Silica Particles: A Novel Drug-Delivery System**

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In recent decades, significant advances in drug-delivery systems have enabled more effective drug administration. To deliver drugs to specific organs, a range of organic systems (e.g., micelles, liposomes, and polymeric nanoparticles) have been designed. They suffer from limitations, including poor thermal and chemical stability, and rapid elimination by the immune system. In contrast, silica particles offer a biocompatible, stable, and "stealthy" alternative. Bioactive molecules can be easily encapsulated within silica particles by combining sol–gel polymerization with either spray-drying or emulsion chemistry. Spray-drying faces challenges, including low yield, surface segregation, and size limitations. In contrast, sol–gel emulsions enable the production of nanoparticles with homogeneous drug distribution, and permits ambient temperature processing, necessary for handling biologicals. Independent control of the size and release rate can be readily achieved. Preliminary in-vivo experiments reveal enhanced blood stability of the nanoparticles, which, coupled with sustained release of anti-tumor agents, show good potential for cancer treatment.

1. Introduction

Contrary to common belief, humans have been developing drug-delivery strategies since ancient times, beginning with the chewing of leaves or roots and the inhalation of smoke particles from the burning of medicinal plants. Over centuries, the delivery mechanisms have been refined through the development of more reliable dosage forms, such as tablets and capsules.[1] During the last decades of the 20th century, a substantial effort was made to move from sustained, but essentially uncontrolled, release systems (e.g., waxes and other polymeric matrices) to controlled-release systems such as transdermal patches, improved oral-inhalation formulations, and erodible implants. In the 1990s, the appearance of new drugs with larger molecular sizes, higher dose sensitivities, and often poorer stabilities in biological environments led to a stronger push towards the development of efficient encapsulation and controlled-release technologies. In addition to better clinical efficacy and patient compliance, economic considerations such as a decrease in both frequency and cost of administering the drug, as well as extension of product life by the use of controlled-release formulation are driving the demand for versatile, high-performance controlled-release systems. This makes drug delivery one of the fastest-growing segments of the pharmaceuticals market, with approximately 10 % annual growth and an estimated value in 2007 of US $82 billion for the US market alone.[2]

■$82x10 9 (U.S. "billion") or $82x10 12 (UK "billion")?■

From a technical perspective, controlled drug delivery implies the ability to control the distribution of therapeutic agents both in space and time. In other words, controlled drug delivery embodies both control of the rate of release of a drug, and the delivery of this drug to a specific organ or loca-

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[**] We would like to thank Mark Blackford, David Cassidy, Rachel Trautman, Renée Beyer, Jeanette Chapman, Vu Nguyen, and Patrice Ballantyne (ANSTO) for experimental help and Laurent Rivory, Mac Christie, and Kim Chan from University of Sydney for useful discussions regarding the biodistribution of silica particles.

 DOI: 10.1002/adma.200400771 © 2004 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

tion in the body (i.e., targeting). Controlled-release systems increase the overall efficacy of the drug (i.e., therapeutic efficiency) by maintaining the drug concentration in the body within the optimum therapeutic range and under the toxicity threshold. For an increasing range of modern drugs, toxicity towards key organs (e.g., liver, heart, kidneys) resulting from indiscriminate delivery can lead to significant and sometimes lethal side effects, thus limiting their therapeutic value. Such non-selective partitioning of the drug between healthy and diseased cells can be overcome by selectively targeting the diseased sites using either passive- or active-targeting strategies. Passive targeting exploits non-specific interactions usually related to the physicochemical properties of the delivery systems (including charge, hydrophobicity, and size) to target specific sites in the body.[3] In contrast, active targeting utilizes specific carrier–site interactions, such as antigen–antibody and ligand–receptor binding, to seek its cellular target. Successful targeting, whether active or passive, requires the production of the drug-delivery system in the form of particles that can breach biological barriers to reach their specific target. The optimum particle size depends both on the route of administration (e.g., oral, inhalation, ocular, vaginal, intravenous, etc.) and the targeted organ or cells. To cater for these various delivery options, a wide range of particulate-delivery systems has been designed.[4,5]Although each system has its advantages, several significant limitations affect their applicability as drug-delivery systems. Liposomes[6a-c] and micelles[6d] suffer from intrinsically poor chemical stability that limits both their route of administration and shelf life. In the blood, liposomes and micelles are also known to be susceptible to disintegration through biochemical attack by high-density lipoproteins.[7] The ability to "design" micelles and liposomes to achieve control over the release rates of therapeutic agents is also limited. The in-vivo degradation of synthetic polymers poses toxicity problems,[8] whereas, for natural polymers such as chitosan and agar, the lack of control over the monomer purity leads to potential lack of reproducibility in their release profiles. Dendrimers suffer also from low blood stability and quick elimination through the kidney and liver, and their extremely small size (typically < 10 nm) allows them to pass through small intercellular openings and thus distribute non-specifically in healthy tissue.[9]

More generally, low blood stability represents a major problem for all organic delivery systems. In the blood, protein markers (opsonins) adsorb on the surface of hydrophobic carriers, thus providing a signal to the immune system (i.e., reticuloendothelial system, or RES) to evacuate these foreign entities from the body. Thus, to enhance circulation time in the bloodstream, the surface of the carrier needs to be functionalized with hydrophilic molecules, such as polyethylene glycol (PEG)[10] or polyethylene oxide (PEO), in order to avoid detection by the immune system.[11] This additional step complicates the production process significantly, by requiring a total reformulation of the chemistry in the case of polymeric micelles,[12] or increasing the manufacturing time of "stealth" liposomes to several days.[10]

In contrast to organic systems, metal oxides have surfaces decorated with hydroxyl groups that render them intrinsically hydrophilic. This natural hydrophilicity should decrease oxide particle clearance by the RES, and thus increase their circulation time in the blood. Metal oxides are also highly biocompatible, as demonstrated by their numerous applications as implants or coatings. More specifically, amorphous silica particles (in contrast to crystalline silica) are not toxic, and are regularly used as food additives and components of vitamin supplements (as colloidal suspensions). Encapsulation in silica has also been found to prolong the shelf life of enzymes.[6d] Bacteria[13] and mammalian cells[14] ■OK?■have been shown to retain their metabolic activities when encapsulated in porous silica, thus confirming the high compatibility of silica with biological systems. Despite all of these intrinsic advantages, metal oxide particles largely remain an untapped resource for the manufacture of controlled-release systems. This is mainly due to the high processing temperatures employed in traditional methods of synthesis (typically $>1000\,^{\circ}C$), which are clearly incompatible with the encapsulation of organic molecules. The relative difficulty of manipulating the internal microstructure of the particles (as compared to polymers) also plays a role in their apparent lack of popularity as a controlled-release matrix. However, both the high processing temperature and lack of control over the microstructure can be easily overcome using sol–gel technology, an ambient-temperature inorganic polymerization technique.[15]

In the following sections, we describe how active molecules can be encapsulated inside a silica matrix using sol–gel technology and how the subsequent release can be controlled by tailoring the porous structure of the sol–gel matrix. We then show how this process can be adapted, by combining sol–gel chemistry with spray-drying or emulsion polymerization, to produce microparticles for controlled drug delivery. Finally, we discuss briefly the use of silica nanoparticles as drug-delivery systems for anti-cancer agents.

2. Encapsulation and controlled release in sol–gel matrices

The sol–gel process can be described as a two-step inorganic polycondensation:

a) Hydrolysis

$$Si(OR)_4 + x\,H_2O \rightarrow (RO)_{3-x}\text{–}Si\text{–}(OH)_x + x\,ROH \quad (1)$$

b) Condensation

$$\text{–Si-OR} + \text{–Si–OH} \rightarrow \text{–Si–O–Si–} + ROH \quad (2)$$

$$\text{–Si–OH} + \text{–Si–OH} \rightarrow \text{–Si–O–Si–} + H_2O \quad (3)$$

Addition of organic and/or bioactive molecules during formation of the oxide backbone at ambient temperature facili-

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tates their encapsulation within the evolving oxide matrix, leading to the production of a composite gel with the active ingredient being homogeneously distributed throughout the resulting gel (or xerogel). Moreover, the physical characteristics (including density, pore size, and nanostructure) of the oxides produced by sol–gel processing can be tailored by controlling the sol–gel reaction kinetics, and in particular, the relative rates of hydrolysis and condensation.[15] This ability to control the gel microstructure has very important consequences for the design of controlled-release systems using sol–gel chemistry. For example, in silica sol–gel chemistry, introduction of acids or bases during the sol–gel process results in significantly different polymeric structures. Acid catalysis promotes hydrolysis and end-of-chain condensation leading to the production of small linear polymeric entities. During gelation, cross-linking between these linear polymers lead to the formation of tenuous, open structures that collapse upon drying to produce microporous gels (i.e., average pore size < 2 nm). In contrast, base catalysis promotes cross-linking and produces ramified polymers which, when coupled with a significant dissolution, leads to the production of smooth, 5–10 nm colloids. Percolation of the colloidal suspension results in a compact gel, which forms a mesoporous solid after drying, with pores typically ranging from 2 to 50 nm.

As expected, the diffusion of molecules inside a microporous solid is much slower than inside a mesoporous gel. This leads to significantly smaller release rates for the gels synthesized using acid catalysis than for those synthesized under basic conditions (Fig. 1a).

A wide range of sol–gel processing parameters influence the final gel microstructure and thus have been used to control the release rate of molecules encapsulated in silica xerogels.[16] Limiting the hydrolysis and condensation rates (e.g., using a low water/alkoxide ratio,[17] choice of catalyst,[18] using a short ageing time, or poisoning of the condensation using alkoxysilane[17,19]) ■OK?■produces tenuous, wet gels that collapse upon drying into microporous xerogels, yielding slow release rates. Increasing drying time and temperature also promotes densification of the porous xerogel structure, and consequently decreases the release rate of the corresponding gels. Increasing the drug loading[17,20,21] and decreasing the gel-fragment size[22] enhance the release rate by increasing the quantity of drug being released and shortening the diffusion distance, respectively. The mechanism of release is a combination of diffusion and dissolution processes.

This flexibility, as well as the extensive range of processing parameters available to control the release rate, has led to the manufacturing and testing of xerogels as sustained release implants and resorbable carriers to deliver a wide range of molecules, including antibiotics,[20] anticoagulants,[17] analgesics,[19] hypotensives,[22] proteins,[23] hormones,[24] and even adenoviruses.[25] In vivo insertion of silica-gel implants was found to cause no abnormal inflammation or adverse reaction,[26] confirming the biocompatibility of these materials. The silica implants were found to dissolve with time at different rates

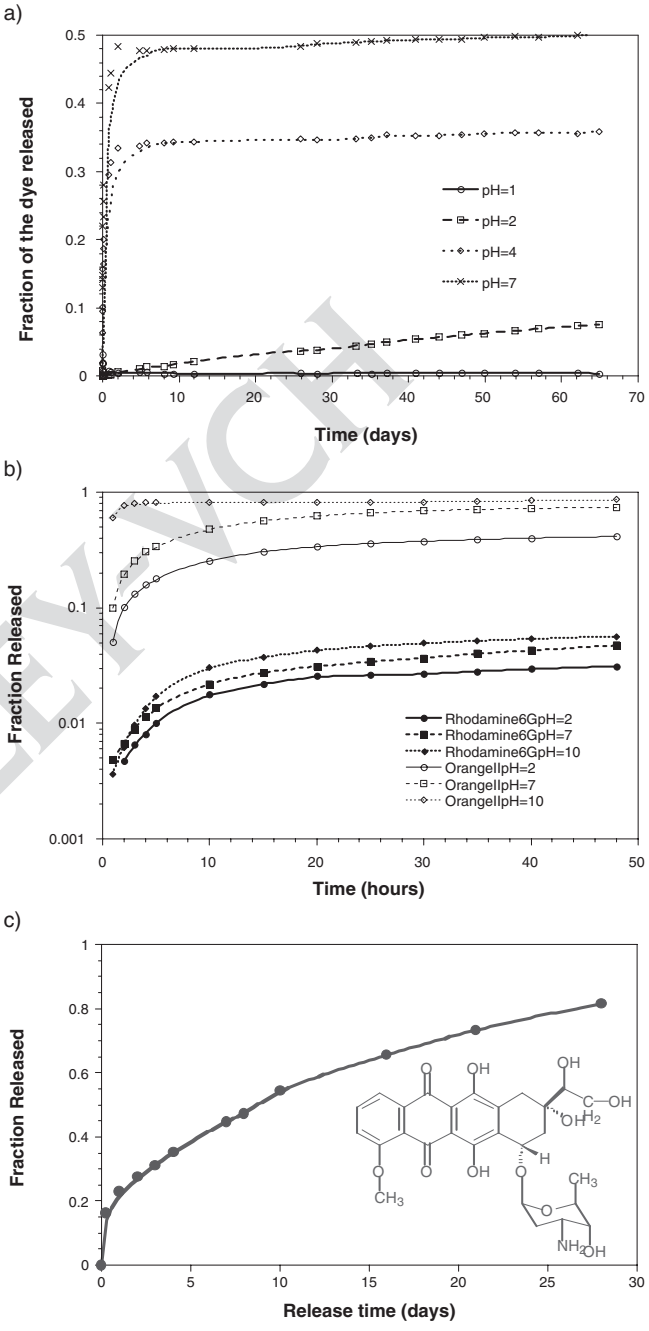

Figure 1. Influence of pH on the release of kinetics of a) Orange II encapsulated in millimeter-sized silica–gel fragments; b) Orange II and Rhodamine 6G encapsulated in 50 μm silica particles; and c) doxorubicin encapsulated in 30 nm particles.

(from 13 wt.-% in 30 days[27] to 76 wt.-% in 56 days[28]), depending on the surface area of the gel, the implant location, and the animal model used. The dissolved silica diffuses through the local tissue surrounding the implant, enters the blood stream or lymph, and is excreted through the kidneys in the urine.[27]

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3. Particle production: using droplets as microreactors

For the purpose of targeting specific sites in the body, release systems in the form of particles (as opposed to implants) are required. In the case of sol–gel silica matrices, the question is how to produce particles with controllable size while preserving the control over the release offered by the sol–gel process. One answer lies in the "compartmentalization" of the sol–gel solution into microdroplets, which will act as microreactors during evolution of the matrix structure, thus producing silica particles with dimensions comparable to those of the microreactors. Two approaches by which such "compartmentalization" of sol–gel solutions can be achieved are spray drying and emulsion polymerization.

In spray-drying, a pre-hydrolyzed sol–gel solution is atomized into a heated reactor, where the fluid within the droplets is evaporated to yield micrometer-sized porous silica particles. The size of the droplet is controlled by the viscosity and surface tension of the sol–gel solution, as well as by the operating parameters (e.g., flow rate) and design of the atomizer (e.g., ultrasonic, spinning plate, etc.). Successful production of two injectable microsphere products containing two different drugs (dexmetomidine and toremifene citrate) was reported by Kortesuo et al.[17,29] The spray-dried microspheres exhibited an average diameter between 10–20 μm and were relatively polydisperse. The particles were nonporous and drug release was mediated by dissolution of the silica matrix. However, a study of the influence of the sol–gel parameters on the release rate of the spray-dried particles revealed that only limited control over the final release rate could be achieved.[30] Indeed, varying the pH of the sol–gel solution away from the isoelectric point led to burst release, due to a significant increase in the rate of matrix dissolution. Although increasing the water to alkoxide ratio successfully reduced the rate of matrix dissolution and associated drug release, this was achieved by increased coagulation of the droplets inside the spray-dryer. The resulting undefined large lumps have a lower aspect ratio than the small microspheres and thus exhibit slower erosion. The coalescence of partially dried droplets, which then adhere to the reactor walls, is also responsible for the relatively low yields (20–50 %) observed in the case of dexmetomidine. Spray-drying of less water-soluble drugs (e.g., toremifene citrate) leads to its segregation at the surface of the (hydrophilic) particles, which results in an undesirable initial burst in the drug-release profile. The size of particles produced by spray-drying is also limited to the micrometer range, thus precluding significant routes of delivery such as intravenous injection. Finally, the intrinsic requirement of a relatively high temperature (i.e., $>120\,^{\circ}C$) during the drying step precludes the application of this method for the encapsulation of temperature-sensitive biological molecules, such as enzymes or proteins.

To overcome these limitations and retain the close control over the release kinetics offered by sol–gel technology, we have developed a simple method of producing microparticles by combining sol–gel technology with water-in-oil (W/O) emulsions (Fig. 2). Combining a surfactant solution in an organic solvent with a polar sol–gel solution consisting of a mixture of silica precursor (e.g., silicon alkoxide), alcohol, water, and the active molecule leads to the formation of an emulsion. The immiscibility between the apolar organic solvent (or oil) and the polar sol–gel solution leads to the compartmentalization of the sol–gel solution within discrete "water" (i.e., polar) droplets stabilized by the surfactant. With time, hydrolysis and condensation leads to gelation inside the

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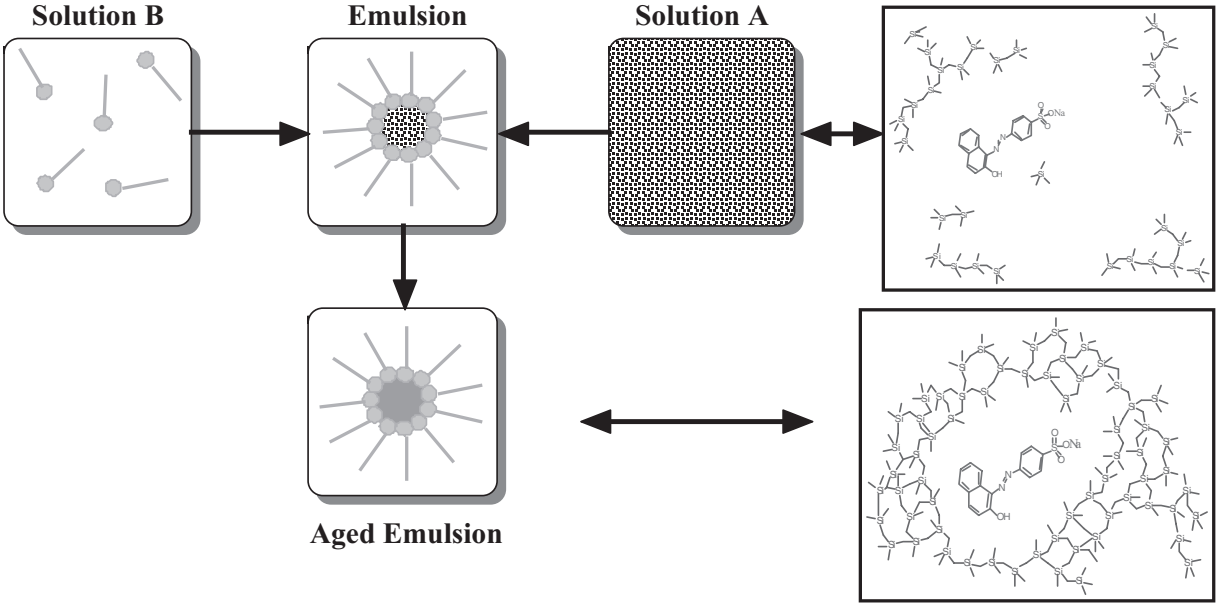

Figure 2. Schematic diagram of the combined microemulsion/sol–gel process for producing silica microparticles.

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"water" pools and the formation of porous particles with the active molecules homogeneously distributed within the particle. In other words, the sol–gel solution droplets can be viewed as microreactors, in which we conduct a normal sol-to-gel transition. Moreover, the size of the microreactor (i.e., the size of the droplets) dictates the size of the particles, whereas the internal nanostructure of the resulting microsphere is entirely controlled by the sol–gel solution chemistry.

There are many appealing features of the second approach for producing matrices for controlled-release applications. First, the size of the water droplets is directly linked to the interfacial tension between the water and oil phases, with a decrease in the interfacial tension leading to a corresponding increase in the stability of the emulsion and a decrease in the size of the droplets.[31] Thus, the water droplet size is controlled by the emulsion parameters, namely the nature of the surfactant and solvent used, the water to surfactant ratio, the presence of co-surfactant, etc. As shown in Figure 3, by changing the nature of the surfactant/solvent combination, particles ranging in size from 50 μm to 50 nm can be produced. Second, the internal microstructure of the sol–gel spheres can be tailored independently by sol–gel chemistry. For example, as in the case of bulk gels, the use of acid- and base-catalyzed sol–gel chemistry produces particles with different internal microstructures. Acid catalysis produces smooth microporous spheres with a release rate significantly slower than their base-catalyzed counterparts (which are mesoporous). Moreover, the same trends in release rates (i.e., the increase of release rate with increasing pH) is observed both in bulk gel and in microparticles, and for different molecules (Fig. 1). This confirms that the release rate of the molecules is controlled by the internal structure of the particles, which is in turn controlled by the sol–gel solution chemistry. Thus, the extended range of sol–gel parameters used to control the release characteristics of gel monoliths (including water/alkoxide ratio, catalysts, introduction of alkoxysilanes, drying temperature and time, etc.) can be used to modify the release kinetics of the microspheres. Third, in contrast to the spray-dried particles, the drug release is mediated mainly by diffusion through the silica matrix. A shorter diffusion path in the microspheres explains their elevated release rates compared with the corresponding gels, and the difference observed between Orange II and Rhodamine 6G can be explained by the difference in the sizes of the diffusing molecules. Finally, the microparticle production yields are better than 90 %, and the encapsulation efficiency (i.e., percentage of the drug encapsulated) varies from 85 to 98 %, depending on the system.[32] In addition, this synthesis, as is generally the case for emulsion processes, is easily scalable, and we currently produce 50–100 g particle batches using a 5 L stirred-tank reactor.

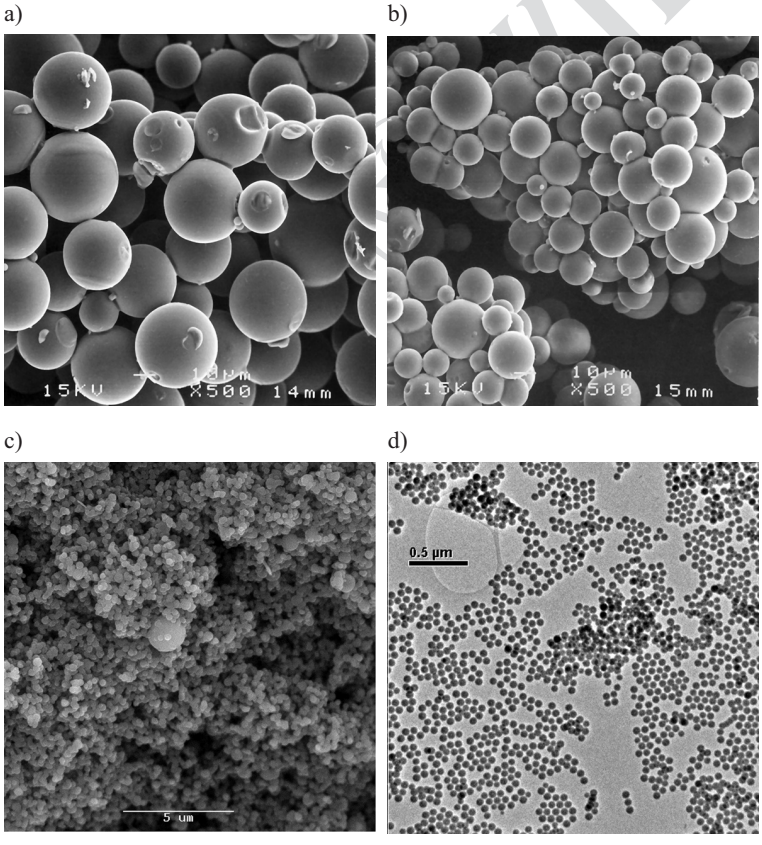

Figure 3. Electron micrographs of silica particles synthesized using a) Span 80/kerosene, b) Span 80/cyclohexane, c) sodium di(2-ethylhexyl) sulfosuccinate (AOT)/cyclohexane, and d) polyethylene glycol nonylphenyl ether (NP5)/cyclohexane. ■Surfactant names OK?■

4. Nanoparticles for targeting of cancer

Applications such as intravenous drug delivery and, more specifically, passive targeting of cancerous tumors, requires particles which are stable in the blood stream and are not detected by the RES.

Hydrodynamic stability in the blood stream is achieved by keeping the particle size between 50 and 300 nm.[33] Above 300 nm, a significant proportion of the silica particles are trapped in the lungs and liver. For example, 24 h after injection of 600 nm silica particles into rats, 50 % of the injected particles were found in the lungs and 40 % in the liver.[34] Particles smaller than 50 nm can pass through small intercellular openings in the normal blood-vessel walls and thus tend to distribute nonspecifically in the body. As mentioned in the introduction, "stealth" is achieved by maintaining a hydrophilic surface and thus avoiding opsonization (i.e., labeling of the particles as foreign entities by adsorption of "flag" proteins called opsonins).

The first challenge then is to remove the surfactant used to form the microreactor walls from the particle surface to provide a pristine hydrophilic silica surface. The second challenge is to prevent aggregation during the processing of the nanoparti-

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cles. Aggregation results in an increase of the average particle size above 300 nm and the elimination of the aggregated particles through filtration by the lungs or liver. Aggregation can occur during particle synthesis when using an unstable emulsion system, when removing the surfactant during washing (surfactant molecules adsorbed at the surface of nanoparticles prevent physical contacts between adjacent particles, and thus, aggregation), or during filtration. To prevent aggregation during these different steps, the process was modified accordingly:

- Aggregation during synthesis was minimized by using stable microemulsions, reducing droplet coalescence.
- Aggregation during washing was prevented by using a decantation washing procedure rather than the classic filtration washing. In the decantation method, the surfactant is removed by destabilizing the emulsion, thus inducing phase separation, followed by further washing of the water-based nanoparticulate suspension using organic solvents. This relatively gentle and gradual removal of the surfactant minimizes aggregation.
- Finally, an innovative method was designed to store the nanoparticles as a dry powder, thus increasing their shelf life dramatically, which is a critical issue for industrial applications of the technology. Addition of a concentrated salt solution to the microemulsion, followed by freeze-drying of the resulting aqueous phase, leads to the encapsulation of the oxide nanoparticles inside a gangue of salt. Re-dispersion can be easily achieved by simply adding the salt matrix containing the nanoparticles to water, which dissolves the salt gangue, thus liberating the nanoparticles. In principle, this approach can also be used to directly produce nanoparticle dispersions with isotonic salt concentrations, suitable for direct in-vivo applications.

As in the case of the microparticles, control of the nanoparticle size can be achieved by changing the emulsion parameters, including the nature of the surfactant/solvent system and the water-to-surfactant ratio (Fig. 3). Despite their small size, the internal structure of the nanospheres is still controlled by the sol–gel reactions occurring within the water pools. For example, base-catalyzed chemistry yields mesoporous nanoparticles which release their payload very rapidly. In contrast, particles produced using acid catalysis are microporous, and release drugs over long periods of time (up to six months). For example, Figure 1c shows that doxorubicin can be easily encapsulated and released at a constant rate over a period of 20 days.

To evaluate the performance of silica nanoparticles in vivo and their potential for passive targeting of tumors, we performed biodistribution studies of 50 and 250 nm particles in Wistar rats.[35] The results summarized in Figures 4a,b show, for both sizes, a relatively low amount of nanoparticles trapped within the liver, lungs, and spleen. This indicates that the immunological response to the nanoparticles is low. Furthermore, the particles trapped in the liver and kidneys are gradually cleared through the normal excretion

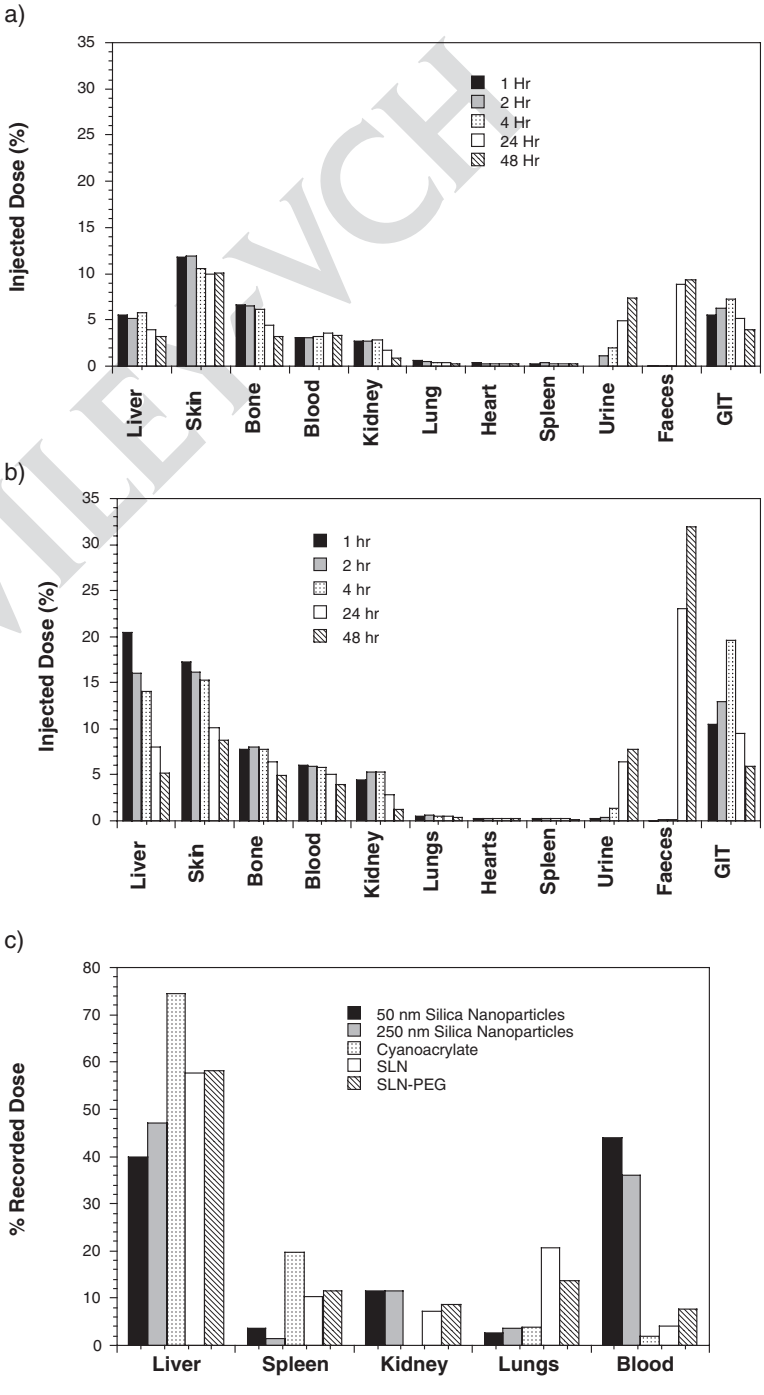

Figure 4. In vivo distribution of nanoparticles in rodents: a) 50 nm silica nanoparticles and b) 250 nm silica nanoparticles. c) Comparison of silica nanoparticles with competing technologies 24 h after injection.

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route (i.e., urine and feces). In addition, they do not become trapped in the capillaries of the lungs, even the larger 250 nm particles, contrasting with reports for 600 nm silica particles.[34] More importantly, 24 hours after injection, both the 50 and 250 nm silica nanoparticles exhibit significantly higher blood: liver ratios than competing systems such as polycyanoacrylate nanoparticles[36] and solid lipid nanoparticles (SLNs) (Fig. 4c),[37] both of which have been coated with PEG to increase their hydrophilicity. Both kinds of organic nanoparticles are smaller than the 250 nm silica nanoparticles (~180 nm), and hence size effects cannot account for their lower blood stability. The increased hydrophilicity of the silica nanoparticles decreases their associated immune response, and increases their blood circulation ratios. The increased blood circulation rates, coupled with long term release of cytotoxic molecules (Fig. 1c), makes silica nanoparticles an attractive technology for antitumor-drug delivery.

A similar strategy is being investigated for the photodynamic treatment of cancer by using 30 nm silica particles to deliver photosensitizing molecules to tumors.[38] Preliminary in-vitro experiments show good uptake by cancer cells and significant cell death after light irradiation. Recent work on the functionalization of silica-nanoparticle surfaces coated with ■OK?■enzyme molecules,[39] DNA fragments,[40,41] or antigens[42] opens the door to the production of "smart" particles capable of seeking specific cells or receptors in the body. On arrival at the desired destination, they would release their drug payload in a controlled fashion, thus ensuring a specific and controlled therapeutic effect. Although a number of obstacles[43] (e.g., "bio-fouling" of the biological ligand) have to be overcome for grafted nanoparticles to selectively target specific cells, recent success with HER-2-functionalized Doxil (i.e., doxorubicin liposomal formulation) in pre-clinical trials[10] paves the way for active targeting of tumors using other nanoparticulate systems.

5. Conclusions

Silica particles offer an interesting alternative to organic delivery systems. Their intrinsic hydrophilicity and biocompatibility, as well as the excellent protection they provide for their internal payload, makes them perfect candidates for controlled drug-delivery applications. The use of sol–gel technology provides enhanced flexibility in both the encapsulation and the release of drug molecules. The release rates can be precisely controlled by tailoring the internal structure of the particles for a desired diffusion (release) profile. Drug-loaded particles can be produced either by atomization or emulsion polymerization. In both cases, the size of the particles is controlled independently by controlling the size of the droplets. However, in contrast to spray-drying, sol–gel synthesis conducted in water-in-oil emulsions which allows the production of micro- and nanoparticles, homogeneous encapsulation of the drug in the particle, and a low processing temperature necessary for the encapsulation of biological molecules. In addition, independent control of the size and release rate can be readily achieved: the size is controlled by the emulsion parameters, and the release rate is controlled by the sol–gel solution chemistry. Preliminary in-vivo experiments show enhanced blood stability of the silica nanoparticles compared to competing technologies (such as liposomes and polymeric nanoparticles). This, coupled with the long-term release of cytotoxic agents (e.g., doxorubicin) demonstrated in vitro, makes this technology very interesting for the delivery of anticancer drugs.

Nevertheless, significant challenges still remain before silica particles can be used successfully and routinely for therapeutic applications. Using a military analogy, if a drug-delivery system were to be represented as a ballistic missile, we have shown that silica nanoparticles can encapsulate an active payload, can avoid detection by the body's "radar", and can slowly release their content to kill the enemy. The missing component needed for the silica nanoparticles to become a successful delivery system is the homing device that will specifically target receptor sites or cancer cells. This should be readily achieved by grafting appropriate seeking molecules onto the surface of silica. Although the grafting of these biomolecules is expected to affect the hydrophilicity of the particles, interaction with other molecules or cells present in the blood could decrease the particles' "stealth". Finally, although all the different aspects of the silica particle drug-delivery technology have been demonstrated in vitro, in-vivo studies of the complete system remain to be conducted to fully validate the concept of using silica nanoparticles to target tumors.

Received: May 17, 2004
Final version: September 8, 2004

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RESEARCH NEWS

Drug Delivery

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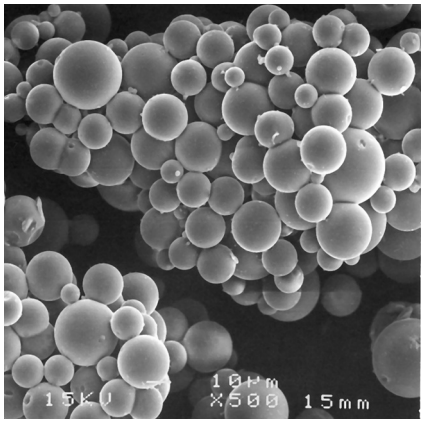
Silica Particles: A Novel Drug-Delivery System



Silica particles present an interesting alternative to organic systems for drug delivery. Combining sol–gel synthesis with emulsion technology can produce particles (see Figure) with independently controlled size and release rates. The particle size is controlled by the emulsion chemistry, while the release rate is controlled by the particle microstructure. Preliminary in-vivo experiments reveal enhanced blood stability of the nanoparticles, which, coupled with sustained release of anti-tumor agents, show good potential for cancer treatment.

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