to enter into cells. However, aptamers have several advantages over standard antibodies, such as smaller size, higher binding affinity and specificity, high stability in physiological medium, good biocompatibility, and low immunogenicity [55]. In this sense, a nanohybrid of mesoporous silica with carbon loaded with doxorubicin and targeted with HB5 aptamer, found a significant improvement in cell uptake and cytotoxic activity over HER2-positive breast cancer cells, by specific interactions with HER2 cell membrane receptor [56]. Moreover, MSNs loaded with emtansine (also named DM1) and surface-decorated with dopamine and a polyethylene glycol, and epithelial cell adhesion molecule (EpCAM) aptamer showed good efficacy against colorectal cancer in xenografts (mice) of the SW480 human colorectal cancer cell line, with about 90% tumor volume reduction in two weeks [57].

However, the most specific targeting ligands are antibodies. They present outstanding antigen-recognition capacity, and have been used frequently as targeting components in SNPs and MSNs [44][45]. Unfortunately, they are normally very sensitive to physical and chemical conditions, which hinder their covalent bonding over silica surface by standard protocols. Furthermore, they may induce a strong immune response under blood exposure, leading to protein corona formation and removal from plasma by macrophages [58]. To overcome these limitations, particles are usually coated by a protecting shield of PEG. Moreover, it is usual to introduce long cross-linkers to connect the antibody molecule to the silica wall, avoiding possible interferences in chemical coupling by other surface moieties [28][59][60].

5. Clinical Testing

Despite the myriad of articles and patents already published on the field, currently no silica-based nanomedicine has completed the clinical stage satisfactorily. There are two main issues that preclude medicine agencies (e.g., FDA and EMA), from giving direct approval to silica-based formulations: (i) No long-term in vivo preclinical toxicity studies are available, yet. A general chronic toxicity evaluation of intravenously administered non-surface-modified SNPs indicate that female and male BALB/c mice needed up to one year to recover from acute tissue toxic effects of SNPs upon single-dose intravenous (IV) administration at their 10-day maximum tolerated dose, prompting the need for monitoring carefully particle physico-chemical properties (e.g., size, shape, surface charge and, mostly, and organic coating) in order to minimized toxic effects [61]. (ii) Most of the silica-based DDSs are hybrid materials, taking advantage of functional properties of several inorganic moieties or inorganic and organic components. However, from the regulatory point of view, this is much more challenging, as it requires the evaluation of every single component, which possibly will delay clinical translation [62]. So far, there are some candidates for drug delivery, imaging, and theranostics systems that are currently in Phases I and II, showing the potential of silica nanoparticle-based formulations [63]; we have compiled them all in **Table 3**.

33. Jia, R.; Teng, L.; Gao, L.; Su, T.; Fu, L.; Qiu, Z.; Bi, Y. Advances in Multiple Stimuli-Responsive Drug-Delivery Systems for Cancer Therapy. Int. J. Nanomed. 2021, 16, 1525–1551.

34. Chen, P.J.; Hu, S.H.; Hsiao, C.S.; Chen, Y.Y.; Liu, D.M.; Chen, S.Y. Multifunctional Magnetically Removable Nanogated Lids of Fe 3O4-Capped Mesoporous Silica Nanoparticles for Intracellular Controlled Release and MR Imaging. J. Mater. Chem. 2011, 21, 2535–2543.

35. Chen, W.; Cheng, C.A.; Zink, J.I. Spatial, Temporal, and Dose Control of Drug Delivery Using Noninvasive Magnetic Stimulation. ACS Nano 2019, 13, 1292–1308.

36. Chen, L.; Wang, W.; Su, B.; Wen, Y.; Li, C.; Zhou, Y.; Li, M.; Shi, X.; Du, H.; Song, Y.; et al. A Light-Responsive Release Platform by Controlling the Wetting Behavior of Hydrophobic Surface. ACS Nano 2014, 8, 744–751.

37. Lu, J.; Choi, E.; Tamanoi, F.; Zink, J.I. Light-Activated Nanoimpeller-Controlled Drug Release in Cancer Cells. Small 2008, 4, 421–426.

38. Croissant, J.; Maynadier, M.; Gallud, A.; Peindy N'Dongo, H.; Nyalosaso, J.L.; Derrien, G.; Charnay, C.; Durand, J.O.; Raehm, L.; Serein-Spirau, F.; et al. Two-Photon-Triggered Drug Delivery in Cancer Cells Using Nanoimpellers. Angew. Chem.-Int. Ed. 2013, 52, 13813–13817.

39. Botella, P.; Ortega, Í.; Quesada, M.; Madrigal, R.F.; Muniesa, C.; Fimia, A.; Fernández, E.; Corma, A. Multifunctional Hybrid Materials for Combined Photo and Chemotherapy of Cancer. Dalt. Trans. 2012, 41, 9286–9296.

40. Paris, J.L.; Manzano, M.; Cabañas, M.V.; Vallet-Regí, M. Mesoporous Silica Nanoparticles Engineered for Ultrasound-Induced Uptake by Cancer Cells. Nanoscale 2018, 10, 6402–6408.

41. Cheng, C.A.; Chen, W.; Zhang, L.; Wu, H.H.; Zink, J.I. A Responsive Mesoporous Silica Nanoparticle Platform for Magnetic Resonance Imaging-Guided High-Intensity Focused Ultrasound-Stimulated Cargo Delivery with Controllable Location, Time, and Dose. J. Am. Chem. Soc. 2019, 141, 17670–17684.

42. Gu, W.; Meng, F.; Haag, R.; Zhong, Z. Actively Targeted Nanomedicines for Precision Cancer Therapy: Concept, Construction, Challenges and Clinical Translation. J. Control. Release 2021, 329, 676–695.

43. Nichols, J.W.; Bae, Y.H. EPR: Evidence and Fallacy. J. Control. Release 2014, 190, 451–464.

44. Castillo, R.R.; Lozano, D.; González, B.; Manzano, M.; Izquierdo-Barba, I.; Vallet-Regí, M. Advances in Mesoporous Silica Nanoparticles for Targeted Stimuli-Responsive Drug Delivery: An Update. Expert Opin. Drug Deliv. 2019, 16, 415–439.

45. Baeza, A.; Colilla, M.; Vallet-Regí, M. Advances in Mesoporous Silica Nanoparticles for Targeted Stimuli-Responsive Drug Delivery. Expert Opin. Drug Deliv. 2015, 12, 319–337.

Unfortunately, currently, no preparation of SNPs with antitumor drugs has obtained approval for the clinical use albeit, according to the milestones already achieved with other silica-based systems, we expect this will happen in the near future. In this context, although SNPs have shown good tolerability in oral administration, including improving the PK of some hydrophobic drugs [64][65][66], the most usual administration route is IV. Here, hybrids of silica with plasmonic nanoparticles (gold nanoparticles and gold nanoshells) have found application for the thermal ablation of tumors that are difficult to fully remove surgically [67], as well as to reduce the risk of coronary atherosclerosis [68]. Furthermore, ultra-small SNPs (Cornell dots) [69] can be applied for clinical imaging by the incorporation of SNPs on fluorescence moieties (e.g., Cy5.5), or positron emission tomography (PET) radiotracers (e.g., ^{89}Zr, ^{64}Cu, and ^{124}I). This allows the detection and localization of the in-tissue malignant nodes of different cancers, also guiding the biopsy with high accuracy and lower risk.

Table 3. Silica-based nanomedicines under clinical investigation [a].

Material	Clinical Trial	Patients	Status	Action	Active Agent	Pathology	Via	Outcome	Ref.
Lipoceramic (silica@lipid)	Clinical Study	16	Completed	Bioavailability study	Ibuprofen	---	Oral	Improved PK	[64]
	ACTRN 12618001929291	12	Completed	Bioavailability study	Simvastatin	---		Improved PK	[65]
MSN	Clinical Study	12	Completed	Bioavailability study	Fenofibrate	---	Oral	Improved PK	[66]
$Au@SiO_2$ and $Au/Fe_3O_4@SiO_2$ (core–shell)	NCT01270139	180	Completed	Photothermal therapy	Gold nanoparticles	Atherosclerosis	IV	Reduced coronary atherosclerosis	[68]
	NCT01436123	62	Terminated	Photothermal therapy	Gold nanoparticles	Atherosclerosis	IV	Reduced risk of atherosclerosis	[68]
Aurolase	NCT00848042	11	Completed	Photothermal therapy	Gold nanoshells	Head and neck cancer	IV	Tumor ablation	[67]

46. Meng, H.; Xue, M.; Xia, T.; Zhao, Y.L.; Tamanoi, F.; Stoddart, J.F.; Zink, J.I.; Nel, A.E. Autonomous in Vitro Anticancer Drug Release from Mesoporous Silica Nanoparticles by PH-Sensitive Nanovalves. J. Am. Chem. Soc. 2010, 132, 12690–12697.

47. Porta, F.; Lamers, G.E.M.; Morrhayim, J.; Chatzopoulou, A.; Schaaf, M.; den Dulk, H.; Backendorf, C.; Zink, J.I.; Kros, A. Folic Acid-Modified Mesoporous Silica Nanoparticles for Cellular and Nuclear Targeted Drug Delivery. Adv. Healthc. Mater. 2013, 2, 281–286.

48. Kim, K.; Choi, H.; Choi, E.S.; Park, M.H.; Ryu, J.H. Hyaluronic Acid-Coated Nanomedicine for Targeted Cancer Therapy. Pharmaceutics 2019, 11, 301.

49. Yu, M.; Jambhrunkar, S.; Thorn, P.; Chen, J.; Gu, W.; Yu, C. Hyaluronic Acid Modified Mesoporous Silica Nanoparticles for Targeted Drug Delivery to CD44-Overexpressing Cancer Cells. Nanoscale 2013, 5, 178–183.

5[illegible] dman, [illegible] st

5[illegible] 2021,

5[illegible] ffective

5[illegible] .; [illegible] cles for

5[illegible] aterials

5[illegible] d Drug Delivery Systems: Current Potential and Challenges. Curr. Med. Chem. 2018, 27, 2189–2219.

56. Wang, K.; Yao, H.; Meng, Y.; Wang, Y.; Yan, X.; Huang, R. Specific Aptamer-Conjugated Mesoporous Silica-Carbon Nanoparticles for HER2-Targeted Chemo-Photothermal Combined Therapy. Acta Biomater. 2015, 16, 196–205.

57. Li, Y.; Duo, Y.; Bao, S.; He, L.; Ling, K.; Luo, J.; Zhang, Y.; Huang, H.; Zhang, H.; Yu, X. EpCAM Aptamer-Functionalized Polydopamine-Coated Mesoporous Silica Nanoparticles Loaded with DM1 for Targeted Therapy in Colorectal Cancer. Int. J. Nanomed. 2017, 12, 6239–6257.

Material	Clinical Trial	Patients	Status	Action	Active Agent	Pathology	Via	Outcome	Ref.
(SiO_2@Au)									
AuroShell (SiO_2@Au)	NCT02680535	45	Completed	Photothermal therapy	Gold nanoshells	Neoplasms of the prostate	IV	Pending [b]	[67]
	NCT04240639	60	Recruiting	Photothermal therapy	Gold nanoshells	Neoplasms of the prostate	IV	Pending [b]	[67]
Cornell dots (ultra small SNPs)	NCT03465618	10	Recruiting	PET Imaging, Fluorescent Imaging	^{89}Zr, Cy5.5	Malignant brain tumors	IV	Pending	[69]
	NCT02106598	86	Recruiting	Fluorescent Imaging	Cy5.5	Melanoma	IV	Pending	[69]
	NCT01266096	10	Active, not recruiting	PET Imaging	^{124}I	Melanoma and malignant brain tumors	IV	Pending	[69]
	NCT04167969	10	Recruiting	PET Imaging, Fluorescent Imaging	^{64}Cu, Cy5.5	Prostate cancer	IV	Pending	[69]

[a] NCT trials: Additional information may be found at www.clinicaltrials.gov.

[b] A former pilot study over 16 patients described in reference 90 showed successful tumor ablation in prostate cancer patients.

6. Conclusions and Future Direction

Studies of a Silica-Lipid Hybrid (Lipoceramic) Formulation: A Phase I Study with Ibuprofen. Drug Deliv. Transl. Res. 2014, 4, 212–221.

65. Meola, T.R.; Abuhelwa, A.Y.; Joyce, P.; Clifton, P.; Prestidge, C.A. A Safety, Tolerability, and Pharmacokinetic Study of a Novel Simvastatin Silica-Lipid Hybrid Formulation in Healthy Male Participants. Drug Deliv. Transl. Res. 2021, 11, 1261–1272.

66. Bukara, K.; Schueller, L.; Rosier, J.; Martens, M.A.; Daems, T.; Verheyden, L.; Eelen, S.; Van Speybroeck, M.; Libanati, C.; Martens, J.A.; et al. Ordered Mesoporous Silica to Enhance the Bioavailability of Poorly Water-Soluble Drugs: Proof of Concept in Man. Eur. J. Pharm. Biopharm. 2016, 108, 220–225.

67. Rastinehad, A.R.; Anastos, H.; Wajswol, E.; Winoker, J.S.; Sfakianos, J.P.; Doppalapudi, S.K.; Carrick, M.R.; Knauer, C.J.; Taouli, B.; Lewis, S.C.; et al. Gold Nanoshell-Localized Photothermal Ablation of Prostate Tumors in a Clinical Pilot Device Study. Proc. Natl. Acad. Sci. USA 2019, 116, 18590–18596.

68. Kharlamov, A.N.; Tyurnina, A.E.; Veselova, V.S.; Kovtun, O.P.; Shur, V.Y.; Gabinsky, J.L. Silica-Gold Nanoparticles for Atheroprotective Management of Plaques: Results of the NANOM-FIM

So far, the efficacy of silica nanoparticle formulations for the precise delivery of anticancer drugs, tumor elimination and relapse inhibition has been already proved in lots of preclinical studies. However, despite so many silica-based nanomedicines proposed, some of them currently at the clinical stage, still the main goal to accomplish in order to achieve a complete development, including the corresponding Medicine Agency aproval for clinical trials, industrial production in good manufacturing practices (GMPs), and commercialization, is to ensure the absolute lack of long term toxicity of these preparations.

a) Small particle diameters: a very small particle diameter (e.g., <10 nm) can favor particle elimination by renal filtration. This has been conducted in the case of Cornell dots [69], with no significant side effects due to a short plasma half-life (<9 h). This is an interesting property for clinical imaging agents, but is not recommendable for drug delivery systems, as the smaller particles may extravasate before reaching the target cells, reducing the therapeutic response, and leading to severe undesired effects.

b) High drug loading: higher drug content in the nanomedicine, the lower the silica accumulation in tissue. This allows reducing the administered dose, also enlarging the therapeutic window. Mesoporous materials, with well-developed internal geometric structures and high external surface areas for the incoporation of organic groups are probably the best choice for this purpose.

c) Targeting: as already shown here, the incorporation of targeting molecules in the nanoparticles favors tumor accumulation, then allowing to reduce the dose.

d) Organic-silica nanomaterials: hybrid nanomaterials containing silica and organic moieties gathered in a single system basically limit the amount of silica administered. Herein, we have presented some potential nanomedicines based in an innocuous and biodegradable organic core (e.g., liposomes, polystyrene, etc.), and a silicate shell containing chemical doors able to be opened by specific stimuli. In these conjugates, the silica content can be reduced as far as 95% with regards the equivalent solid silica nanoparticles.

e) Replacing silica by structured organic materials. In the last decade, many groups have focused their research on novel materials for bioimaging and drug delivery, as coordination polymers [70][71], and covalent organic frameworks (COFs) [72]. These nanomaterials present well-defined topologies and high surface area, facilitating the incorporation of large quantities of active principles and other functional molecules. Furthermore, they are mostly organic (100% in case of COFs), and can be fully degraded inside the cells releasing their building components, which are later on eliminated by the renal route. In this way, toxicity issues should be no longer an obstacle for the development of novel nanomedicines able to perform efficient and selective chemotherapies, fully free of side effects.

Trial. Nanoscale 2015, 7, 8003–8015.

69. Zanoni, D.K.; Stambuk, H.E.; Madajewski, B.; Montero, P.H.; Matsuura, D.; Busam, K.J.; Ma, K.; Turker, M.Z.; Sequeira, S.; Gonen, M.; et al. Use of Ultrasmall Core-Shell Fluorescent Silica Nanoparticles for Image-Guided Sentinel Lymph Node Biopsy in Head and Neck Melanoma: A Nonrandomized Clinical Trial. JAMA Netw. Open 2021, 4, e211936.

70. García-García, P.; Moreno, J.M.; Díaz, U.; Bruix, M.; Corma, A. Organic-Inorganic Supramolecular Solid Catalyst Boosts Organic Reactions in Water. Nat. Commun. 2016, 7, 10835.

71. Suárez-García, S.; Solórzano, R.; Novio, F.; Alibés, R.; Busqué, F.; Ruiz-Molina, D. Coordination Polymers Nanoparticles for Bioimaging. Coord. Chem. Rev. 2021, 432, 213716.

72. Oliveira, A.D.S.; Rivero-Buceta, E.M.; Vidaurre-Agut, C.; Misturini, A.; Moreno, V.; Jordá, J.L.; Sastre, G.; Pergher, S.B.C.; Botella, P. Sequential Pore Wall Functionalization in Covalent Organic Frameworks and Application to Stable Camptothecin Delivery Systems. Mater. Sci. Eng. C 2020, 117, 111263.