Nanophase Ceramics for Improved Drug Delivery:

Current Opportunities and Challenges

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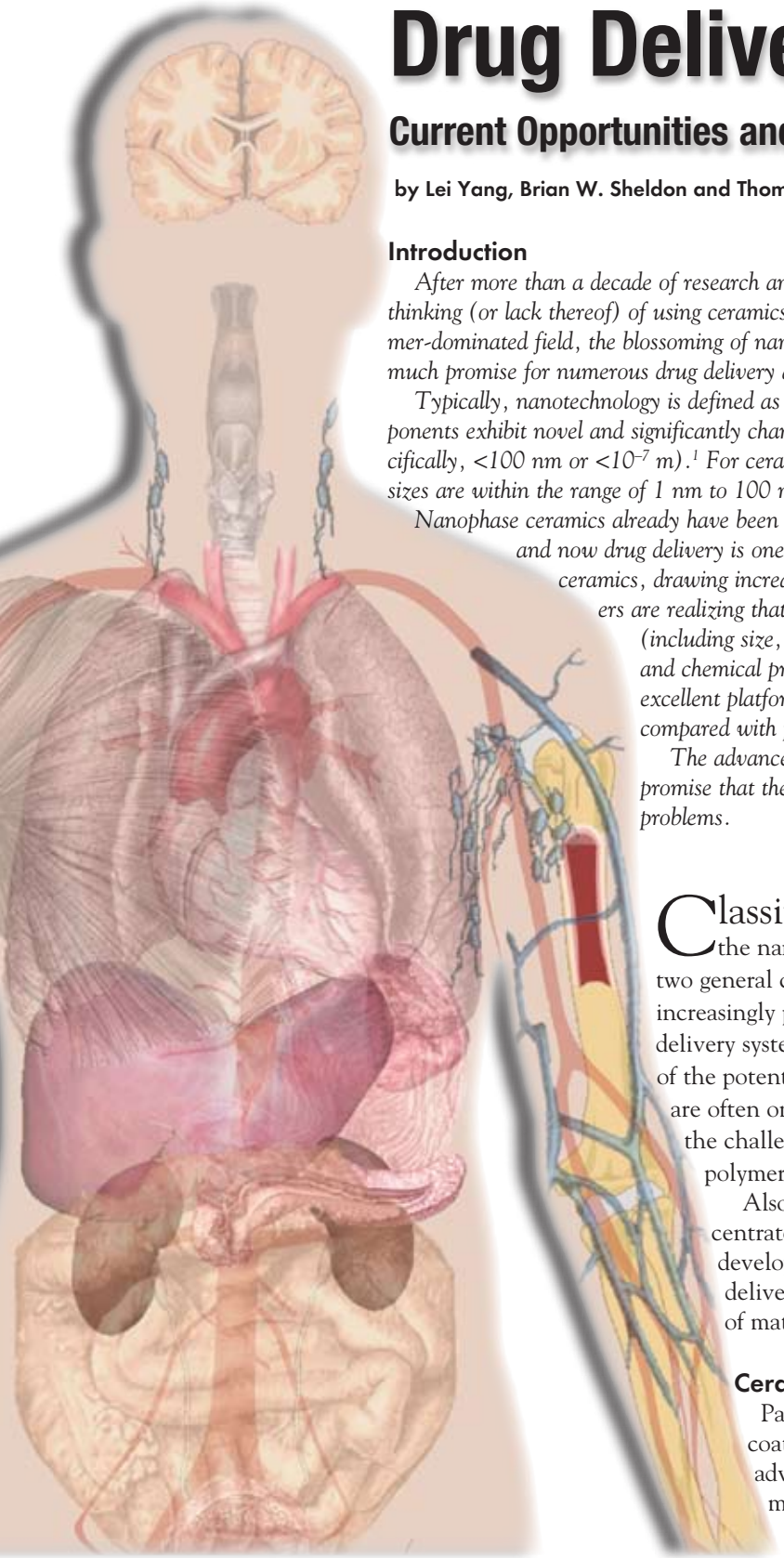


Introduction

After more than a decade of research and development, nanotechnology has reshaped the traditional thinking (or lack thereof) of using ceramics for drug delivery. Although drug delivery has been a polymer-dominated field, the blossoming of nanotechnology means that ceramic materials are now showing much promise for numerous drug delivery applications.

Typically, nanotechnology is defined as the use of materials and systems whose structures and components exhibit novel and significantly changed properties when control is gained at the nanoscale (specifically, <100 nm or $<10^{-7}$ m).[1] *For ceramics, this means fabricating ceramics whose grain or particle sizes are within the range of 1 nm to 100 nm).*

Nanophase ceramics already have been widely used in a broad spectrum of biomedical applications, and now drug delivery is one of the fastest emerging and developing arenas for nanoceramics, drawing increasing attention over the past few years. Indeed, researchers are realizing that the extraordinary characteristics of nanophase ceramics (including size, structural advantages, highly active surfaces, unique physical and chemical properties and ease of modification) suggest that they can be excellent platforms for drug transportation and controlled prolonged release compared with polymeric platforms.

The advances nanophase ceramics are making in drug delivery seem to promise that these materials will solve many of today's challenging medical problems.

Classifications based on their architectural differences, the nanophase ceramics reviewed below can be placed into two general categories: nanoparticles and nanoscaffolds. Alhough increasingly popular, both of these categories of multifunctional drug delivery system are still in their infancy. On the other hand, analyses of the potential risks of using nanophase ceramics as drug carriers are often omitted. Therefore, the last part of the article discusses the challenges that nanophase ceramics face when compared to polymeric drug delivery systems.

Also, ilt also should be note that although this article concentrates only on ceramic materials, the potential and development of hybrid or composite ceramic–polymer drug delivery systems that incorporate the benefits from other types of materials should not be neglected.

Ceramic nanoparticles

Particulate drug carriers (as opposed to two-dimensional coatings or three-dimensional scaffolds) have a variety of advantages for use in drug delivery and are probably the most common ceramic drug delivery platforms today.

Particulate carriers can easily transport drug entities in volume-confined administration routes (such as blood vessels, the digestive tract, across cell membranes, etc.) and, thus, can deliver drugs in minimally invasive methods just as their polymeric counterparts. Particulate carriers also possess large surface area-to-volume (or surface area-to-mass) ratios that allow for a high drug payload and a prolonged drug-release profile. Another plus is that from a process and production point of view, particulate materials are also easy to fabricate and inexpensive to produce, especially in terms of mass production.

Advances in nanotechnology have further strengthened these advantages by providing ultrasmall particles of high purity and extremely high surface area-to-volume ratios as well as affordable fabrication processes with a high control of particle size, morphology or porosity. Nanoscale drug-carrying particles can enhance endocytosis of drugs by target cells and can also facilitate deeper penetration into capillaries and through fenestrations to, ultimately, enhanced cellular uptake.

For example, studies have shown that nanoparticles with sizes from 10 nm to 70 nm in diameter can penetrate capillaries, and those with sizes 70 nm to 200 nm have the most prolonged circulation time compared with other sizes.[2] High surface area-to-volume ratios of nanoparticles and their associated high surface activities can further improve drug-loading efficiencies and stability. These means that medical professionals can achieve better drug control and sustained release.

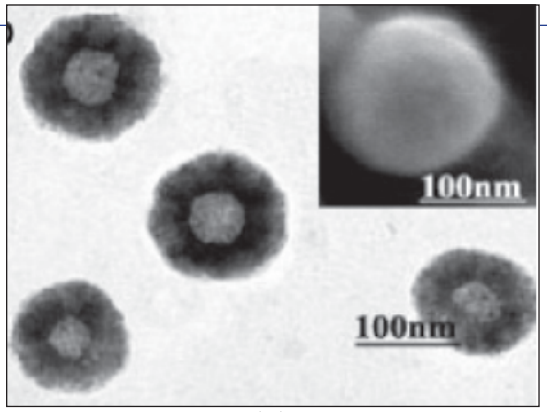
Moreover, nanotechnology offers various novel approaches to control drug transportation throughout the body, whereby pharmaceuticals can be released in precise, timely, targetable or environment-responsive manners. For example, a thermosensitive nanogel with the ability to target tumors was developed recently.[3] The poly(N-isopropylacrylamide-co-propyl acrylic acid) nanogel, conjugated with an arginine-glycine-aspartic acid (RGD) containing peptide and transferin, has a dual ability: it can target tumor cells and release embedded doxorubicin – a DNA-interacting anticancer drug – in responses to temperature changes above 34.4°C.[3]

However, all of the above benefits are generally true for polymers too, and are associated primarily with their nano size. So, how are nanoparticles of ceramics different from polymers in terms of drug delivery? Ceramic nanoparticles possess several unique properties compared with polymeric or metallic nanoparticles.

First, ceramic nanoparticles usually have longer biodegradation times, a property crucial to diffusion-controlled drug release kinetics. Slowly degradable – or even close to nondegradable – ceramic matrices can retain drugs for longer times after administration. In these cases, drug release is dependent on concentration gradients and can be prolonged.

Second, unlike polymers, ceramic nanoparticles in aqueous conditions generally do not swell or change porosity and are more stable when variations in pH or temperature are encountered. For instance, the small swelling ratios of ceramics prevent the release of a burst of drugs – a problem commonly seen in hydrogels, such as poly(2-hydroxyethyl methacrylate) (pHEMA) drug-delivery systems.

Third, and possibly the most intriguing of all, properly fabricated ceramic nanoparticles can possess the same chemistry, crystalline structure and size as the constituents of targeted tissues (e.g., various types of calcium phosphate in bone). Their fabrication enhances the material's bioactivitiy and biocompatibility even before releasing drugs. In addition, the nanoparticles can be engineered with favorable electrical (e.g., ferroelectrical and diaelectric properties), mechanical (e.g., pizeoelectrical properties, ultrahigh hardness,



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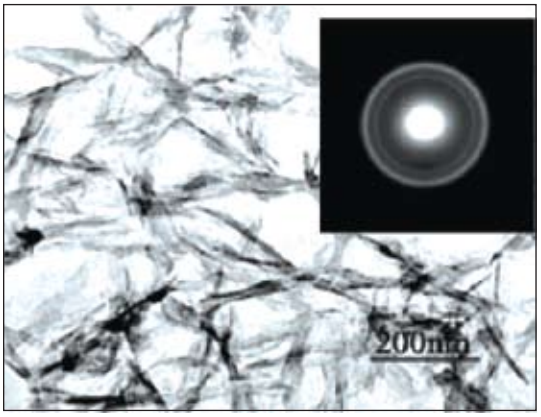

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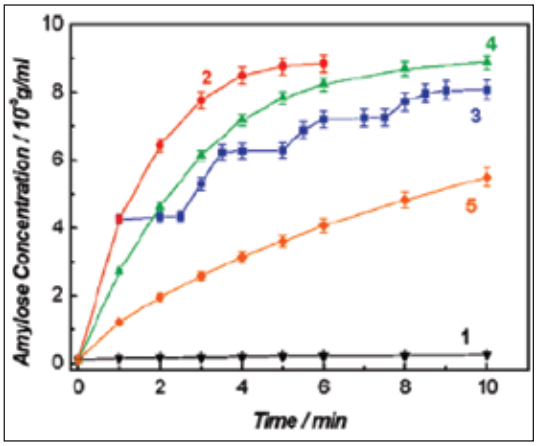


(c)

Fig. 1. Hollow calcium phosphate nanospheres (a) before and (b) after ultrasonic applications. (c) Release profiles of amylose from the hollow calcium phosphate nanospheres under various applied ultrasonic power densities: (1) no ultrasonic application; (2) continuous ultrasonic treatment (150 W); (3) 1-min treatment of ultrasound (150 W) between an interval of 1.5 min; (4) continuous ultrasonic treatment (100 W); and (5) continuous ultrasonic treatment (50 W). (Modified from Ref. 10)

Table 1. Representative ceramic nanoparticle for drug-delivery applications

Ceramics	Structural feature	Applications
Calcium phosphate	Hollow apatite nanospheres	On–off drug release con trolled by sonication[10, 11]
	Apatite nanocrystals	Enhancing protein adsorption and prolong desorption[37]
	Nanocomposites	Enhancing gene transfer and controlling the extent of gene transfer[42]
Iron oxides	Nanoparticles	Magnetic liposomes for BMP delivery;[39] Drug release controlled by magnetic heating;[4]; Multi-functional drug carriers with capacities of imaging and targeting
	Ferrofluids	Colloidal solutions of iron oxide surrounded by coatings of targeting molecules for delivery of drugs[41]
Silica	Nanoparticles	Photosensitizer for photodynamic therapy (PDT)[24, 25]
	Hollow nanospheres	Enhance drug loading capacity[13]
	Hollow nanotubes	Improve drug loading capacity and biocompatibility of drug delivery system;[14] Gene delivery[43]
Titania	Nanotubes	Enhance drug loading capacity and prolong drug release[30]
Alumina	Hollow nanoshells	Drug loading agents[15]
Calcium carbonate	Hollow spheres	Drug release vectors and diagnostic markers[16]
Layered double hydroxides (LDH)	Anionic nanoclays $(M^{2+}_{1-x}M^{3+}_{x}(OH)_2)^{-}(A^{m-})_{x/m}\cdot nH_2O$; M: Metal cations and A: Interlayer anions	Highly efficient, bio-resorbable drug and gene delivery platforms[26, 27]

etc.), magnetic (e.g., superparamagnetic properties) and optical (e.g., photothermal effects, electroluminescence, etc.) properties rarely seen in polymeric or metallic nanoparticles.

Controlling the release

Medical professionals often seek a specific drug-release profile pattern. Drug delivery patterns can be divided into either continuous or discrete ("on-off").[2] Nanotechnology can be used to control drug delivery in each category.

For example, medical professionals in cases, such as diabetes therapy and inflammation suppression after surgery, prefer continuous but time-delayed drug delivery followed by a stable release profile rather than initial drug-burst release.[4] Conversely, for discrete delivery, such as a drug release to cancer cells or pathogen sites, a burst release of drugs at a designated time is often desirable.

Researchers are taking this a step further, targeting the drug to specific sites, such as pathogens, specific tissues or cells. This targeting ability is highly desirable (and challenging) because it increases drug efficiency and decreases toxic side effects. Because of their extraordinary characteristics, ceramic nanoparticles have considerable potential to tackle these challenges.

Several recent examples of nanophase ceramics used as novel drug delivery platforms are summarized in Table 1. Most significantly, calcium phosphates have been widely studied due to their biocompatibility, tailorable bioabsorbability and bioactivity. Calcium phosphates have been used as novel delivery carriers for antibiotics (e.g., gentamicin sulphate, flomoxef sodium, tetracycline, etc.), anti-inflammatory agents (e.g., salicylic acid, indomethacin), analgesic and anticancer drugs (e.g., mercaptopurine, estradiol), growth factors (e.g., bone morphological proteins, transforming growth factors β (TGF-β), etc.), proteins (e.g., collagen I and osteocalcin) and genes (e.g., DNA).[5, 6]

Nanotechnology-derived calcium phosphates also have successfully maintained a sustained and steady drug release over time. A bovine serum albumin-loaded calcium-deficient hydroxyapatite system revealed a single-stage slow-release profile in which only about 55 percent of the BSA released during the first 8 hours and an additional 35 percent after 90 hours.[7] Recent studies have also indicated that the drug-release kinetics could be further controlled by tailoring calcium phosphate nanoparticle grain size, surface area and calcium-to-phosphorus ratios.[8, 9]

More interestingly, researchers have designed and fabricated calcium phosphate nanoparticles that achieve the on–off delivery of drugs triggered by programmable external forces, such as ultrasonic vibration with a specific power density. As an example, one group has developed a type of hydroxyapatite-like hollow nanospheres (sizes 145 ± 20 nm) that can collapse and transform to pin-shaped HA-like nanocrystallites under ultrasonic treatment.[10] Knowing this, the group successfully encapsulated drugs in the hollow structures that were then triggered by ultrasound. A drug release study of these HA nanospheres using amylose as a drug model revealed that the drug release rates can be controlled by altering ultrasound power density to collapse various amounts of nanospheres (Fig. 1).[10, 11]

Various versions of hollow nanostructures composed of other ceramic materials also have been highlighted in recent studies. All of these have one thing in common: They have an extremely high drug-loading capacity and time-delayed release behavior (pulse or discrete release) compared with bulk nanopheres. For example, studies have shown that hollow silica nanospheres are capable of entrapping an eightfold increased quantity of drug species compared with solid silica nanospheres.[12] Another study revealed that hollow silica nanospheres had a time-delayed multiple-stage release profile (including an initial burst release for 20 minutes, a prolonged steady release up to 10 hours and a final fast release for another 2 hours).[13]

Hollow silica nanospheres have pioneered such research and have been fabricated into well-controlled shapes and sizes by using templates or self-templating molecules.[12, 13] Other studies on hollow ceramic nanostructures for drug-delivery purposes include magnetic silica nanotubes,[14] nanoshell alumina spheres[15] and calcium carbonate nanospheres[16] (Fig. 2).

Perfect for multifunctions

Besides applications in controlled drug release, a new trend is to use ceram-

ic nanoparticles as advanced multifunctional platforms for diagnostic imaging and therapeutic purposes. As an example, magnetic iron oxide nanoparticles (including magnetite γ-Fe_2O_3, magnetite Fe_3O_4 and associated compounds, also known as superparamagnetic ION) have been actively studied for these purposes.

Targeted drug delivery can be realized by biochemically modifying such drug carriers to specifically bind to target cells, or more directly, by using external measures to move drug carriers to the pathological sites. Monoclonal antibodies (such as anti-HER2, anti-VEGF McAb, etc.) and peptide sequences (such as the HIV-Tat peptide) have been conjugated to ION to target them to tumors, myocardial infarctions or beta-amyloid plaques.[17] A specific example is that ION conjugated with the synapotagmin I protein can target apoptotic tumor cells. These cells express anionic phospholipids that specifically bind to the protein.[18]

In the case of applying external forces to target drug delivery, an external magnetic field is applied to guide ION-conjugated drugs to specific sites after intravenous delivery of the particles. This technique has reached clinical trials for cancer therapy.[19] Similarly, several recent studies using ION to treat bone diseases (such as osteoporosis, osteoarthritis, bone cancer, etc.) proposed a strategy of delivering ION-based drug systems to osteoporosis sites by using a directional magnetic field.[20,21] Here, the idea can be taken a step further. By directing magnetic nanoparticles to the pores of osteoporotic bone, bone strength can be immediately increased without releasing any drug.

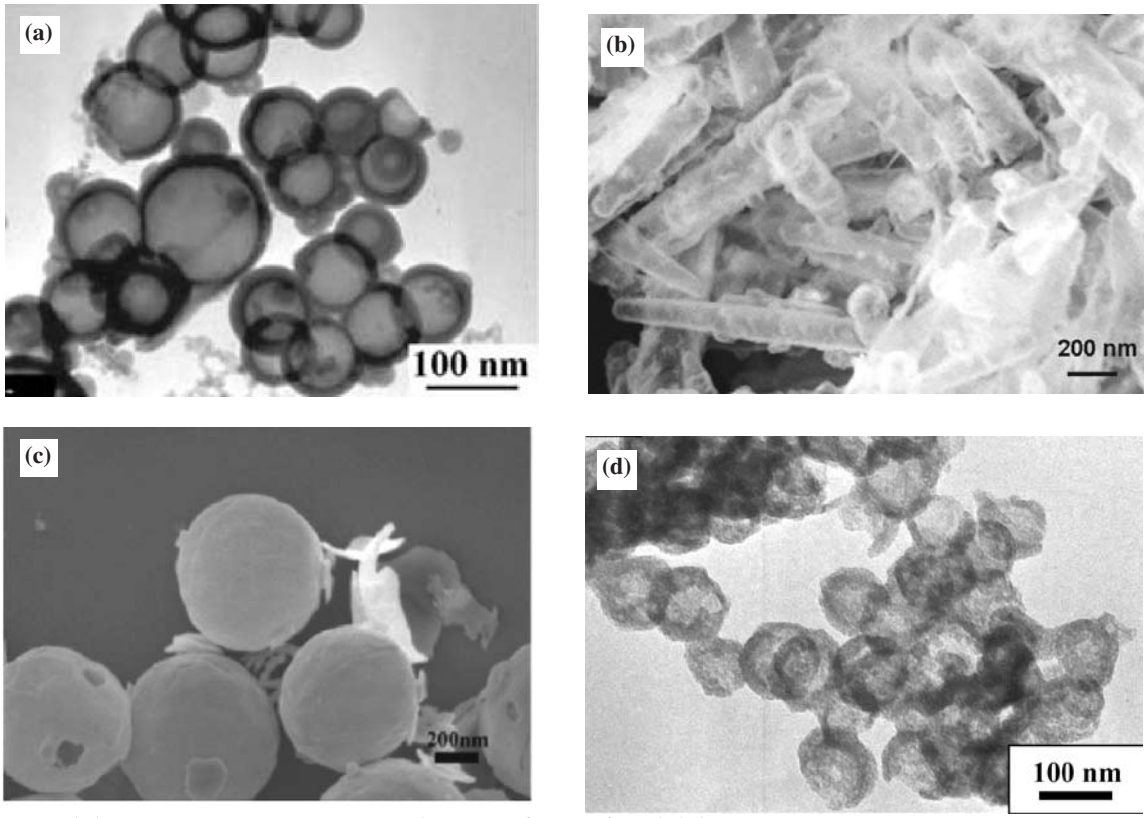


Fig. 2. (a) Hollow siliceous nanospheres (Adopted from Ref. 12.); (b) magnetic porous hollow nanotubes (Adopted from Ref. 14.); (c) hollow alumina nanospheres (Adopted from Ref. 15.); and (d) hollow carbonate nanospheres (Adopted from Ref. 16.).

In summary, coupled with their extraordinary magnetic properties for enhancing magnetic resonance imaging and ability to damage cancer cells through magnetic thermal effects,[22,23] ION-rendered drug-delivery systems can be made to be multifunctional to image, sense, diagnose and treat various diseases.

Finally, there are two fast-emerging topics toward using ceramic nanoparticles in drug delivery worth further attention. One is photodynamic therapy (PDT) and the other is nanoscale layered double hydroxides (LDHs).

PDT is an emerging method for the treatment of various diseases, including oncological, cardiovascular, dermatological and ophthalmic diseases. PDT involves the uptake of a photosensitizer (such as silica) by pathological tissue, such as tumor tissue, followed by photoirradiation. The photoirradiation triggers singlet oxygen ($^1O_2$) formation as a result of the combined action of excited photosensitizers and molecular oxygen, and the $^1O_2$ induces cellular death.[24]

Ceramic nanoparticles are ideal photosensitizer carriers due to their photostability, easily controlled size, shape and monodispersity and appropriate pore sizes (0.5 nm – 1 nm) for oxygen diffusion and drug retention.[24] Typical ceramic materials for PDT applications are silica-based nanoparticles. A recent systematic study demonstrated that silica-based nanoparticles, approximately 30 nm in size) successfully entrapped a photosensitizing anticancer drug (2-devinyl-2-(1-hexyloxyethyl) pyropheophorbide) and can be synthesized by hydrolysis. These drug-doped nanoparticles revealed high aqueous stability, efficient generation of $^1O_2$, active uptake by tumor cells and, most importantly, significant damage to tumor cells after photoirradiation.[25]

LDHs refer to a class of anionic layered ceramic materials (or anionic nanoclays) made of charged metal hydroxide layers and charge-balancing hydrate gallery anions. The metallic cations in the LDHs can be Mg^{2+}, Zn^{2+}, Ni^{2+}, Cu^{2+}, Al^{3+}, Fe^{3+}, etc., and the interlayer anions can be CO_3^{2-}, NO_3^-, SO_4^{2-} or other anionic species.[26]

LDHs are bioresorbable and have a

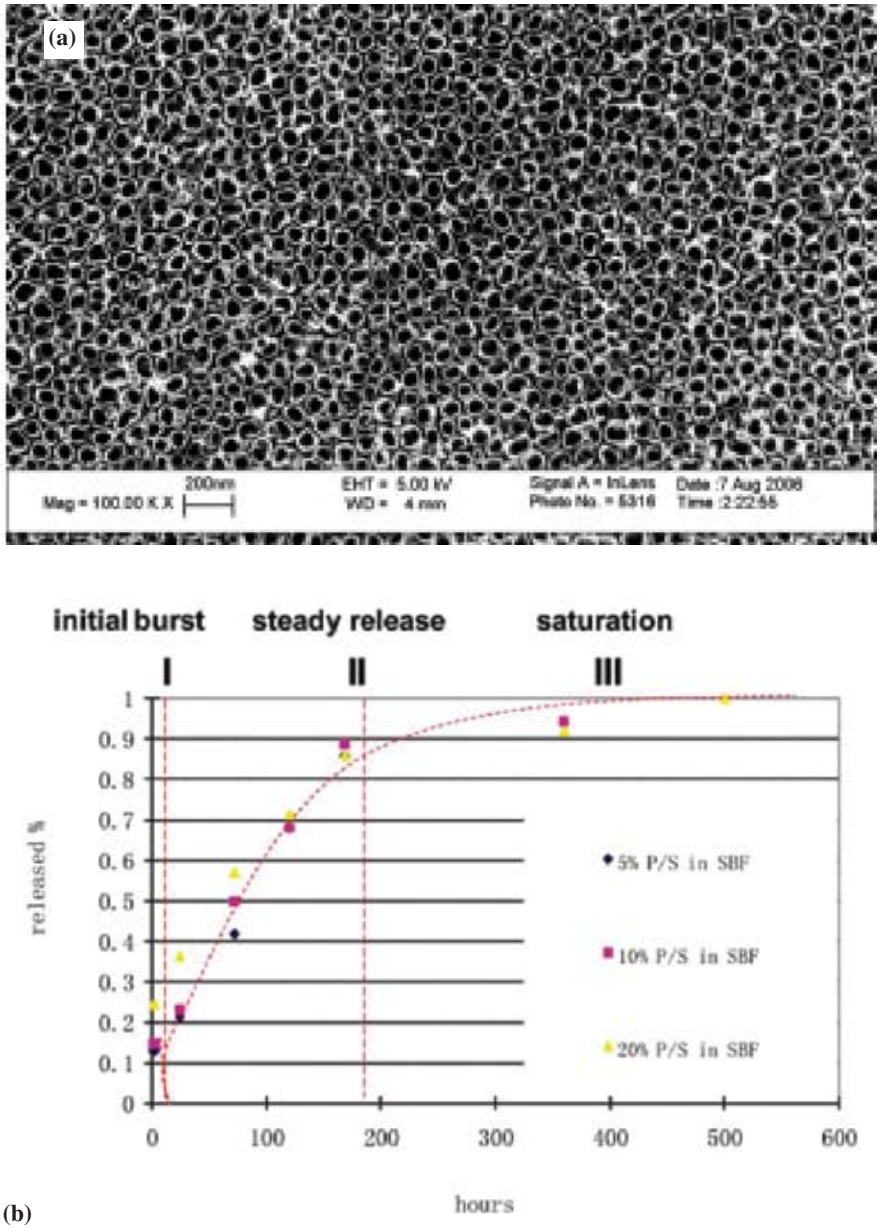


Fig. 3 (a) Nanotubular titania produced by anodizing titanium orthopedic implants. (b) Release profiles of coprecipitated penicillin/streptomycin (on nanotubular titania by immersing in simulated body fluid (SBF)) in phosphate-buffered solution (PBS) for up to 3 weeks. (Adopted from Ref. 30.).

high anionic-exchange capacity, high swelling properties and pH-mediated solubility. These are the properties that make them promising for drug and gene delivery.[26, 27] LDHs can be readily synthesized though aqueous coprecipitation by adding a strong base solution into the solution containing metallic cations. The sizes of LDHs can be easily controlled by pH, temperature and reaction time.

In particular, researchers have demonstrated that the anticancer drug methotrexate conjugated to LDH has a much greater in vitro anticancer effect compared with clinically used doxorubicin. They believe this is probably because of enhanced cellular drug uptake via clathrin-mediated endocytosis and controlled release inside cells.

Recent in vitro and in vivo studies further indicated that LDHs in the size range of 100–200 nm might have the highest delivery efficiency of drugs, and reduced toxicity effects compared to LDHs of other sizes.[26]

Ceramic nanoscaffolds for drug delivery and tissue regeneration

Like their nanoparticle counterparts, nanotechnology-created ceramic scaffolds have also demonstrated great potential for controlled drug delivery. These ceramic scaffolds were initially designed as supportive architectures to control and direct cellular behavior by creating a biomimetic environment. Examples are calcium phosphate scaffolds that mimic the natural bone structure and chemical composition.

Calcium phosphate scaffolds provide not only initial structural integrity for bone cells, but also direct their proliferation and differentiation, and they can assist in the ultimate assembly of new tissue. Therefore, ceramic nanoscaffolds are usually 3-D and porous, although in some cases they are 2-D coatings or films. They mimic the in vivo environment of cells more completely than do nanoparticles.

It is easy to understand that there is an urgent need for developing nanomaterials scaffolds that are biomimetic. That is because so many natural tissue architectures are hierarchical with micron as well as nanostructured features. For example, in the connective tissue, nanoscale structural proteins, such as collagen fibers and elastin-fibers entangle into a nonwoven micron-structural mesh that provide mechanical strength and elasticity for the tissue.

Similarly, at the nanoscale, bone is composed of periodically assembled collagen fibers and calcium phosphate crystals, both nanomaterials. The development of ceramic scaffolds for biomedical applications that mimic natural tissue structure is increasingly related to nanotechnology. These techniques have been playing an extremely important role in the design, fabrication and modification of sophisticated drug-delivery scaffolds.

The structural advantages of ceramic nanoscaffolds include high porosity, high volume-to-area ratios, high surface area, high structural stability and long degradation times. These properties make them potent systems for the storage and controlled release of drugs, especially drugs for in-situ

anti-infection and anti-inflammatory purposes. Therefore, most drug-eluted ceramic nanoscaffolds serve multiple functions, such as drug delivery, directing cell growth or tissue generation, and mechanical support. Indeed, the mechanical support provided by ceramic scaffolds far exceeds that provided by polymeric scaffolds.

Table 2 summarizes the ceramic nanoscaffolds that are under active research for drug delivery purposes. Researchers, for example are looking at nanotubular titania and calcium phosphate-based nanoscaffolds for drug and growth factor delivery. In particular, nanotubular titania structures with a tube width of tens of nanometers and a tube length of a few hundred nanometers increase bone growth more than the forms of titanium that are currently in use. A form of nanotubular titania can release antibiotics and growth factors after implantation (Fig. 3(a)).

Nanotubular titania structures can be readily fabricated by direct anodization of existing titanium orthopedic implants in an electrochemical cell that uses the titanium as an anode and platinum as a cathode in the presence of fluorine-based electrolytes.[28, 29] In fact, anodization theoretically can be applied to any metal that is stable to oxidation to fabricate nanoscale tubular or porous surfaces.

Researchers recently demonstrated an example of using nanotubular titania as a drug delivery platform when they showed they could load penicillin-based antibiotics by coprecipitating the drug and calcium phosphate crystals on the nanostructures.[30] This delivery system showed a time-delayed release of antibiotics for up to three weeks. It accomplishes this with a small initial burst, in contrast to a 150-minute complete release of drugs after being physically adsorbed on nanotubular titania (Fig. 3(b)).[30] This system also demonstrated good cytocompatibility properties, as tested by osteoblasts, or bone forming cells. This means the material has a strong potential for supporting bone growth.

In another study, researchers modified nanotubular titania by attaching amine or methyl groups. An examination of orthopedic implants that used this system showed an increase in drug-loading efficiency and prolonged drug release, and the drug delivery system showed reduced *Staphylococcus Epidermis* colonization and initial adhesion.[31]

Besides antibiotics, another research project to improve bone implant efficacy has shown that growth factors like the amino acid peptide sequence of a segment of bone morphogenetic protein-2 (the knuckle epitope, CKIPKASSVPTELSAISTLYL) can be successfully incorporated into the nanotubular titania structures to promote osteoblast adhesion.[32]

Special cements are also being incorporated into nanoscaffolds. For example, one group has been fabricating self-setting calcium phosphate cements into injectable high-strength nanoscaffolds by incorporating chitosan and various porogens, such as absorbable fibers and mannitol. These components strengthen the scaffolds and provide sequentially formed pores that promote new bone growth.[33]

Controlled release is also an important property here. The CPC nanoscaffolds can deliver growth factors and proteins in a time-delayed manner by simply altering the CPC-to-chitosan ratio in the fabrication process.[33] Another recent study on scaffolds comprised of BONIT matrix, a biphasic nanophase composite of silica and calcium phosphates (HA/tricalcium phosphate), showed the material can deliver a continuous release of gentamicin, an aminoglycoside antibiotic extensively used for orthopedics, from the scaffolds for 70 days without an initial burst release.[34]

Table 2. Representative ceramic nanoscaffolds for drugdelivery applications

Ceramics	Material and structural features	Applications
Titania	Nanotubular surfaces	Improving drug loading efficiency and prolonged drug release of antibiotics for orthopedic implant applications;[30, 31] growth factor delivery[32]
Calcium phosphate (CaP)	Calcium phosphate cement (CPC) nanoporous scaffolds	Controllable delivery of growth factor and promotion of new bone growth[33]
	Silica/CaP nanophase composites	Prolonged continuous release of drugs up to 70 days[34]
Silica	Silica nanospheres incorporated with glass scaffolds	Improving loading capacity and delivery amount of the drug[44]

Electrospun scaffolds

Many researchers are also looking at electrospun nanostructured scaffolds as drug-delivery materials. Although electrospun nanostructured ceramics are rare compared with polymers for drug delivery and their potential for drug delivery has yet to be fully explored, the advantages of electrospinning are clear: The method allows for the convenient fabrication of ceramic nanostructures with controllable morphology and size.

The principle of electrospinning is to charge solutions containing polymers, ceramics or metallic precursors with a high voltage. The charged solution is drawn by electric field from a nozzle onto collector plate to form desirable structures. The structures can be fabricated to mimic various architectures of biological systems, such as fibrous proteins assembled in a native extracellular matrix or collagen fibrils in bone (Fig. 4).

For example, investigators have electrospun a mixture of calcium phosphate precursors with polyvinyl chloride and then sintered the material into highly interconnected nanofibrous networks. They believe this electrospun scaffold will work well for treating bone defects and drug delivery.[37]

Challenges

As mentioned above, targeted drug delivery and precise control of drug release kinetics (continuous or on-off release) are two challenging topics faced by all drug delivery researchers. Nanophase ceramics seem to offer solutions to traditional drug delivery prob-

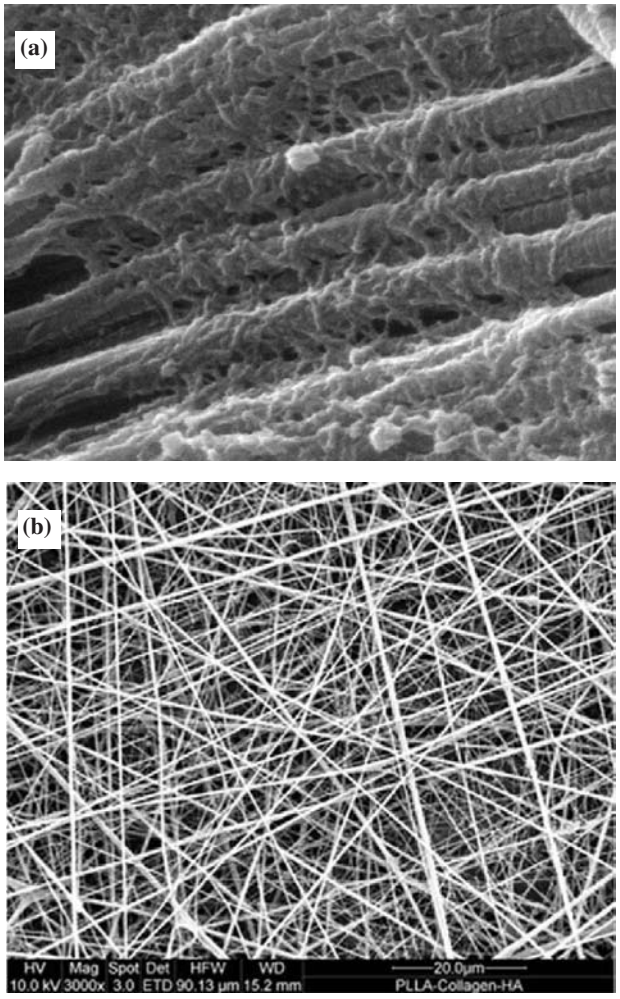


Fig. 4. (a) Microstructure and nanostructure of rat tendon showing collagen fibrils and collagen-bound proteoglycans, the image size is 2×2 µm (Adopted from Ref. 35.); (b) Electrospun poly-L-lactide (PLLA)/collagen/hydroxyapatite nanofibers mimicking bone structures (Adopted from Ref. 36.).

lems because of their unique material properties centered on greater surface areas. Unfortunately, targeting efficient and controllable drug release is still not a reality for clinical use.

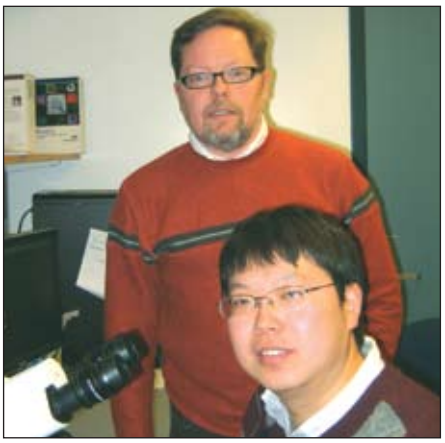
In fact, efforts to aim them at desirable sites and employ multiphase-drug release or quantity-controlled drug release are still in the early stage of application. In nearly all the current studies, researchers have primarily used in vitro models to assess the efficacy of nanophase ceramic drug delivery systems (such as targeting efficiency, drug release kinetics and biocompatibility).

There is a great difference between in-vivo and in-vitro systems. Clearly, further verification of their properties and overall more assessment of nanophase ceramic systems are still needed in actual clinical trials.

Because of slow biodegradation or non-degradation, all ceramic drug platforms also face the potentially large challenge of removal from the body after delivering drugs. The challenge becomes much more serious for nanophase ceramics, because their size allows them to easily penetrate cell membranes and biological barriers, including, perhaps, the blood–brain barrier. Once in the cells, these materials may be difficult to get out. The truth is that little knowledge exists in understanding removal mechanisms of ceramic nanocarriers. In part, there has been a lack of studies on the metabolism and elimination routes of nanoparticles. Another concern is the vast variations in nanomaterials' physical and chemical properties that cause such studies to be inconsistent and incomprehensive.

Even more important, the toxicity of nanophase ceramics is still unclear and, like other nanomaterials, becoming an increasing concern to the scientific and medical community. Although some studies exist,[38] gaps in knowledge concerning the interaction of nanoparticles within the body are still significant.

Already, it seems that in some cases the advantages nanoceramics have for improving drug-delivery efficacy may unfortunately be their downfall. For example, some ceramic nanoparticles (such as iron oxide and semiconductor) revealed cytotoxic effects when their concentration is above only 10 µg/mL.[38] Although the generation of reactive oxygen species and the internalization of nanoparticles are two common nanomaterial-induced cytotoxicity pathways, the causes for cytotoxicity are material specific and not fully understood. Again, because these preliminary findings are mostly based on in-vitro cell models, a systematic approach to test the toxicity of nanoceramics, especially in-vivo toxicity, is highly desirable.



Authors: Thomas J. Webster, left, is an associate professor of engineering and orthopedics at Brown University. Lei Yang is a graduate student at the school. Brian W. Sheldon (not pictured) is a professor of engineering at Brown.

Extraordinary opportunities ahead

In summary, nanophase ceramics have exceptional opportunities to assist targeted drug delivery efforts due to their unique ability to modulate drug release kinetics, incorporate multifunctional molecules and target specific focus sites. Although the challenges that nanophase ceramics face are serious and the toxicity of nanomaterials is an increasing concern, the extraordinary properties of nanophase ceramics and the continual advances in understanding their metabolism and elimination routes from the body offer more promising avenues to diagnose, understand and treat numerous diseases through drug delivery. ■

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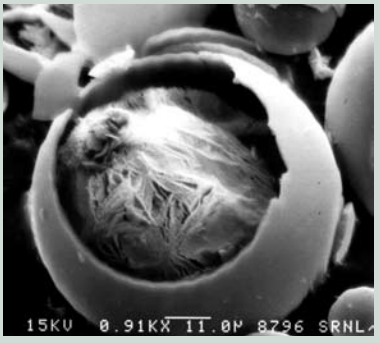
Mo-Sci licenses SRNL's porous, drug-delivering microballoons

The Department of Energy announced that a licensing agreement has been reached between Savannah River National Lab and specialty glass provider Mo-Sci Corp. The Missouri-based Mo-Sci will use SRNL's unique porous-walled hollow glass microspheres as a transport mechanism for targeted drug delivery, hydrogen storage and other uses. "Mo-Sci had the background in glass manufacturing and processing porous wall hollow glass microspheres," says Ted Day, president of Mo-Sci. "We've been doing this for research purposes for about 5 years."

"This isn't like making hollow glass beads. We manufacture the PW-HG spheres to exact specifications, and the customer loads the microspheres with the materials, like medical drugs," says Ted Day, president of Mo-Sci.

The microspheres typically have a 50 µm diameter, but can range from 2 µm to 100 µm. The shells are about 10,000 Å. The June 2008 issue of the *Bulletin* has a lot of good information about how they are made and the wide range of potential uses.

Microspheres, per se, aren't new, but there are three things particularly important about the PW-HG microspheres. The first is that they have a network of interconnected pores engineered into the thin shells. Moreover, the SRNL researchers figured out how to customize the properties and dimensions of these pores. Thus, solid, liquid and gaseous materials can pass into and be confined within the microspheres. Several mechanisms are available to attain a controlled release of the microsphere's contents.



(Credit: SRNL/*Bulletin*.)

SRNL microsphere filled with palladium. The top of the microsphere has been removed to display contents.

Another feature is that these microspheres can be coated and/or lined with nanomaterials and structures to, for example, improve absorbency. Proteins or fluorescent indicators can be attached to guide and monitor the

Mo-Sci licenses SRNL's porous, drug delivering microballoons

spheres for drug-delivery purposes or to have them act, for example, as a superior MRI contrast agent.

A third feature is that, at a macro level, large volumes of the PW-HG spheres can be made to flow like a fluid They even look like water when poured from container to container. Moreover, they are recyclable.

"This isn't like making hollow glass beads. We manufacture the PW-HG spheres to exact specifications, and the customer loads the microspheres with the materials, like medical drugs," says Day.

SRNL originally developed the unique microspheres as a solid-state storage method for hydrogen. They have been successfully demonstrated to store and release the gas.

Mo-Sci's involvement is a good sign. The company was founded in 1985 by Missouri University of Science & Technology professor Del Day found much success in using a different type of glass microspheres to deliver tiny amounts of strong radiation in cancer treatment. Mo-Sci's spheres have been particularly successful in the treatment of cancerous liver tumors, where the spheres can be targeted fairly precisely to deliver radiation. They have the secondary benefit of blocking the blood supply to tumors.

Mo-Sci has worked with medical institutions, such as the Cleveland Clinic, and likely understands the ins and outs of getting PW-HG microsphere applications to market.

An article ("Porous-wall hollow glass microspheres as novel potential nanocarriers for biomedical applications") jointly written by Wick, other SRNL researchers and investigators at the Medical College of Georgia will soon be published in the print version of *Nanomedicine: Nanotechnology, Biology and Medicine* and is now available online.

The article provides more detail about the uses of the PHWG microspheres for the delivery of anti-cancer drugs.

Visit: www.mo-sci.com. ■

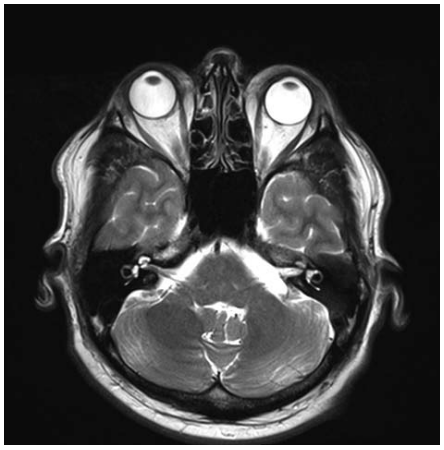
Nanodiamond-Gd complex: 'Contrast agent on steroids'

Dean Ho's nanodiamond team at Northwestern University always seems to be coming up with something new. This time, Ho and a team led by NU cancer researcher Thomas J. Meade say they have figured out a way to couple gadolinium with nanodiamonds to make a MRI contrast agent that delivers greatly improved images.

"The results are a leap and not a small one," says Meade in a NU news release, "It is a game-changing event for sensitivity. This is an imaging agent on steroids. The complex is far more sensitive than anything else I've seen."

In the past, Ho has shown, at least with in-vitro studies, that nanodiamonds seem to have excellent biocompatibility and can be used for drug, protein and DNA delivery. However, researchers in that area are looking for a system to deliver drugs that has a second function: tracking. (The ideal drug-delivery system adds one more function that allows the material to be targeted to a particular tissue or site.)

In a paper study published online by the journal *Nano Letters*, the team says it has developed a Gd(III)–nanodiamond complex that demonstrated a greater than ten-fold increase in "relaxivity." Relaxivity refers to ability of magnetic compounds to increase the relaxation rates of the surrounding water proton spins. Relaxivity is used to improve the contrast of the image.



Researchers have figured out a way to couple gadolinium with nanodiamonds to make a MRI contrast agent that delivers greatly improved images.

"Nanodiamonds have been shown to be effective in attracting water molecules to their surface, which can enhance the relaxivity properties of the Gd(III)–nanodiamond complex," says Ho. "This might explain why these complexes are so bright and such good contrast agents."

"The nanodiamonds are utterly unique among nanoparticles," Meade says. "A nanodiamond is like a cargo ship – it gives us a nontoxic platform upon which to put different types of drugs and imaging agents."

The team also studied the toxicity of the Gd(III)–nanodiamond complex using fibroblasts and HeLa cells as biological testbeds, and it found that that the material didn't negatively affect the hybrid complex on cellular viability.

Now the focus is on moving from in-vitro to in-vivo. The researchers hope to be moving into preclinical application of the new contrast agent in various animal models.

They also think they can fine tune and improve the agent by nailing down how the structure of the Gd(III)–nanodiamond complex governs increased relaxivity.

Visit: www.n-base.org/research/nanodiamonds.html. ■