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Synergy Effects of Magnetic Silica Nanostructures for Drug Delivery Applications

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

This article presents a capable strategy to use hybrid nanostructures to improve the magnetic-based performance jointly with the internalization process into cells, for drug delivery applications. The promising combination stems from the concept of magnetic silica nanostructures, referred to magnetic nanoparticles of transition metal ferrites, coated with a silica (or hydroxyapatite) shell or included in a hollow silica nanostructure, such that they can offer a proper and controlled drug delivery. The synergy effects are brought on considering several characteristics; the magnetic properties of the transition metal ferrites as aggregates, the increased biocompatibility, the reduced toxicity, the porosity, the suitable chemical functionalization of the silica and different effects such as local heating based on hyperthermia or other triggering effects for a time-space controlled drug delivery.

The cornerstone review article published 10 years ago, about applications of magnetic nanoparticles in biomedicine by Pankhurst et al.1 established different lines of research aimed to focus on the synthesis of nanoparticles on which the combination of magnetic properties and chemistry at the surface would be directed to attain the conditions indicated for the magnetic separation, drug delivery, hyperthermia and MRI contrast enhancement. Another important and more recent review by Guerrero-Martinez et al.,2 in this case about the silica coating of nanoparticles to increase their colloidal stability, has pointed out important aspects that should be taken into account for the implementation of these materials into bio-related applications. In line with that, we want to highlight possible synergistic perspectives to be established when using magnetic silica nanostructures, referred in this particular case to magnetic nanoparticles of transition metal ferrites coated with a silica shell or included in a hollow silica nanostructure.

Magnetic Properties of Transition Metal Ferrites

According to the relevant concepts of magnetism involved in applications in biomedicine (such as the classification of different magnetic materials, the size of the nanoparticles, how a magnetic field can exert a force at a distance, etc.), there are nowadays lines of research fully directed to optimize the different parameters involved (for example, magnetic anisotropy – coercivity ($H_c$), magnetic moment – saturation magnetization ($M_s$), etc.). We focus this description in the ferrospins due to the bio-related context. Particularly we want to focus on the use of transition metal ferrites ($MFe_2O_4$, $M$: Fe, Co, Ni, Mn, Zn) because they offer a wide range of magnetic and bio-related (depending on the release of different ions, see below) behaviors. These are cubic ferrites that crystallize in the spinel structure ($AB_2O_4$ being A and B transition metal cations). The oxygen anions are packed in a face-centered cubic arrangement offering tetrahedrally coordinated (A) sites, and octahedrally coordinated (B) sites, though only 1/8 of the tetrahedral spaces and ½ of the octahedral spaces are occupied. In the inverse spinels, the Fe$^{3+}$ are divided equally between A and B sites, with the divalent ions displaced to the remaining B sites. In case of considering Fe, Co and Ni ferrites, they are ferrimagnetic (FiM) and in this situation, the magnetic moments of all Fe$^{3+}$ ions cancel and make no net contribution to the magnetization of the solid. However, all the divalent ions have their moments aligned parallel to one another, and it is this total moment the responsible for the net magnetization.3

Figure 1. Magnetization curves of some cubic ferrites. Reprinted from reference 4 by permission from Pearson Education.

Figure 1 includes the magnetization curves of different cubic ferrites and can be compared at the temperature of interest for bio-related applications ($T$=25ºC, indicated by the dotted vertical...
As mentioned, these spinels can have different magnetic properties attending to the divalent metallic cation $M^{2+}$. For example, in its bulk form ZnFe$_2$O$_4$ is antiferromagnetic as a consequence of its crystalline structure while due to the strong spin-orbit coupling at Co$^{2+}$ cation sites, CoFe$_2$O$_4$ has a large magnetocrystalline anisotropy and behaves as a ferrimagnet. Despite the fact that Fe$_3$O$_4$ and MnFe$_2$O$_4$ are good aspirants to combine superparamagnetism with high magnetization, the $M_S$ becomes lower due to surface contribution (spin canting, lattice distortions, stoichiometry variations, cation distribution and absorbed species) when considering nanoparticles.

According to Lindner and Farle, magnetic anisotropy describes the fact that the energy of the ground state of a magnetic system depends on the direction of the magnetization. The effect occurs either by rotations of the magnetization vector with respect to the external shape of the specimen (shape anisotropy) or by rotation relative to the crystallographic axes (magnetocrystalline anisotropy). This is therefore the quantity that determines the easy and hard magnetization direction of a magnet and it is also decisive for the magnetization reversal in external fields. These contributions are classified according to their physical origin; magnetic anisotropy due to spin–orbit coupling (magneto-crystalline) or due to long-range dipolar coupling of magnetic moments (shape anisotropy). In the case of nanoparticles, other contributions to the total magnetic anisotropy can reach the same order of magnitude as magnetocrystalline and shape anisotropies, and can consequently comprise important options to tune the effective anisotropy energy, for example, by introducing interfaces and surfaces or by perturbing local stresses and strains. In line with that, an important contribution related to interfaces considers the exchange bias interaction. The nature of the interactions, generally between FM (or FiM) and AFM materials, depends upon interatomic distances since this exchange coupling is produced by overlap of electronic orbitals and therefore is necessarily short-ranged. Accordingly, hybrid nanostructures, on which a significant fraction of atoms reside at or near surface or buried interfaces, become good candidates to study this effect. Lee et al. for example, have reported exchange-coupled magnetic nanoparticles as a new means of modulating their magnetism, resulting in a significant enhancement of magnetic heat induction.

Having the transition metal ferrite nanoparticles in mind to be used in the bio-related applications, and considering the need to adapt or tune their magnetic properties, we would like to underline the very suitable path to modify and optimize the magnetic behavior through the controlled aggregation of nanoparticles, rendering for example possible to obtain both superparamagnetism and higher $M_S$ values, or tuning the magnetic anisotropy and consequently $H_C$ (in the corresponding blocked state). Different groups have attained very convenient strategies to produce these aggregates by miniemulsion, or by thermal decomposition in the presence of tri(ethylene glycol). We have employed the one based on a solvothermal reaction in an autoclave system in which, precursors and some additives, like reducing agents (NaOAc) and/or ligands like polyvinylpyrrolidone (PVP) or polyethylene glycol (PEG) are added into an organic reducing medium like ethylene glycol. The mixture is heated up to 180-200 °C during several hours to offer nanocomposites built up from small primary single domain units of transition metal ferrites. This synthesis renders rather easy the control of the size (of both primary single nanoparticles or the final nanocomposites) changing the amount of precursor or/and reaction time, and allows modifications such that we can introduce primary units of two different oxides. Figure 2 shows M-H hysteresis loops and temperature dependence of the magnetization of the MnFe$_2$O$_4$ nanocomposites synthesized following this solvothermal method. The size of the primary units is ~8 nm in diameter while the nanocomposites have an average diameter of 65 ± 7 nm (Gaussian analysis). The attained

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Figure 2. Field (a) and temperature (b) dependent magnetization of manganese ferrite aggregates synthesized by the solvothermal method.

Solid solutions of single or mixed ferrites can be formed readily, allowing the values of these properties to be tuned precisely since combinations in the stoichiometry offer infinite options. For example, Venkateshvaran et al. tuned the saturation magnetization of Zn$_{1-x}$Fe$_x$O$_4$ by Zn substitution and/or finite oxygen partial pressure during growth (in thin films), and more complex combinations (Mg$^{2+}$0.45Mn$^{2+}$0.55Mn$^{3+}$0.23Fe$^{3+}$1.77O$_4$, for example) can offer very desirable characteristics such as fast switching times or minimal temperature variation (increased $T_C$).

In addition to single-phase nanoparticles on which tuning the stoichiometry and consequently the magnetic properties, there is a very promising option based on tuning the magnetic anisotropy.
morphology offers a large \( M_g \) value (considering the nanometer size both of the single units and the composites) (figure 2a) and no blocking temperature can be appreciated in the ZFC-FC curves shown in figure 2b, with both characteristics justified in terms of the important interactions established in the final assemblies of the primary units or nanoparticles.

**Silica Coating and Functionalization**

Silica coating of nanoparticles has turned out to be a very important topic due to the increased stability these colloids can attain.\(^2\) Jointly with the high stability in aqueous media, we can underline the easy regulation of the coating process, its chemical inertness or controlled porosity.\(^7\) For that reason, silica has been employed not only for coating but also to combine with different functionalities to include in a final nanostructure,\(^23\) for example, in order to manipulate its topological complexity for the creation of designed materials with specific endeavors such as nanoreactors.\(^24\) The highly permeable mesoporous shell of silica becomes also very convenient for loading in or out different species, and therefore also very attractive in drug delivery.

The sol-gel-derived hydrolysis of the tetraethylortosilicate (TEOS)\(^25\) has been modified to obtain subtle variations in composition of the silicon oxide. Though these changes were initially thought to make a selective removal of the silica, they can be very convenient in the controlled dissolution of the silica in physiological conditions to deliver different drugs previously loaded inside. Yin and co-workers have developed the surface-protected etching method, which involves the adsorption of a layer of PVP on the outer surface and the subsequent preferential etching of silica from the interior.\(^26\) Poly-ethylenimine (PEI) is a positively charged polymer that can also interact with the negatively charged surface of silica nanostructures and becomes therefore a good candidate too. Similar effects were also observed when using silica coated magnetite and cobalt ferrite nanoparticles functionalized with several layers of polyelectrolytes and fragments of DNA.\(^27\)

An alternative selective etching was achieved by introducing a structural difference between the interior and the surface layer of the silica precipitated. This can be accomplished precipitating silica in several steps, using TEOS as the silica precursor that provides the pure inorganic form of the silicon oxide or the combination of TEOS with different organosilanes. These organosilanes change the hydrolysis and condensation processes favoring the formation of organic-inorganic hybrid silica, which etches differently.\(^28\) In line with that, Wong et al. have revisited the Stöber method reporting the inhomogeneity of the silica as a source for preferential etching.\(^31\) The complete hydrolysis of TEOS and subsequent condensation of silicic acid give a network of tetrahedral \( \text{SiO}_2 \) units with share vertices that is expected to be uniform. However, through controlled experiments, they were able to demonstrate the inhomogeneity of the silica precipitated by etching the interior of silica nanoparticles with hot water. Figure 3 shows TEM images of silica-coated gold nanoparticles after dissolving the silica preferentially, depending on the sequential hydrolysis followed for its formation.\(^31\) According to their hypothesis, the outer silica shell that persisted must be porous and permeable to allow the solvent to diffuse in, and the etched part to dissolve out. Since no protecting agent was employed, they postulated the inhomogeneous nature of the silica formed due to a possible sequential hydrolysis, to explain the preferentially dissolved inner silica.

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![Image](https://via.placeholder.com/150)

Figure 3. TEM images of nanostructures derived from nanoparticles coated with silica after etching one (top) or three (bottom) concentric volumes of the silica shells. Scale bars = 50 nm. Reprinted by permission from reference 31.

The postulated gradient of chemical stability can indeed be justified considering the consecutive hydrolysis of TEOS in water to give hydroxyl groups,\(^32\) reaction that becomes slower as advancing on the process and as decreasing the concentration of TEOS in solution. These differences can become accentuated in case of carrying out the reaction in a confined space, for example, the volume available in the microemulsions used to coat inorganic nanoparticles with silica.\(^33\) In such a case, the inner silica can become more easily etched because since formed faster it presents a more porous structure while the outmost layers can persist since derived from silicic acid and derivatives and has reached an important degree of cross-linking. This has led to a partial etching of the silica surrounding magnetic nanoparticles in the moderated acid conditions attained when trapped in cell
endosomes.\textsuperscript{27} This partial etching occurred at the interface between the silica and the magnetic core, likely because of the less linked silica formed in the first steps of the hydrolysis and condensation processes.

The free hydroxyl groups left inside or at the outer surface of the silica shell provide important gates and ways for further functionalization. Though silica has been demonstrated to facilitate the internalization of nanoparticles compared to uncoated ones, there are alternative strategies to favor an initial interaction of the coated nanoparticles with cells in cultures. Anchoring PEG molecules at the surface of the nanoparticles is one of these widely used functionalizations, mainly due to its biocompatibility and non-toxicity.\textsuperscript{26} It has become indeed such a popular route that appears in a recently published science fiction best-seller.\textsuperscript{35} PEG molecules are able to provide steric hindrance between nanoparticles avoiding their aggregation in aqueous medium.\textsuperscript{36} In physiological conditions however, the increased ionic strength weaken this repulsion, effect that can be counteracted by the introduction of PEI molecules that provide stronger cationic repulsion. As an example of their convenience, Nel and co-workers have reported an enhanced cellular uptake of silica nanoparticles if functionalized with the PEI molecules and have demonstrated the possibility of adjusting the cytotoxicity values according to the PEI molecule length.\textsuperscript{37} Brinker and co-workers have on the other hand, coined the term “protocell” platforms using lipoid-coated silica nanoparticles, by which porous nanoparticle-supported lipid bilayers synergistically combine properties of liposomes and nanoporous particles, simultaneously addressing the complex requirements of targeted, multicomponent delivery.\textsuperscript{38–40}

The use of silica nanoparticles as drug delivery agents has indeed experienced an impressive growth during the last decade when considering mesoporous silica, that is, silica with a stable mesoporous structure and the consequently extremely large surface area. These characteristics, together with their sophisticated internal and external surface chemistries, allow them to host a plethora of molecules with different sizes, compositions and chemical properties, being thus ideal candidates for this particular application,\textsuperscript{41–43} especially considering the fact that we can trigger independently the delivery of different compounds as partially etching the silica where they can be previously loaded.

The chemical modification of the mesoporous silica nanoparticles for the accommodation of the host molecules can be performed during their synthesis via co-condensation or by post-synthetic grafting of organosilanes, both in the pore interiors and on the outer surface.\textsuperscript{44,45} Another route consists in the electrostatic interaction between positively charged moieties and deprotonated silanols present at the surface of the particles at neutral pH, as already mentioned. Typical cationic polymers used for this purpose are poly(allylamine hydrochloride) (PAH),\textsuperscript{36} PEI,\textsuperscript{37} or PEG/PEI\textsuperscript{36} or other polyelectrolyte (poly (sodium 4-styrene-sulfonate) (PSS)/poly (diallyldimethylammonium chloride) (PDADMAC)\textsuperscript{37}) combinations. Such functionalizations have proved to enhance cellular uptake, transfection efficacy, colloidal stability and EPR (enhanced permeability and retention) effect.

Since the pioneering work by Vallet-Reguï and coworkers,\textsuperscript{47} mesoporous silica nanoparticles have been demonstrated to be excellent materials for the loading of a wide range of therapeutic agents including pharmaceutical drugs,\textsuperscript{48,49} proteins,\textsuperscript{50} genes,\textsuperscript{51} as well as the combinations of two or more of these molecules.\textsuperscript{38–40,51} In the particular case of anticancer drugs, their encapsulation within the mesoporous silica nanoparticles allows their dispersibility and internalization in aqueous media, feature otherwise limited by their strong hydrophobicity. For example, Lu et al. loaded mesoporous silica nanoparticles with camptothecin (CPT), a drug that has proved to be effective against stomach, colon, bladder, breast and lung carcinomas.\textsuperscript{52} The same agent has been also used in nanohybrids composed by an iron oxide core coated with a mesoporous silica shell,\textsuperscript{53} on which further surface modification with folic acid led to an increased uptake by cancer cells thanks to the overexpression of their α-folate receptors if compared with normal ones. Other commonly used anticancer drugs as cargo for drug delivery are doxorubicin (DOX),\textsuperscript{54} paclitaxel (PTX)\textsuperscript{55} or 2-devinyl-2-(1-hexyloxethyl)pyropheophorbide (HPPH).\textsuperscript{56} Bleomycin, an anticancer drug with potential in oncology but with important side effects that limit its study, has been covalently attached to silica-coated Fe$_2$O$_3$ nanoparticles through NH$_2$–PEG groups. This functionalization led to a very high specificity and biodistribution, together with a high interaction with both nucleus and mitochondria that result in cell growth inhibition.\textsuperscript{57} Indeed, some of these anticancer drugs are already under clinical trials in nanoparticulate conjugates (liposome and polymer based, for example, liposome delivery of DOX, liposomal PTX and polymer conjugate of CPT).\textsuperscript{57,58}

An additional way to encapsulate anticancer drugs into silica exploits the use of silica-coated Fe$_2$O$_3$ nanoparticles as molds for the formation of hollow structures.\textsuperscript{59} We can actually take advantage of this approach but from the different perspective herein proposed. Indeed, the main reason why we have focused the interest on the transition metal ferrites is the fact that once the nanostructures have reached the target site and we can trigger the drug delivery process, we can also consider the lethal combination of antitumoral compounds with the release of metal ions. The acidic dissolution of the nanoparticles or nanostructures if loaded for example into the endosomes can trigger the delivery of metal ions (Fe, Co, Ni, Mn, Zn, etc.) from the magnetic cores and consequently increase the cytotoxicity results to be attained by the antitumoral drugs. Davidson et al. have summarized some of the molecular responses exhibited by cells that come in contact with metal ions, which interfere with the essential metals of some enzymes.\textsuperscript{60} Iron is an essential metal whose regulation is controlled by both uptake and export proteins since deficiency and excess of this metal can be potentially toxic to cells. The protein transferrin, capable of binding two ions of ferric iron (Fe$^{3+}$), is also able to bind nickel, vanadium and other metals.\textsuperscript{61} The transferrin gets internalized into an acidic endosome where iron is subsequently released, reduced and transported out of the endosome into the cell via the divalent metal transporter (DMT 1), which is actually able to transport other metals including nickel, manganese, cobalt, copper and zinc, though some authors state that besides iron only cobalt ions can be transported.\textsuperscript{52} Accordingly, we can favor this process by which proteins can help to transport the ions released from the magnetic cores. We can also take into account the reactive oxygen species (ROS),
which are highly reactive molecules with unpaired electrons formed during oxidative metabolism, such as O$_2^-$ ions, OH radicals or hydrogen peroxide (H$_2$O$_2$) molecules. They are continuously generated and eliminated in biological systems and play important roles in the regulation of cell proliferation or apoptosis processes since they can cause oxidative damage to cellular macromolecules, including DNA, proteins, and lipids. Exposure of cells to As, Cd, Co, Cr, Cu, or Ni (and even excess of Fe$^{6+}$) can generate excessive ROS in cells (or depletion of cellular antioxidant capacity) by Fenton-type reaction, Haber-Weiss reaction or by reacting directly with cellular molecules. The high ROS levels can damage cells by peroxidizing lipids, disrupting DNA, modulating gene transcription, altering proteins and consequently resulting in decline in physiological function and cell apoptosis/death.$^{60}$

Figure 4. Schematic representation of a multifunctional mesoporous silica nanoparticle with multiple stimuli-responsive surface groups. Reproduced with permission from reference 41. Copyright 2013, American Chemical Society.

One of the most important challenges nowadays is the design of drug delivery vehicles with the ability to release the cargo at the target with previous “zero release”, that is, a time-space controlled drug delivery, improving therefore the activity of the drug and avoiding unwanted side effects. To reach this goal, the latest investigations focus on the synthesis of carriers with stimulus-responsive capabilities.$^{65}$ In particular, the modification of the mesoporous silica through reversible capping of their pores surface, allows the control over the drug release under an external stimuli such as temperature,$^{64,66}$ light,$^{66,67}$ pH,$^{66-70}$ magnetic fields,$^{1,72}$ redox reactions,$^{73,74}$ enzymes,$^{73,76}$ or antibodies.$^{77}$ Correa-Duarte and co-workers have developed in this regard, a unique route to obtain such carriers. The nanocapsule configurations they have reported exhibit important morphological distinctive features that render them rather attractive for different and sophisticated applications related to sensing, catalysis and biomedicine. A clear example of such structure was reported by Vázquez-Vázquez et al.$^{78}$ showing a straightforward synthetic approach for the development of submicron capsules capable of concentrating light for the simultaneous performance and optical monitoring of thermally activated reactions (see the very representative TEM images included in figure 5). This possibility of encapsulating nanoparticles in silica can become a very useful approach to the development of novel complex nanostructures and in case of drug delivery the field broadens considerably because of the possible combinations of functionalities to be exploited. Besides the magnetic functionality already proposed and the benefits that porous silica offers, the nanocapsules bring about the possibilities of time and space control of the delivery, considering triggering parameters such as pH, temperature (local heating induced considering the magnetic or the plasmonic nature of the nanoparticles included inside),$^{78}$ catalyzed reactions (including Pt$^{79}$ or Pd nanoparticles inside), etc. Indeed, these structures are excellent candidates for the development of smart multidrug nanocarriers, which is a promising area of research.$^{80-83}$ Further efforts can actually focus on these nanocarriers, such that we can render them able to release different chemical compounds controlled under different external stimuli while working as imaging or sensing agents.

Figure 5. TEM images of the capsules pointed out as suitable vehicles for drug delivery. Reproduced with permission from reference 78. Copyright 2013, American Chemical Society.

**Hydroxyapatite as an alternative**

Even though silica remains the inorganic material of choice for the biofunctionalization of magnetic nanoparticles and nanostructures, other materials have been explored during the last years to obtain magnetic nano-hybrids that could be exploited in various biomedical applications including the drug delivery. In this context, nanostructured calciumapatites are an interesting alternative to silica due to their inherent biocompatibility and stability at physiological pH, and a suitable mesoporous nature. Calcium apatites (generally formulated as Ca$_{10}$$(PO$_4$)$_6$(X)$_2$, where X can be OH, Cl$^-$ or F$^-$ ions), are the most ubiquitous phosphate minerals in nature.$^{84}$ Among them, hydroxyapatite (Ca$_{10}$$(PO$_4$)$_6$(OH)$_2$) is of particular interest nowadays due to its high biocompatibility and osteogenic potential. Hydroxyapatite is the main component of bone and teeth and its multilayered arrangement with proteins (mostly collagen fibers) is responsible for the extremely complex biomineralization of these tissues.$^{85}$ Synthetic hydroxyapatite particles are however fragile if compared with bone or teeth and therefore, its combination with other materials has been explored to create nanocomposites with outstanding mechanical properties for replacement of damaged tissue.$^{86,87}$ Moreover, hydroxyapatite nanoparticles have a great potential in the stimulation of bone cell proliferation and thus, are also being studied as healing material for bone reconstruction, especially after partial ablation of bone tumors.$^{88,89}$ Over the last years, magnetically-doped hydroxyapatite
nanocomposites have been designed for a broad range of bioapplications. In the particular case of drug delivery, reports on magnetically doped hydroxyapatite nano/microparticles have gained relevance, thanks to the combination of the high cellular transfection rates and pH-dependent dissolution properties of HAp and the magnetofection capabilities given by the magnetic component. In most cases, once internalized within the cell membranes, the cargo is released into the cytosol through the fast degradation of the hydroxyapatite at low pH values, due to the acid-catalyzed dissolution of surface phosphates. Interestingly, the majority of the reports that present the dissolution of hydroxyapatite nanoparticles in the cytosol highlight their negligible cytotoxicity. This resides in the fact that such dissolution does not imply an increase in cellular reactive oxygen species (ROS) that could promote oxidative stress and subsequent cell damage.

All above described just exemplifies the enormous potential that hydroxyapatite presents for a broad range of applications in the nascent field of bionanotechnology, especially as ideal platform for drug delivery. Nevertheless, the generally poor control over morphology and composition of the final nanocomposites leaves room for further improvements. We believe that new synthetic routes for the formation of core-shell magnetic/hydroxyapatite nanocomposites will allow a better understanding of the physical and chemical interaction between the individual components together with a tight control of the transfection processes in cell culture. Such developments will pave the road towards the formation of more suitable materials for the bioapplications envisaged.

Conclusions
We have described the synergy effects that can be exploited in drug delivery applications when using magnetic silica nanostructures, that is, magnetic nanoparticles coated with silica (or hydroxyapatite) or trapped inside silica capsules. The synergistic associations can take place considering the (inverse) spinel ferrites as the magnetic materials to be employed, given their tunability in composition and morphology and consequently in magnetic behavior. Additionally and in line with that, the metallic cations forming part of these ferrites offer a secondary role since possible to be delivered in combinations with specific compounds for drug delivery, modifying the options for toxicity when required. Last but not least, it is the possibility of triggering this synergy with the time and space control given by the nanocapsules, which just remarks the great aspects to explore in drug delivery applications.

Notes and references
