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"Smart" Surface Capsules for Delivery Devices

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This review describes emerging trends, basic principles, applications, and future challenges for designing next generation responsive "smart" surface capsules. Advances and importance of "surface" capsules which are not deposited onto the surface but are built into the surface are highlighted for selective applications with specific examples of surface sponge structures formed by high intensity ultrasonic surface treatment (HIUS). Surface capsules can be adapted for biomedical applications, membrane materials, lab-on-chip, organ-on-chip, and for template synthesis. They provide attractive self-healing anticorrosion and antifouling prospects. Nowadays delivery systems are built from inorganic, organic, hybrid, biological materials to deliver various drugs from low molecular weight substances to large protein molecules and even live cells. It is important that capsules are designed to have time prolonged release features. Available stimuli to control capsule opening are physical, chemical and biological ones. Understanding the underlying mechanisms of capsule opening by different stimuli is essential for developing new methods of encapsulation, release, and targeting. Development of "smart" surface capsules is preferable to respond to multiple stimuli. More and more often a new generation of "smart" capsules is designed by a bio-inspired approach.

1. Introduction

Encapsulation systems nowadays find a great number of advanced applications. Capsules can be adapted for biomedical applications: drug delivery, tissue engineering, cell encapsulation, theranostics. They are used for sensing, membrane materials, for template synthesis and provide attractive self-healing anticorrosion and antifouling prospects. Active chemicals, cells, biomolecules are encapsulated to prevent their interaction with an aggressive environment or to regulate their activity. They can be regulated by internal or external stimuli. Time prolongated activity is possible for "smart" capsules to achieve needed advanced functionalities. Material types used for capsule formation are all available species from synthetic systems to natural or bio-mimetic species, live cells. There are also a great number of methodologies for capsule design available for the time being in synthetic chemistry.

The capsules can be used as "free" suspended particles or being integrated/developed into the surface ("surface" capsules) (**Figure 1**). This paper reviews the state of the art of surface capsules with advanced functionalities produced using new strategies, including HIUT. Before focusing on surface capsules, brief summary on classic "free" capsules provided. The past decade, a variety of capsules have been designed and produced through creative combinations of emerging technologies, soft matter physics, and chemistry. These new approaches have provided tremendous control over the size, shape, structure, and materials.[1]

"Free" capsules can be composed of differently formed empty core and shell membranes and permit the encapsulation of freely suspended materials in the interior of an enclosed membrane (Figure 1a). The inner compartment of a capsule can be used to encapsulate active species that are then release upon the breakup of the shell membrane, e.g., because of chemical, physical or biological stimuli. Membrane engineering through optimization of the composition and structure can be used to design impermeable shell membranes, or selectively permeable shell membranes that permit the passage of molecules smaller than a critical size. Hollow capsules, e.g., polymer capsule, can be fabricated be self-assembly, layer-by-layer assembly, single-step polymer adsorption, bio-inspired assembly, surface polymerization, and ultrasound assembly. These techniques can be applied to prepare polymer capsules with diverse functionality and physicochemical properties, which may fulfill specific requirements in various areas.[2]

Porous particles comprise a single body of materials without distinct layers and they enable active species to be directly embedded in the body. There are in Figure 1b, left shown two examples of formation of "free" encapsulation systems based on porous particles. The mesoporous silica (MCM 41) is shown in left image (Figure 1b, left) as effective carrier for encapsulation of active species, e.g., corrosion inhibitor.[3] Such carriers as $CaCO_3$ nanosheets and layered nanostructures (e.g., layered double hydroxide (LDH)), one-dimensional nanostructures, nanotubes such as carbon nanotubes, tubule aluminosilicates (halloysites) can be mentioned.[4] Important the particle used as a body for encapsulate active chemical possesses a huge surface

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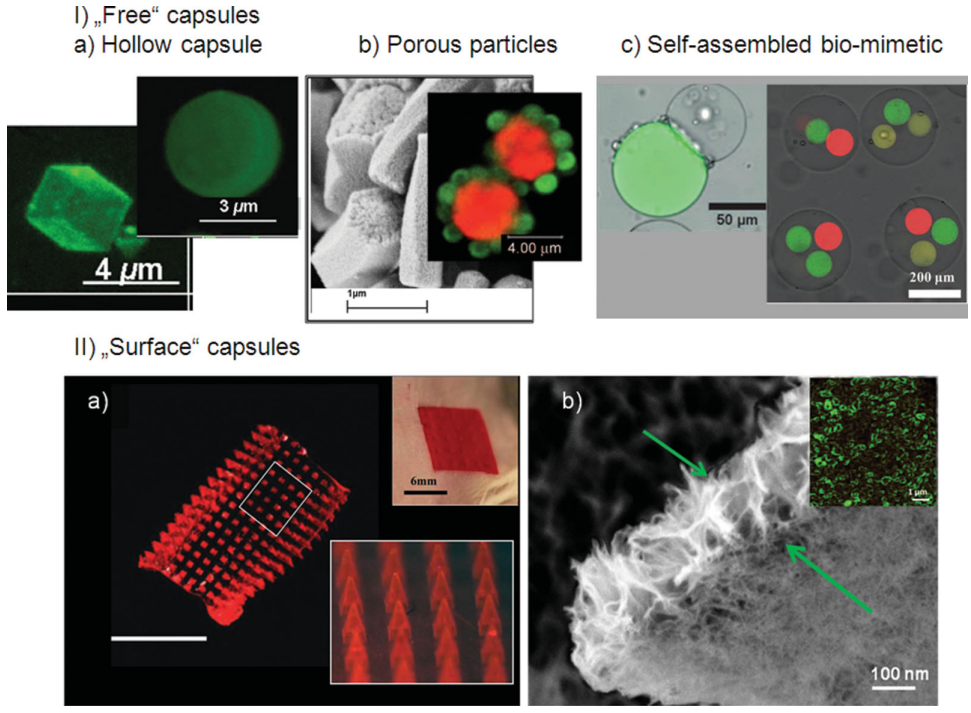

Figure 1. I) “Free” capsule systems. a) Confocal images of three dimensional (3D) reconstructed cubic ($CdCO_3$ cores) and spherical (SiO_2 cores) microcapsules. Reproduced with permission.[3a] Copyright 2011, American Chemical Society. b) SEM image of mesoporous silica used for active chemicals delivery (left) and fluorescent confocal image of multicompartment capsules based on porous $CaCO_3$ particle (red labeled) with SiO_2 (green labeled). Reproduced with permission.[3b,5a] Copyright 2009 and 2010, Wiley c) Vesicles templated by double-emulsion drops: confocal microscopy image of the dumbbell-shaped polymersomes containing two distinct materials in separate lumens (left); multiple vesicles-in-vesicle structures (right). Reproduced with permission.[6] Copyright 2011, American Chemical Society. II) “Surface” capsule systems. a) A curled microneedle array, showing the flexibility of the array. Scale bar is 1 cm. Inset below shows higher resolution brightfield macroscopic images of a microneedle patch. Reproduced with permission.[17] Copyright 2013, Wiley. Above inset show injection of microneedle array into skin. Reproduced with permission.[17] Copyright 2012, Wiley. b) Sonochemical metal surface nanostructuring for the formation of “surface” metal sponge for encapsulation of active chemicals (inset show confocal fluorescent microscopy of doxorubicin loaded surface (top-view)). Reproduced with permission.[3] Copyright 2012,Wiley.

area, large pore volume, and cage-type porous structure, leading to efficient materials sequestration from solution.

The second example is shown the promise of multicomponent systems for drug delivery based on $CaCO_3$ particle (Figure 1b, right).[5] Subcompartmentalization was achieved by decorating a larger subcontainer with smaller subcompartments (liposomes). It was found that porosity, ionic strength, and particle concentration are critical factors controlling the adsorption of nanoparticles (NPs) and liposomes onto the larger inner core of capsules. The simultaneous incorporation of small and large molecules, for example, an enzyme and its substrate, in the same particle or capsule so as to induce a specific biochemical reaction in a well-defined three-dimensional architecture was possible. Enhanced mechanical stability of the particles in comparison with hollow capsules is a characteristic feature of this system. Furthermore, it was shown that an enzyme-substrate reaction can occur in the same porous $CaCO_3$ particle upon disruption of the outer subcompartments; thus the substrate is released while the enzyme is maintained in the confined and protected volumes of the capsules.

Important issues need to be addressed in the fields of soft matter and biomedical science. Biological systems are very complex, and no panacea microcarrier is available that is useful for all purposes with optimal performances. Each application is associated with specific optimal conditions under which a capsule application should function, such as the release profiles of one or multiple drugs, or biological specification. Last years it becomes increasanly important the application of bio-mimetic concept for the understanding and design of novel applicable bio-materials (Figure 1, Ic). In Figure 1 it is presented vesicles templated dumbbell-shaped polymersomes containing two distinct materials in separate lumens (left) and multiple vesicles-in-vesicle structures (right).[6] Formation of such self-organized bio-compatible systems is increased area of scientific interest.

We can't touch all available materials used for capsule development, methodologies and application in our review. However, we can guide to some specific examples which illustrate modern trends. In particular as a guideline we choose the sonochemical approach to show how one methodology can be used to design various materials (**Figure 2**): oxides, metals, silicon, polymers, hybrids, etc.[7] We highlight the importance of cooperation between synthetic chemistry with theoretical modeling to design process the regulation and effective use of a powerful methodology for design of various types of effective encapsulation systems.

Capsules can be engineered in one step or, as in most cases, nanostructured in several steps. We discuss the most effective universal methodologies which are used for multi-step capsule adaptation to a needed application. Thus self-assembled monolayers (SAM)[8] are effective for nanostructuring of a

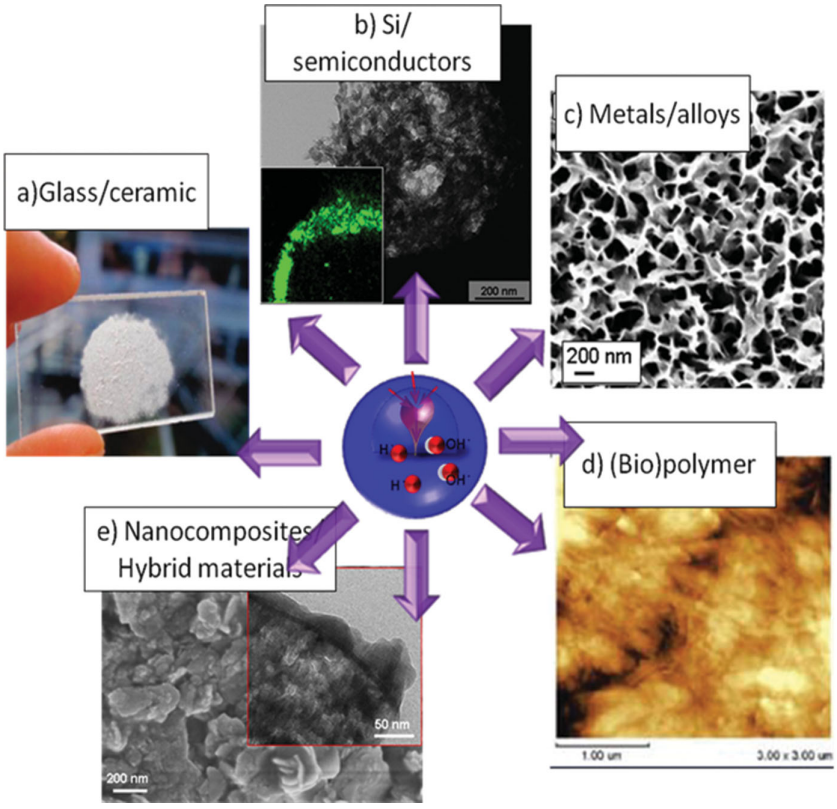

Figure 2. Example how one methodology, sonochemical material treatment, can provide effective modification of various materials which in following can be effectively adapted for a design of "smart" capsules. Materials with different properties after sonochemical treatment: a) optic image of silica glass (Reproduced with permission.[143b] Copyright 2012, Americal Chemical Society); b) TEM image of porous silicon formed in water-alcohol solution. The inset shows its micro-confocal photoluminescence (Reproduced with permission.[143a] Copyright 2012, Wiley); c) SEM image of sonochemically formed aluminium surface sponge (Reproduced with permission.[14a] Copyright 2010, Royal Society of Chemistry); d) AFM tapping-mode image in air of bacterial cellulose thin film; e) SEM and TEM images of formed hybrid magnesium/polypyrrole implant structure in ethanol + pyrrole solution. Frequency of 20 kHz; I_{ac} = 40–60 W cm^{-2}, except for the case of biopolymers (d) where I_{ac} was less than 20 W cm^{-2}.

surface of synthesized inorganic materials, e.g., oxides, silicon, metals, to follow the regulation of physico-chemical capsule properties, for example hydrophilicity. Layer-by-Layer (LbL) organization[9,10] of oppositely charged polyelectrolytes is discussed as very effective universal methodology for the formation of a capsule shell for both "free" and "surface" capsules. We discuss in this review the pore architecture, e.g., regular oriented 1D-nanotubes or 3D- mesoporous organization. The importance to have pronounced release kinetics for "smart" surface capsules is highlighted. Some other possibilities for effective design are mentioned, e.g., sol-gel methodology and plasma polymer deposition, thermal coatings, to achieve a needed functionality. Thus the techniques are suggested as promising to provide an effective variation of the interfacial properties.

For the time being there are two types of responsive surface encapsulation systems (**Figure 3**): 1) capsules should have such functionalization, for example by SAM, to have stimuli-changeable interfacial properties (hydrophilic/hydrophobic or surface layer thickness, functional groups); 2) capsules should be able to release encapsulated material to activate processes on the surface (termination of corrosion, cell metabolism regulation, drug delivery, antifouling, etc.). There are examples which point to the importance of changes in interfacial properties or of release of biocide to regulate the cell behavior on the surface: 1) cell detachment from the surface after a change of interfacial properties via a stimuli-responsive change in polymer surface conformation; and 2) stimuli-responsive release of biocide from "surface" capsules for antifouling surface activity.

The construction and optimisation of systems with synergetic properties are now of high actuality. Sonochemical, cavitation-assisted, processes for active "surface" encapsulation system construction are at the frontier of different fields of science, such as nanometre-scale engineering and biotechnology (implants, antifungal and antibacterial systems) and therefore are presented here as example. In Figure 3, the patterning of surfaces with simultaneous formation in selected patterned "surface" capsules is presented as prospective and interesting for the formation of neighbouring regions with different adsorption abilities with respect to biological objects. Surface micro-patterning techniques, can be used for controlling cell adhesion and cell-microenvironment interactions, such as homotypic and heterotypic cell–cell interactions.[11] Formation of encapsulation regions in a patterned way is preferable. To regulate adhesion, sonochemically modified patterned surfaces, as shown in Figure 3 can be used. The patterned array system can be fabricated by a photolithography technique.[12] A change in interfacial properties, e.g., wettability and functional terminal groups regulate cell adhesion and protein adsorption. To demonstrate the hypothesis, patterned arrays with additional functional terminal groups, such as an amine (NH_2) group (3-aminopropyltriethoxysilane), a methyl (CH_3) group (trichlorovinylsilane), and a fluorocarbon (CF_3) group (trichloro(perfluorooctyl)silane), can be used. The contact angle can be measured to determine the hydrophilic and hydrophobic properties. Bacteria adhesion and feedback properties of patterned surfaces in the following can be regulated as described, for example, in Figure 3, Example 1.

Unlike traditional patterning methods, the presented systems contain feedback properties through the design of loaded capsule patterns (Figure 3, example 2). Mesoporous metal sponges are effective bases for the construction of surface-attached capsules for the storage of active components and their stimuli controlled release.[13,14] Sonochemically formed metal-polyelectrolyte capsules loaded with active chemicals introduce the possibility of providing metal surfaces with important properties, including high biocide activity, anti-friction properties, and the ability to release active components to stimulate activities of attached cells, such as in stem-cell research. Different

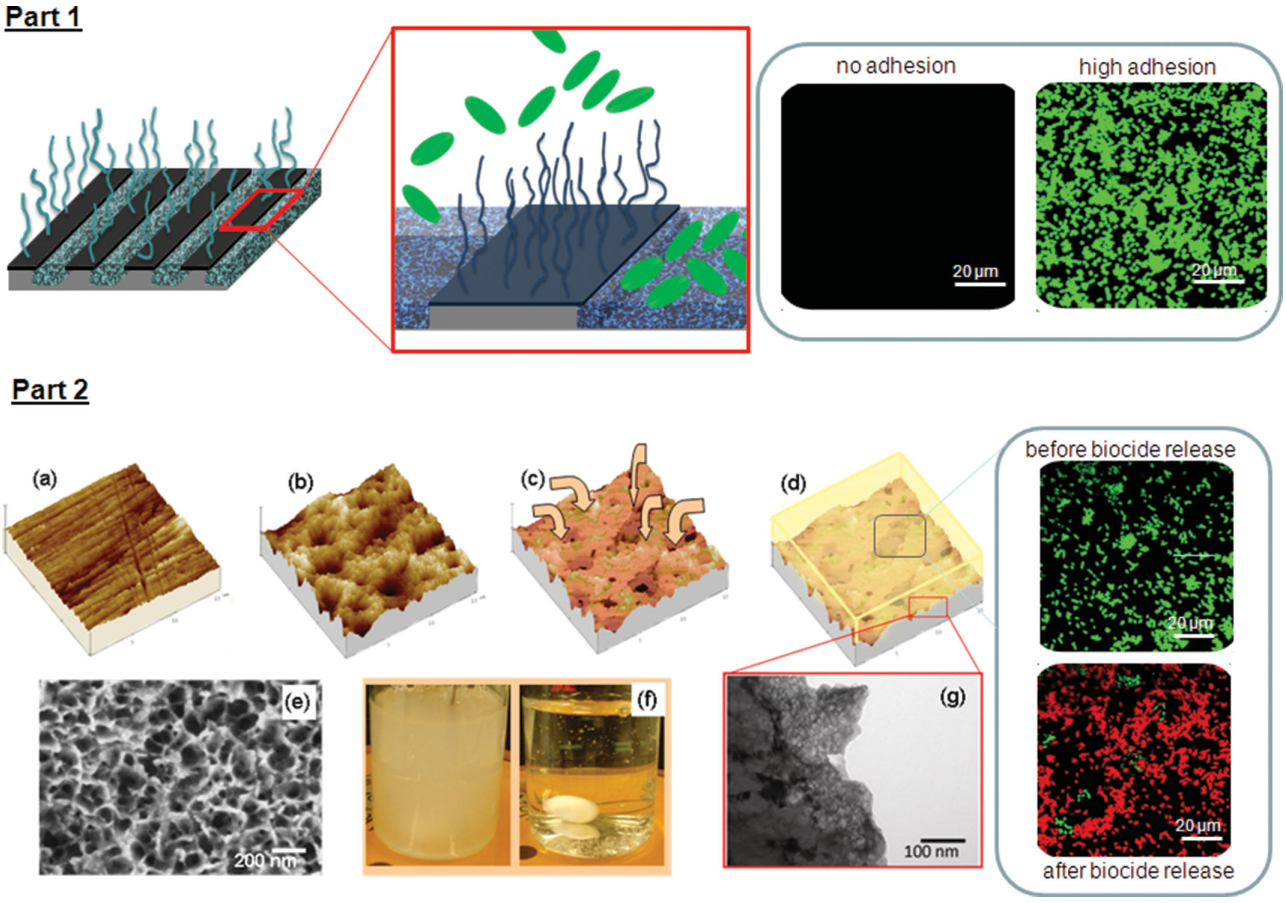

Figure 3. Example 1. Formation of a patterned surface with defined ability to adsorb biological objects: scheme of patterned surface (right part) and confocal microscopy study of adsorption to the surfaces with suppressed (left) and high bacteria (*E. Coli*) adhesion ability (right). Example 2. Scheme based on AFM images of polished aluminium (a) before modification; (b) sonochemically modified aluminium; (c) aluminium with incorporated surface metal/polymer capsule loaded by active chemicals (AC); complexation between AC and the polyelectrolyte (PE) prevent the release of the chemicals in the pore; (d) aluminium protected on the top by polymer or sol-gel film; (e) SEM top view of sonochemically formed surface metal-based core for subsequent surface capsule construction; (f) optical observation of complex AC (biocide)/PE(PSS) stability at different pH levels: left is at pH = 7 (turbid) and right is at pH = 10 (clear); (g) TEM image of aluminium with surface-formed capsules for AC storage. The right inset shows biocide activity of the surface with capsules loaded with a biocide agent before and after its release. *E. Coli* was visualised with LIVE/DEAD *BacLight*, which allows inactivated (red) and living (green) bacteria to be distinguished. Reproduced with permission.[13] Copyright 2012,Wiley.

ultrasonic intensities result in the formation of structures with different features that determine their subsequent use for active surface construction. At a lower sonication intensity (30 W/cm^2), just an increase in the surface roughness was observed, without the formation of a base for subsequent capsule construction. However, as shown in Figure 3 (Example 2), high-intensity sonication (57 W/cm^2) of metal surfaces results in the formation of highly porous surfaces. The thickness of the modified mesoporous layer, as estimated by TEM analysis of the ultramicrotomed plates, is about 200 nm with a pore size of approximately 7 nm. This layer exhibits strong adhesion to the surface and is continuous; it is therefore a promising surface capsule support. The pores of the sonochemically formed metal (here, aluminium) surface are loaded with biocide,[13] and the pores are then closed using a complexation reaction between the active incorporated agent and the polyelectrolyte.[15] Thus, the constructed smart surface capsules formed by the walls of the metal pores and polyelectrolytes are effective for the prolonged storage of the active component. The metal walls provide the high stability and adhesion of the capsules to the metal plate; the polyelectrolytes are responsible for the loading and release of the active species (here, biocide) on demand. The smartness and possibility to trigger biocide release from the system by adjusting the pH level is evident in Figure 3f (left image, neutral pH, turbid due to complexation). The ability to destroy the complex and to release biocides when necessary is a high priority. In the described case, the pH change could be an effective trigger for the destruction of the complex. In Figure 3f (right image, alkaline pH, clear), the destruction of the complex is evident. In the right insets of Figure 3, the surface before and after the biocide release and its effective influence on *E. Coli* bacteria is shown.[13] In this case a high biocide activity of the surface is evident.

Means to control capsule opening are physical (temperature, laser light, electric and magnetic field, ultrasound, and mechanical action), chemical (ionic strength, pH, electrochemical and solvent) and biological stimuli (enzymes and receptors).[5b] For the time being the attention of scientists

focuses on the direction of designing of encapsulation systems which are sensitive to more than one stimulus. The capsule sensitivity to external/internal stimuli is based on the sensitivity of its building block. Most common stimuli are acting on the soft organic part of the system. Stimuli responsive macromolecules are capable of conformational and chemical changes on receiving a stimulus (T, pH, ionic strength, electromagnetic irradiation or magnetic field, electric potential, chemical composition or applied mechanical force). The discussed systems are planar films, coatings and non-planar capsules, micelles, as well as combinations of two non-planar in planar systems (surface capsules + coating). Different architectures and fundamental approaches in the area provide specific advanced applications which are also highlighted in the review. Different architecture provides control of dynamics (system response) and amplitude of changes of the interfacial properties, reversibility of the changes and the intensity of the external signal that could trigger the changes. The inorganic part of the encapsulation system, for example mesoporous particles themselves or being a core of polyelectrolyte 3D capsule, could be bonded with an encapsulated chemical with relatively mobile bonds (chemisorbed). The release from such systems is responsive to external or internal stimuli. This review discusses trends and challenges in designing next generation carriers. There is high attention for bio-mimicking both encapsulation material and release processes. There are some background ideas presented in the review.

This review provides an overview of the various encapsulation materials and techniques that have been proposed to control the release of (bio-)active molecules of interest in biomedicine and drug delivery, optical materials, bio-sensors and biomembranes, template for synthesis, surface coatings, sensing, self-healing and antifouling surfaces. Some specific examples of advanced applications are presented in the review. Finally, an outlook on future directions and a glimpse into the current developments are provided.

2. Basic Properties of "smart" Surface Capsules

Significant recent application driven progress has been made with regards to the main properties of "smart" surface capsules. In particular, for advanced applications multifunctional capsules are in focus with the possibility of multi-component delivery and multi trigger stimuli response of the capsule system.[16] The main properties of capsules are their interaction with active components to deliver: 1) loading, 2) storage and 3) release (**Figure 4**).

Active components can i) be material of the capsule (see following section), ii) be composite or hybrid capsule which can provide several materials to deliver, iii) be loaded into capsules, or iii) active materials to deliver can be capsule building blocks and loaded materials (**Figure 5**).

Loading of capsules with active material can be performed through a manifold of mechanisms and strategies. They can be physically entrapped (Figure 5a) in capsules[3] or adsorbed to the capsule material by specific interactions, non-covalent or covalent binding via degradable linkers[13] and subsequently released via diffusion, swelling, erosion, degradation or a

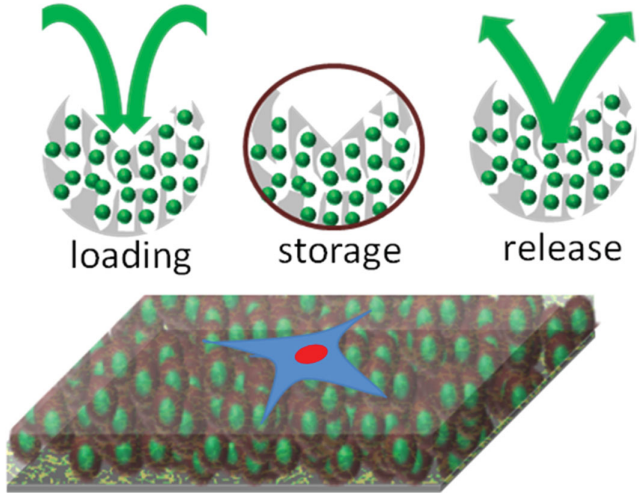

Figure 4. Scheme of the processes of loading, storage and release of active components, shown for a single capsule (upper row); active feedback surface design, which will influence surface adhering biological objects, e.g., cells and bacteria (below). Reproduced with permission.[13] Copyright 2012,Wiley.

specific trigger such as pH, temperature, etc. Also, a combination of multiple delivery systems can be used to achieve multimodular release of multiply active substances.[16] Depending on the loading/release mechanism, different release profiles can be obtained.

Physical entrapment of active species in a capsule is a frequently applied technique for local delivery.[3] Its relative simplicity represents a clear advantage over more sophisticated encapsulation/release methods and the majority of encapsulation systems rely on this loading process. Loading is done by incubation of the preformed capsule with the species of interest or by adding the species to the capsule forming prematerial, e.g., for polymer capsules monomers/prepolymers.

The release mechanism in the case of physically entrapped species depends on both the characteristics of the capsule material and the active substance. If there are pores and they are bigger than the dynamic radius of the loaded molecules, diffusion is the driving force for release, with a diffusion rate depending on the loaded molecule size and the 'free-volume' in the capsule.[18] For most cases relatively slow release due to diffusion is of interest to retain a high quantity of loaded materials after capsule formation. However, the active species, e.g., protein, should be released in sufficiently high concentration

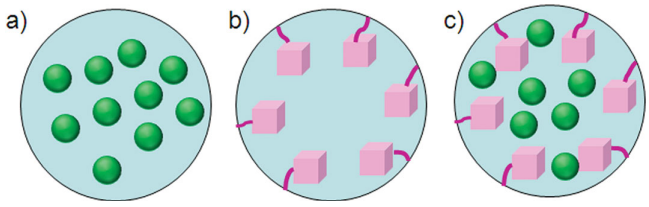

Figure 5. Examples of possible loading mechanism: a) physical entrapment of encapsulated materials into capsule; b) chemical bonding of material to capsule; c) multi-modal loading: one of component is physically entrapped into capsule and one is chemically bonded. Moreover active components can be material of capsule.

to initiate the necessary function/response of cells. Simultaneously the concentration of released species should not be higher than the toxic limit. Thus the majority of the gel based encapsulation systems[18] reported to date exhibit diffusion controlled release, following Higuchi's kinetics, implying that the release is proportional to the square root of time. This release profile was shown to be particularly beneficial for the delivery of several growth factors for tissue engineering applications.

On the other hand, when the pores are smaller than the loaded molecule diameter, degradation of capsule material (free or surface) is needed for release. For example, hydrogel encapsulation systems can be swelling-controlled depending on water uptake and changes in drug diffusivity within the matrix. Swelling increases polymer flexibility and makes pores bigger, resulting in higher mobility of active molecules. As a consequence, release depends on Fickian diffusion, polymer disentanglement and dissolution in water.[19] The other example can be erosion-controlled systems, e.g., biodegradable magnesium implants[20] or of biodegradable polymers.[21] In these systems, the mobility of active molecules in the homogeneous non-degraded matrix is limited and release is then governed by the degradation rate of the capsule material and porosity increase.

Covalent binding is another loading mechanism (Figure 5b).[13] Let's take as example proteins as active encapsulated chemicals. Mostly exploiting their reactive amine and thiol groups, they can be covalently bound to polymer matrices via functional groups like hydroxy, amine, carboxyl groups that, if not naturally present in the structure of the polymer, have to be introduced by functionalization reactions, blending or co-polymerization. The release of the protein can be provided either via hydrolysis, reduction reactions or (cell-mediated) enzymatic cleavage. This type of mechanism leads to on-demand release of loaded proteins, mimicking the enzymatic activity naturally occurring in the 'healthy' extracellular matrix (ECM).[18] However, stability and maintenance of biological activity of the protein may be an issue. It is important to remain an active species in active conformation, e.g., one should be careful that after release protein escapes denaturation and inactivation. The release mechanism from capsules can be adjusted by diffusion, swelling, erosion, internal or external stimuli or combinations thereof.

The design of "smart" capsules may offer the possibility to deliver multiple species with independent release rates and loading (Figure 5c).[16] It is still a challenge to develop capsules with multiple species delivery. An appropriate control over temporal and spatial release is of high priority for such systems. Encapsulating various compounds with different physiochemical properties and achieving their synchronized and sustained release seem too hard to realize.

However, currently technologies are available that have a proven potential of modulation of release profiles according to the specific application needs. These include traditional diffusion/swelling/degradation mediated release on-demand, affinity, covalent binding based delivery and special surface nanostructuring. Some specific examples are presented later.

A sustained multi-delivery system for herbal medicines was suggested recently.[22] An injectable nanoparticulate system based on poly(ethylene glycol)-poly(lactic-co-glycolide) (PEG–PLGA) platforms was prepared for co-encapsulation and sustained release of four active components (ginkgolides A, B, C and bilobalide) in Ginkgo biloba extract. Carriers were screened by a macrophage uptake experiment for their ability of long-circulation. Sustained and synchronized release of four components from an encapsulation system was observed both in vitro and in vivo. The half-life times of four terpenoid compounds were also significantly improved by incorporation into carriers. The results indicated that despite the physiochemical properties of the compounds themselves, the release of ginkgo terpenes depends mainly on the degradation of PEG–PLGA based platforms. The reported system might be a potent drug carrier for injectable delivery of multiple drug components, especially those found in herbal medicines.

It was shown[23] that structural swelling of bicontinuous cubic lipid/water phases is essential for overcoming the nanoscale constraints for encapsulation of large therapeutic molecules in network-type lipid carriers. SAXS scans permitted monitoring of tuning of the diameters of the aqueous nanochannel compartments in cubosome structures by external stimuli and membrane curvature modulating agents. They revealed that coexisting nanochannel structures and intermediate states can be typical for multicomponent amphiphilic mixtures subjected to thermal treatment. The encapsulation of small proteins occurs without perturbation of the cubosome structure. The entrapment of proteins with sizes bigger than the water channel diameters occurs via a "nanopocket defects" mechanism and spontaneous nanocubosome generation in the interior of the cubic lipid/protein assembly. Further questions that require investigations should consider the role of the structural asymmetry of the double diamond-type nanochannel network for protein loading and release, the conformation of the entrapped proteins, the mechanism of fragmentation and steric stabilization of the cubosomes by biocompatible polymers, their functionalization for targeted delivery of therapeutic proteins, and the interaction with the cellular environment.

Multifunctional capsules are also achievable by making capsules sensitive to different stimuli. Thus one capsule can be sensitive to more than one stimulus. For example the formed magnesium-polypyrrole capsules are sensitive simultaneously to pH (due to Mg) and electric current flow (due to the conductivity of polypyrrole).[24]

It is also clear that for different applications capsules made from different materials are needed. Metals have to be protected from corrosion. Polymers are used for single component capsules or as one of the capsule components. Silica, especially, mesoporous silica, such as MCM-41, is often suggested to deliver active substances due to the unique nature of mesoporous systems. Mesoporous luminescent Si is used when capsules need to be visualized, for example to follow their track in the body. Light carbon structures, carbon nanotubes, are used as capsule material. Calcium carbonate and other ceramics can be effective to deliver different substances.

Specific applications are required for integration of capsules on surfaces. Examples of such applications are corrosion protection, implants and antifouling surfaces, sensors and membranes, lab-on-chip and organ-on-chip systems. Recently it was suggested that for such applications it is of high priority to incorporate capsules into surfaces: "surface capsules".[13,25] The following advanced features can be mentioned for "surface"

capsules in comparison with "free capsules" which are used to be integrated in coatings: 1) regular "surface" capsule distribution throughout the surface; 2) possibility of multicomponent loading; 3) spatially resolved encapsulation. Examples of such surface capsules layers for metal surfaces are: 1) anodized oxide layers on metal surfaces, e.g., on aluminum, anodic aluminum oxide (AAO), or on titanium, titanium dioxide nanotube (TNT), with the formation of a porous layer with oriented nanotubes (Me-1D);[26] 2) metal surface mesoporous sponge layers (Me-meso).[13] Both Me-1D and Me-meso have their advantages. Thus Me-1D can be very precise for control of release kinetics, time-resolved release of multi-components which are loaded into Me-1D. Me-meso due to the complex mesoporous nature of the sponge layer provides all advantages for mesoporous silica or titania: high free volume, time prolongated storage of even physically entrapped species.

3. "Free" and "Surface" Capsules

Mostly when one mentions capsules for delivery devices, one means "free", "classical" capsules which are used being either in the suspension or integrated into a coating. There are numbers of papers, including some competent reviews,[27] which present "free" encapsulation systems for delivery devices in their variation: different size, shape, texture, compartments, etc. In the presented review we point on "surface" encapsulation systems. There are some tendencies of "free" capsules which can be used to design also "surface" encapsulation systems. Some ideas and background are presented below.

In background of polymer "free" capsules there are two main approaches to produce polymer capsules; template-free and template-assisted techniques.[2] It is now feasible to prepare polymer capsules of diverse size, composition, morphology, and properties. Recent trend in the organization of encapsulation system is self-assembled biomimetic (Figure 1, Ic). An attractive option for the design of delivery systems is to mimic structures already present in vivo. Thus, a great deal of research has focused on the design of liposome-based systems.[28] The structure of a liposome consists of a vesicle assembled from a lipid bilayer, with an aqueous interior and a hydrophobic membrane. Lipids are readily degradable in vivo, allowing the components of the delivery system to be removed easily from the body. Vesicles templated by double-emulsion drops: confocal microscopy image of the dumbbell-shaped polymersomes containing two distinct materials in separate lumens (left); multiple vesicles-in-vesicle structures (right) are presented as the example for such systems highliting also possibility of multi-component delivery by this systems. Self-assembling during the formation of advanced systems relies on either the spontaneous ordering of molecules into engineered structures (polymer complexes, liposomes, micelles, and polymersomes) or the templated-assembly, e.g., of LbL.[2] Biological mimics, such as virus-like particles,[29] have also found application.

Various nanotechnological nanocarrier systems for cancer therapy are focusing on recent development in polyelectrolyte capsules for targeted delivery of antineoplastic drugs against cancer cells.[30] Biodegradable polyelectrolyte microcapsules (PMCs) are supramolecular assemblies of particular interest for therapeutic purposes, as they can be enzymatically degraded into viable cells, under physiological conditions. Incorporation of small bioactive molecules into nano-to-microscale delivery systems may increase drug's bioavailability and therapeutic efficacy at single cell level giving desirable targeted therapy. LbL self-assembled PMCs are efficient microcarriers that maximize drug's exposure enhancing antitumor activity of neoplastic drug in cancer cells. They can be envisaged as novel multifunctional carriers.

Due to its versatility and ease of use the layer-by-layer (LbL) assembly technique has been under intensive investigation for delivery applications.[31] Especially the development of responsive LbL materials has advanced significantly in recent years. Responsiveness plays an important role in many delivery applications, either for loading of therapeutics or controlled and triggered release.

Nanoengineered multifunctional capsules with tailored structures and properties are of particular interest due to their multifunctions and potential applications in diverse fields.[16] The past decade has witnessed a rapid increase of research concerning the new fabrication strategies, functionalization and applications of multifunctional capsules. The advances in assembly of capsules by the LbL technique can be introduced with focus on tailoring the properties of hydrogen-bonded multilayer capsules by cross-linking, and fabrication of capsules based on covalent bonding and bio-specific interactions. The multi-compartmental capsules can transform providing advanced applications, e.g., drug carriers, biosensors and bioreactors.

Embedding of nanoparticles into "free" capsules opens up the opportunities to navigate the capsules with magnetic field and in-situ trigger the release of encapsulated material in response to the physical stimuli, such as light and ultrasound.[32]

Self-healing property is in focus. Thus capsules is obtained by adding healing agents to the material to be repaired, and intrinsic materials, where self-healing is achieved by the material itself through its chemical nature. The crosslinking chemistries used in self-healing materials is in focus.[33]

Some specific features of specifically bonded capsules can be potentially interesting for their application. For example, capsules assembled through the use of neutral or polar hydrogen bonding interactions have the ability to orient and control the position of the encapsulated guest molecules represents their stand-out feature.[34]

The field of metallosupramolecular self-assembly has emerged as a promising research area for the development of intricate, three-dimensional structures of increasing complexity and functionality.[35] The advent of this area of research has strongly benefited from design principles that considered the ligand geometry and metal coordination geometry, thus opening up routes towards rationally designed architectures. Three classes of metallosupramolecular assemblies can be mentioned: architectures formed through the combination of a single ligand and metal, heteroleptic structures and heterometallic structures.

Often a surface layer is degradable and itself can be an active layer to provide release of material or being the released material, e.g., "surface" capsules-microneedles (Figure 1, IIa). "Surface" capsules, as was mentioned above, can be formed by

surface nanostructuring and encapsulation of active species into a surface (Figure 1, IIb).

Large biomolecules, such as peptides, proteins, antibodies, and nucleic acids can be too large, fragile, or insoluble for delivery by traditional "free" capsule routes.[36] In this case the delivery into the body is desired not by oral delivery, but by hypodermic injection. A novel and mild technique for the production of microneedles for the delivery was suggested (Figure 1, IIa).[37] The "surface" needles are made of biodegradable and water-soluble polymers with the drug encapsulated in the polymer needle matrix. After application, the needle patch remains in the skin for a short time period that allows the polymer to dissolve while it releases the drug. This simple approach enables an inexpensive and fast fabrication process. Large, fragile biomacromolecules could be incorporated into microneedle matrices for successful delivery through the skin. The group of Prausnitz[38] has demonstrated the efficacy of microneedle vaccines in vivo; they showed for a mouse that a single dose of influenza vaccine with microneedles exhibited immune response superior to the same dose administered intramuscularly. Microneedles have been applied for administration of a human growth hormone.[39] It is important to achieve really access to controllable release with high efficacy profiles of drug as well as to control of the behavior of the devices under storage at various conditions to assess their robustness over time. Microneedles as "surface" capsules may be expanded to treat many disease models that are currently unexplored, including skin and breast cancers. A novel transdermal-based approach of "surface" capsule microneedles could serve as an avenue for a local and possibly systemic, yet minimally invasive, therapy.

Degradable hydrogels are another possibility for "surface" delivery. Hydrogels can be coated on the surface and be carriers for active species. Moreover available patterning techniques have been used to adjust the surface area and consequently modulate the release profiles of the biomolecules from hydrogels in a spatially resolved manner.[40] Deviation from the expected release behavior is observed when a specific stimulus – typically temperature, pH, presence of certain molecules – leads to a physical or chemical change in the network structure, for instance, hydrogels swell or shrink in response to a certain trigger thereby modulating the release of encapsulated drugs/proteins. The techniques are effectively used for advanced applications, e.g., tissue engineering.

The other possibility in developing of "surface" capsule arrays is surface nanostructuring with the formation of a porous surface with the free volume to be loaded with active chemicals. Thus pore formation during high intensity ultrasonic surface treatment was shown for various metals.[13,14] Moreover the effective variation of the pore structure is possible through variation of parameters of sonication. Great advantage of the synthetic methodology is a large number of synthetic parameters which can be optimized to tune surface nanostructuring in a controllable manner. Our study has shown that high power ultrasonic surface treatment results from the interplay of conceptually different mechanisms. 1 – There is physical impact due to a pressure wave and a jet impinging on the surface and deep into it, while 2 – extreme temperatures and pressures create highly reactive radicals derived from the solution, dissolved gas or additive. The ultrasound-driven modification of metals in water-based solutions leads to the development of an outer surface and, following the modification of the inner structure of the metals, an increase in the specific surface area. Metal surfaces are simultaneously oxidised, and the pore structure is stabilised. We have demonstrated the potential of formation of surface metal sponges together with defined roughness variation (**Figure 6**). It is worth to note here, that the effect of erosion of the metals has long been regarded a possible damage mechanism due to high pressure, casting of metals during the ultrasonic process. Melt impingement and erosion have also been proposed to be an important step leading to soldering. The present analysis, based on existing erosion theories, has shown that the use of cavitation assisted processes for pronounced formation of mesoporous structures or any

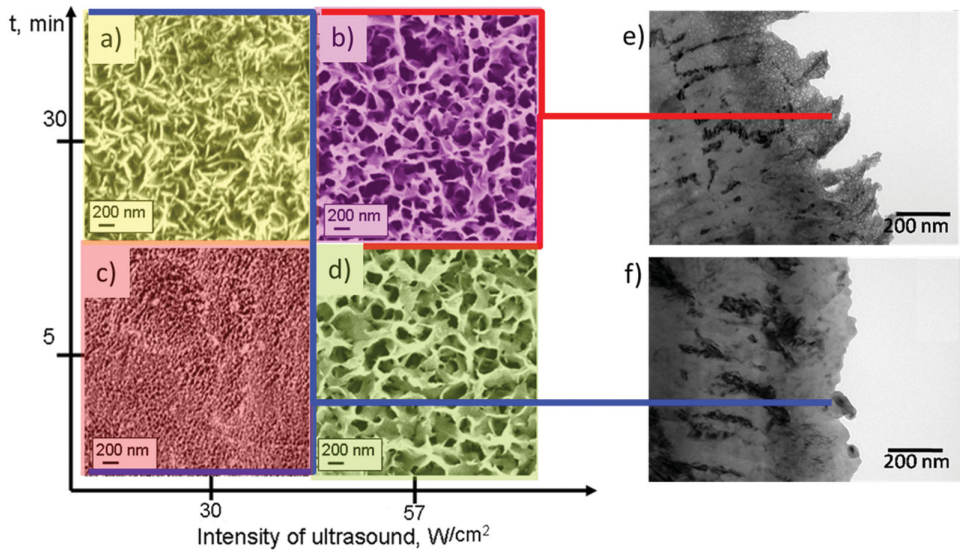

Figure 6. High intensity ultrasound for metal surface nanostructuring. Electron microscopy images of aluminium after sonochemical modification at different intensities and duration. Reproduced with permission.[14] Copyrights 2009, Royal Society of Chemistry.

pronounced metal structures, has not been shown before our recent studies. Moreover the methodology might be very interesting (see below) to provide single-step hybrids and effective loading of porous structures with active chemicals.

Another possibility is to use surface oriented nanotube arrays for delivery of active chemicals, e.g., formed by anodization. Pore formation during anodization is reported for selected metals including Al, Ti Ta, Hf, W, Zr, Nb (frequently called valve metals) and their alloys, under appropriate experimental conditions. The process is influenced by the type of electrolyte, the electrolyte concentration, pH, temperature, applied voltage and current, as well as the surface pre-texturing. Tuning the pore to nanotube morphology is possible by changing the anodization parameters.

Nanotube "surface" carriers were selected for drug delivery due to their unique features, such as low fabrication cost, controllable pore/nanotube structure, tailored surface chemistry and high surface area. Mechanical stability, chemical inertness, biocompatibility, controllable pore size and pore volumes, along with tunable surface chemistry have made nanotubes of Si, AAO and TNT an excellent platform for loading a large amount of drugs and facilitating their controlled release. Elegant work was presented by the Losic group[41] where an anodized nanotube layer is used as "surface" capsule layer. Thus insoluble drugs can be encapsulated into micelles and then micelles are encapsulated into AAO for therapeutic implants.[41a] The release kinetics from the suggested encapsulation system was especially useful in bone implant therapies that require a large initial dose followed by a prolonged dose over a few weeks. Additionally, by applying a plasma polymer film on the top of AAO, the release could be extended considerably, the burst release almost suppressed and zero order drug release kinetics over a period of more than 4 weeks was achieved.

It is very exiting that two types of micelles with different hydrophilicity can be effectively loaded into nanotubes by layer post functionalization with spatially resolved matter (**Figure 7**). Thus after growing of the first nanotube layer and its modification to make the surface hydrophobic, e.g., by silanization, the formation of an encapsulation layer for hydrophobic micelles is provided. The following further growth of the nanotube layer then provides a hydrophilic surface which can be loaded by hydrophilic micelles. The micelles can be released in a time-controllable manner. In all "surface" drug delivery is interesting because of the stimuli-responsiveness.

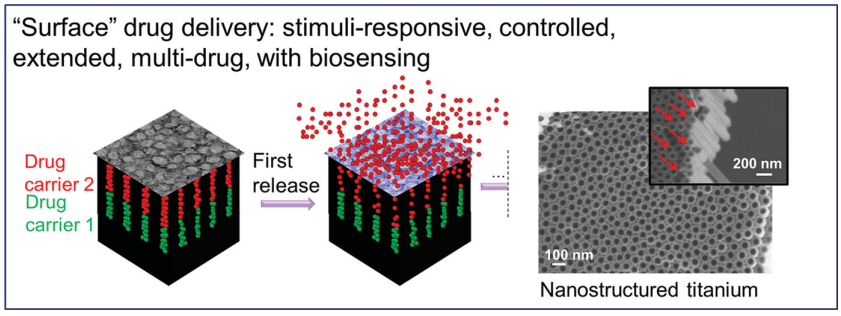

Figure 7. Example of formation of "smart" surface encapsulation system based on grown of TNT on titanium by its anodization. It is pointed the advanced features highly preferable and possible for "surface" drug delivery.

4. Engineering of Encapsulation Systems

Advanced approaches for structure engineering of interfaces/surfaces to generate new properties and applications are of high priority. The surface modifications and functionalization expanded significantly the number of applications of already developed encapsulation systems both as "free" and "surface" capsules. Thus for example some surface is chemical instable, e.g., some inorganic oxides, in acidic environment which is a disadvantage for some applications. This limitation can be overcome by changing the surface properties and by adding new surface functionalities. Emerging techniques for the fabrication and nanostructuring of capsules: self-assembly, layer-by-layer assembly, single-step polymer adsorption, bio-inspired assembly, surface polymerization, and anodisation, ultrasound assembly or structuring.

There is the strategy of the design of surface dynamic encapsulation system presented in **Figure 8**. It is suggested that the porous surface layer, e.g., meso-Me or AAO, TNT, can be encapsulation layer to deliver active chemical. Release of active chemical is prevented by LbL hybrids coating. LbL may response to different stimuli. The physical changes of the multilayers are possible. The thickness and roughness of the multilayers can be changed The mobility of the polyelectrolytes within the multilayers can be expected. Besides physical changes, chemical changes in multilayers are possible, e.g., change of pH and ion fluxes from the surface. The stimuli are preferable to varies simultaneously (i) response of dynamic layer and (ii) release of active species which provide, for example, of bio-response of adsorbed on surface microorganisms (cells, tissue, bacteria and viruses).

Surface chemistry plays a key role in targeted delivery. One of the major breakthroughs in this area was the finding of a way of surface nanostructuring for capsules for a chosen application. For example, hydrophobic capsules coated with hydrophilic polymer molecules, such as polyethylene glycol (PEG) can resist serum protein adsorption and prolong the particle's systemic circulation.[42] For the formation of delivery devices the surfaces of encapsulation systems can be nanostructured by different methods: electrochemical anodization, sonochemical methodologies, laser irradiation, etc.[18] Moreover targeted delivery is achieved by surface functionalization of capsule material with polyelectrolytes;[43] polymers to achieve mechanostereochemical[44] pore closure or coating prevented any molecule diffusion; biocompatible substances such as hydroxyapatite;[45] biomolecules,[46] such as peptides and antibodies. Thus surfaces can be modified via modification with organic molecules with the desired functionality. The surface modification techniques that have been explored to improve the surface properties and to add new functionality can be divided into two groups: wet chemical synthesis and gas-phase techniques. Examples of wet chemical approaches are self-assembly processes (silanes, organic acids), layer-by-layer deposition, sol-gel processing, polymer grafting. Gas-phase surface modification techniques used for surface

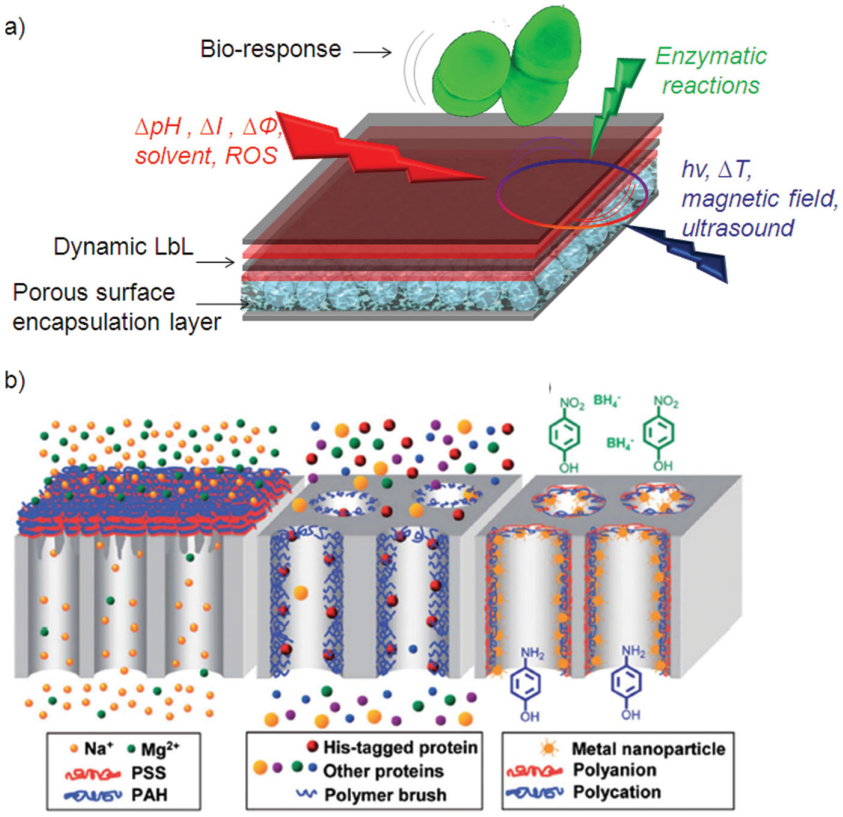

Figure 8. "Surface" capsule systems. a) Schematic of design of encapsulation system based on porous surface layer, e.g., surface metal sponge, with encapsulation into it active molecules and control the release of active molecules with dynamic layers, e.g., polyelectrolytes LbL hybrids sensitive to different stimuli, e.g., physical, chemical and biological, to provide response of cells on top of such surface. b) Nanostructuring of surface encapsulation system to regulate release behavior or sensing properties. Reproduced with permission.[9] Copyrights 2012, Royal Society of Chemistry.

modifications include thermal chemical vapor deposition, vapor metal deposition, plasma processing and polymerization.

Interfacial interactions of encapsulation systems are often manipulated with self-assembled monolayers (SAMs). There are passive and active SAMs known. Passive SAMs change surface chemistry; however does not response to any stimuli. Active SAMs are sensitive to various stimuli: physical, chemical and biological.

The first monolayer of SAMs were prepared with alkyl siloxanes,[47] and soon the coupling with thiol groups became very popular. These are able to form strong and specific noncovalent coordination bonds with gold, which result in the formation of a monolayer of thiolate molecules on a gold-coated substrate.[48] Especially alkanethiols with long, saturated, unbranched alkyl chains are known to self-assemble into well-defined monolayers on gold through both sulfur-gold coordination bonds and van der Waals interactions between alkyl chains.[49] An advantage for formation of complex multifunctional encapsulation systems is the synthetic flexibility of alkanethiols for providing various terminal groups enables presentation of a variety of ligands on a surface for tailoring surface properties.[50] Moreover the substances attached to the capsule by thiol groups can be released on demand. Release of alkanethiolates is known to be possible by electrical potentials, both reductively and oxidatively (**Figure 9**).[51]

Alkylsilanes on inorganic surfaces are presenting hydroxyl groups. Silane derivatives with functional head groups and hydrolysable silane head groups are used for the modification of inorganic substrates bearing hydroxyl groups, including silicon oxide, quartz, glass, and oxides of various metals such as Al, Cu, Sn, Ti, Fe, Zn. The reactive functional head groups allow introduction of other compounds to the capsule surface to afford another class of widely used substrates with tunable surface properties, like SAMs of alkanethiolates on gold.[52] Silane-based modification of surfaces requires a more elaborate treatment than alkanethiolate SAMs on gold. However, alkylsilane on SiO_2 is more chemically and thermally stable than thiolates on gold surfaces due to the strong covalent linkage between hydroxyl groups on the surface and the silane head groups.

Examples of passive SAMs are PEG and poly(ethylene oxide) polyethelenoxide (PEO) systems. The SAMS are used to provide possible encapsulation systems with antifouling properties.[53] A monolayer of oligo(ethylene glycol) groups ensures that the surfaces are inert to nonspecific protein adsorption.[54] The inertness of the surface is an essential factor for biological applications using cells and biomolecules such as proteins, which tend to bind nonspecifically to any artificial surface. Passive SAMs are widely used in microfluidics, but it is becoming clear[55] that greater functionality can be provided in more sophisticated systems with the use of active SAMs that can change their surface chemistry in response to stimuli such as pH, heat, light, applied voltages, etc.

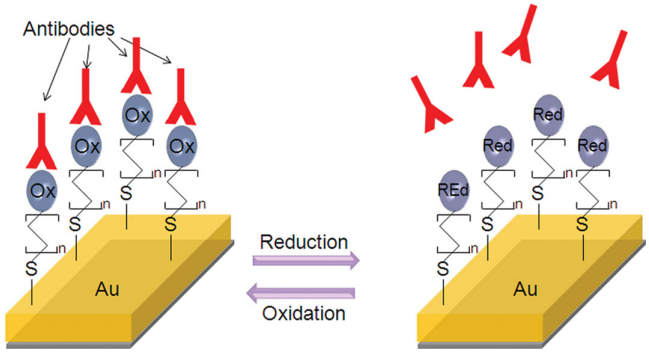

Figure 9. Stimuli for regulation of drug delivery. Electrochemical: antibodies have a high affinity for benzoquinone but not for its reduced form, hydroquinone. They can thus be reversibly attached to an electrode and released in solution through the oxidation and reduction, respectively, of the quinone moiety. Adopted from.[51] Copyright the Nature Publishing Group.

An example of a thermo sensitive active material with this switchable SAMs is an end-tethered monolayer of poly(Nisopropylacrylamide) (PNIPAM). This polymer exhibits a lower critical solution temperature (LCST), a temperature above which the polymer becomes insoluble, in water at about 35 °C.[56] At room temperature, the polymer swells in water to create a relatively hydrophilic surface with a water contact angle that can be as low as 30°. Above the LCST, the water is expelled, the polymer collapses, and the surface becomes hydrophobic in air.[57] Such systems can be effective used for delivery of proteins whose adsorption to SAMs depends on temperature. At room temperature, the adsorption of large globular proteins such as human serum albumin (HSA) is negligible on a tethered PNIPAM and is comparable to that on PEO SAMs. Above the LCST, HSA adsorption is extensive. Complete protein monolayers form at rates comparable to those seen on hydrocarbon-terminated octadecyltrichlorosilane surfaces. For large globular proteins such as HSA, complete desorption is normally observed on cooling the PNIPAM films to room temperature.

SAMs with specifically designed electroactive groups have been successfully employed to control functionalities in response to an applied potential. Especially electroactive functionalized surfaces based on the hydroquinone (HQ)/benzoquinone (BQ) redox couple have provided real-time control over molecular-level interactions between surfaces and cells or biomolecules such as peptides, carbohydrates, DNA, and proteins.[58,59] The group of Mrksich[59] reported various dynamic substrates that can electrochemically regulate interfacial interactions with proteins and cells. First, they demonstrated electrochemical release of immobilized ligands from the surface. Quinone ester groups tethered to ligands such as biotin and RGD (Arg-Gly-Asp) peptide were presented on SAMs on gold. On reduction to the corresponding HQ by an electrical potential, an intramolecular cyclization reaction ensued to give a lactone with release of the ligands. This allowed electrochemical control of specific binding of streptavidin to the monolayer and selective release of cells from the substrate on demand.[60] Mrksich et al. also introduced HQ-presenting monolayers, on which electrochemical oxidation provided BQ that acted as a molecular handle for immobilizing diene-modified molecules through Diels–Alder cycloaddition.[61] Next, they expanded their strategy to the construction of a dynamic substrate with two dynamic properties: release of one ligand followed by immobilization of another.

Azobenzene chemistry provides active dynamic modulation of surface characteristics by photoswitching by means of reversible trans-cis isomerization.[62] For example chymotrypsin delivery is possible by such a system.[63] Photochemical exposure with UV (or visible) light reversibly controls the geometry of the trans-form of azobenzene, which shows a low affinity towards chymotrypsin, or cis-form azobenzene, which strongly binds to chymotrypsin, leading to photochemical dynamic modulation of the protease binding to the surface.

o-Nitrobenzyl groups have been widely used for construction of phototriggering substrates that reveal various functional groups such as free amine and carboxylic acid.[64] Light irradiation induces cleavage of the bond at the benzylic position with the release of a caging molecule. Thus for example, Maeda and co-workers introduced a method for photoactivation of selective regions of a substrate for cell adhesion using photocleavable 2-nitrobenzyl-presenting substrate and bovine serum albumin (BSA).[65]

Benzophenone chemistry also provides photosensitive active SAMs. Under the illumination at 330–365 nm wavelength light, the photoactivation takes place repeatedly without loss of activity of benzophenone, which is chemically and photochemically robust enough to be handled in ambient light and under biological conditions. For example, benzophenone was used for photoactivated immobilization of biomolecules onto the inner wall of a capillary (internal diameter of 100 mm).[66] In the presence of biomolecules, an inner capillary surface with benzophenone that is irradiated to immobilize biomolecules can be used as a capillary bioassay system, with applications that include DNA hybridization and immunoassays. Bailey et al. introduced an approach to generate multicomponent immobilized biomolecular patterns and gradients on surfaces by sequential exposures of benzophenone -presenting substrates.[67]

Enzyme-triggered activation of surfaces is an attractive research theme in the area of dynamic substrate construction, because enzymes in living systems dictate cellular behavior and precisely control many functions of systems by performing biochemical conversions. Cutinase, a serine esterase, is one example. It can change a surface property from being redox-inactive to redox-active. SAMs of 4-hydroxyphenyl valerate-terminated alkanethiolate were treated with cutinase, and the acyl group was removed from the surface by cutinase to give HQ. The redox activity of the resulting HQ was then monitored to quantify the enzyme activity.[68] Control over surface properties has also been reported for proteolytic enzymes such as protease K, matrix metalloproteinase, trypsin, chymotrypsin, a-thrombin, and elastase.[69] Todd et al.[70] designed an enzyme-responsive surface that presented a Fmoc-protected RGD peptide precursor (Fmoc-AARGD), which prevented adhesion of cells due to poor accessibility of the RGD sequence to the integrin receptor caused by a bulky Fmoc group. Treatment with elastase broke the peptide bond between the two alanine residues, which revealed ARGD and thus activated the surface to a cell-adhesive state. Electrochemical monitoring of thrombin and trypsin activity was demonstrated by using a monolayer grafted with ferrocene-labeled enzyme substrate peptides.[71] In the presence of proteases, the electroactive reporter ferrocene was cleaved and diffused away from the surface. Analysis of the electric current signal then enables quantification of ferrocene-labeled peptides on the surface, and thus proteolytic enzyme activity can be assayed.

SAM layers can be the effective first layer for synthesis of longer functional chains to achieve a needed functionality, including multi-functionality, which was widely developed in the group of Minko.[72] Thus hybrid brushes composed of two liquid polymers, poly(dimethylsiloxane) (PDMS) and a highly branched ethoxylated polyethylenimine (EPEI), were synthesized on Si wafers by the "grafting to" method and by applying a combinatorial approach (fabrication of gradient brushes).[73] The combinatorial approach revealed a strong effect of "layer assisted tethering", which allowed us to synthesize hybrid brushes twice as thick as the reference homopolymer brushes. The hybrid brushes are stable thin films that can rapidly and

reversibly switch between hydrophilic and hydrophobic states in water and air, respectively. The switching in water affects a rapid release of amino functional groups which can be used to regulate adhesion and reactivity of the material. The switching in air rapidly returns the brush to a hydrophobic state. The hybrid brush is hydrophilic because of two mechanisms: (1) exposure of EPEI chains to the brush-water interface under water, and (2) retention of some fraction of water via swollen EPEI chains (the EPEI chains swell by 2–3 times), which are conserved by a PDMS cap in air. The hybrid brush is wettable under water, and at the same time, the brush is nonwettable in air, because water droplets are trapped in a metastable state when the water contact angle is above 90°.

In some cases passive layers can be active due to their release from the substrate. Jiang et al.[74] prepared patterned monolayers with 1-octadecanethiols amongst oligo(ethylene glycol)-terminated alkanethiols which were inert to nonspecific adsorption of proteins and cell adhesion. Cells were allowed to selectively attach to the patterned region where extracellular matrix (ECM) proteins were coated. On electrochemical treatment of the monolayer the oligo(ethylene glycol)-terminated alkanethiolates were released and the inertness of the monolayer was compromised. ECM proteins, either in the culture medium or secreted by cells, were then adsorbed onto the surface, and cell migration took place across the entire surface.

In order for an encapsulation systems to be usable in a reversible protein trap, at least three requirements must be met: (i) the polymer used form an encapsulation system needs to be in a configuration that supports the stimuli, e.g., desired thermal, activated phase transition, (ii) the layer must be robust and strongly attached to the surface, and (iii) protein adsorption must be reversible and rapid.

Many elegant studies have been performed using the Layer-by-layer (LbL) technique.[9,10,75] The LbL deposition procedure involves the step-wise electrostatic assembly of oppositely charged species (e.g., polyelectrolytes and inhibitors or others: proteins, nanoparticles) on the substrate surface with nanometer scale precision and allows the formation of a coating with multiple functionality. The coating properties can be controlled by the number of deposition cycles and the types of polyelectrolytes used. Polyelectrolytes are macromolecules carrying a relatively large number of functional groups that are charged or could become charged under certain circumstances. The macromolecules may be polycations and/or polyanions depending on the charged groups. Depending on the degree of dissociation the polyelectrolytes can be "weak" or "strong". The LbL layers could also be hydrogen-bonded, for example poly(methacrylic acid) and poly-(vinylpyrrolidone) can be self-assembled and form multilayers due to formation of intermolecular hydrogen bonds. The response of the hydrogen bonded systems to external stimuli is due to the introduced electrostatic charges into ionisable groups within the layers.

Polyelectrolytes exhibit very good adhesion to the substrate surface. The conformation of polyelectrolytes is mostly dependent on their nature and adsorption conditions and much less dependent on the substrate and charge density of the substrate surface. Polyelectrolyte coatings are expected to cover many kinds of surfaces including non-ionic and apolar substrates.

One should have in mind that the charge of encapsulation systems, which is essential for the systems LbL modified by charged polyelectrolytes affects the functions. Thus positively charged particles have been shown to exhibit higher internalization by macrophages and dendritic cells compared to neutral or negatively charged particles.[76]

Sol-gel chemistry is known for encapsulation system nanostructuring. Thus "surface" encapsulation systems can be formed by the sol-gel assembly process. The process involves the hydrolysis of precursor solutions. The precursor solution and the surfactant play significant roles in the self-assembly process of sol-gel structures forming. The profit of using the sol-gel technique is (1) high purity materials are synthesized at relatively low temperature, (2) homogenous and multi-component structure are obtained by mixing precursor solutions and (3) processing parameters can be controlled allowing the synthesis of materials with different properties such as structure, thermal stability and surface reactivity (using precursors with additional functional groups).[77] An example can be the work of Yamaguchi et al.[78] They employed a rather simple fabrication procedure of spotting precursor solutions containing cationic cetyltrimethylammonium bromide as structure directing agent and tetraethoxysilane as the silica source onto the anodized aluminum surface, and obtained aligned and columnar ordered silica nanochannels.

To provide sustained release of poorly soluble drugs from implants, extended drug release based on applying a thin plasma polymer film on the top of nanotubes arrays after drug loading.[79] A plasma polymer layer with different thickness deposited on nanotube arrays allows control over pore diameter and hence rate of drug release. It was possible to achieve favorable zero order release kinetics from AAO implants by controlling the deposition of a plasma polymer layer.

Self-ordering and biomimetics are of high relevance for synthetic chemistry, including in the development of encapsulation systems. The most significant feature of nature-designed structures is their multifunctionality and creation through unique genetically guided self-ordering, -organization, -assembly processes. The spontaneous organization of small individual subunits into larger scale ordered and stable structures, is ubiquitous in nature.[80] Self-assembly and self-organized (or self-ordered) fabrication processes are recognized as cost effective, and the most elegant route in nanotechnology leads to the generation of complex and functional nanostructured materials.[81] Several synthetic approaches based on chemical, electrochemical, sol–gel and hydrothermal methods involving self-organization have been explored for their synthesis using both top-down and bottom-up approaches.[82]

Using one inspirational system one can come up with a set of new approaches to the synthesis of materials at the hierachical scale. Thus echinoderms, provide new approaches to the synthesis of ordered, oriented crystalline materials at the nanoscale. The same organism also inspires the design of tunable nano- and microlens structures. The novel, hybrid hydrogel-actuated nanospines and nano traps act similar to echinoderm skin. One can also consider how to generate unusual chirality on the assembly.[83] These bioinspired structures have the potential for use in a variety of fields, including actuators for controlled release, self-healing artificial muscles.

Obviously, echinoderms provide new, bioinspired concepts in materials chemistry, nanotechnology, and engineering.

Diatom structures, e.g., silica based structures as well as titania, are important for development of capsules for delivery devices. For the time being diatoms have enormous ecological importance on this planet and display a diversity of patterns and structures at the nano- to millimetre scale. Diatoms are unicellular, eukaryotic, photosynthetic algae that are found in aquatic environments. Diatom nanotechnology for capsules emphasizes recent advances in diatom biomineralization, biophotonics, photoluminescence, microfluidics, compustat domestication, multiscale porosity, silica sequestering of proteins, detection of trace gases, controlled drug delivery and computer design.[84] More sophisticated drug-delivery systems, such as self-propelled swimming microrobots, could also benefit from the unique properties of diatom frustule structures.[85] Designing of microdevices that can travel inside the human body and carry out a range of complex medical procedures, such as monitoring, drug delivery and cell repair[86] is discussed. Recent developments in micro- and nanoscale engineering have led to the realization of various miniature mobile robots, but one can have an intriguing opportunity to integrate whole biological organisms or their parts.[87]

Porous structures from the molecular to the macro-level are widely used in nature.[88] These pore structures with their elegant and intricate designs have played pivotal roles in many biological processes. These processes include transport of nutrients through the cell wall, selective transport of small or specific molecules or solutes, energy or charge transport, gas adsorption, ion exchange, signalling, and many other activities. It is therefore not surprising that the concept of mimicking porous, complex structures has attracted a considerable amount of attention in materials science. Important are the control of the free volume and shape arrangements.

Shape of capsules and parts for delivery device have come into focus next. First capsules of interest were mostly spherical in shape. However, the biological world is mostly non-spherical in shape. The peculiar shape of the different biological entities plays an important role for their function.[89] Bacteria and viruses exhibit a variety of peculiar shapes. For example, rod-shaped *Escherichia coli* and *Tobacco mosaic* virus and *Bacillus anthraci*, spiral-shaped *Campylobacter jejuni*, and bullet-shaped *Rabies* virus.[90] This initiates also studies of capsules which are not spherical in shape or with complex pore organization. The major problem in performing experiments with particles of different shapes was the difficulty in their fabrication. However, with recent advances in materials science and technology, this limitation is being addressed. Some of the methods for fabrication of anisotropic shapes include self-assembly,[91] lithography,[92] nonwetting template molding,[93] microfluidics,[94] and sonochemical synthesis.[14,95]

Some examples of anisotropic particles that have been already fabricated include PEG-based trapezoids, bars, cubes, cones, discs, cylinders, and many other shapes fabricated by the top-down particle replication in nonwetting template technology.[96] Dendukuri et al. have developed a high through put continuous-flow lithographic technique that combines the advantages of microscope projection lithography and microfluidics to form morphologically complex polymeric particles suitable for encapsulation systems of a variety of different shapes. Some of the shapes generated by this technique include rings, triangles, cylinders, cuboids, polygonal structures, and curved particles.[97] Various shaped particles bearing segregated hydrophilic and hydrophobic sections have also been synthesized using the same technique.

Here again we can show that the sonochemical nanostructuring (sononanostructuring) is very prospective, as it enables modification of many different materials (Figure 2). But also the shape and texture of the resulting material can be manipulated,which in the following will be shown to be very prospective for encapsulation systems for “free” and “surface” capsules. Thus zinc particles, could be used to form a core@shell ’’hedgehog’’ zinc-based material by a ’’green’’ ultrasound method.[95] The core@shell ’’hedgehogs’’ consist of a metallic zinc core covered by zinc oxide nanorods. Due to the ’’hedgehog’’ morphology, the novel zinc-based material exhibited increased surface area, high accessibility for substrate molecules and could be a promising component of sensors, catalysts, active feedback coatings, and photovoltaic systems.

A direct replica method enabled to synthesize an array of plastic micro-objects of different shapes, such as cones, bicones, hollow cylinders, rings, test tubes, clubs, and vases. Dimethyl formamide-based colloidal nanoparticles with tunable size and shape have been fabricated by wet chemical methods.[98]

Such complex shaped capsules with diverse physical features will open up new avenues in engineering carriers for drug delivery and imaging. They can also be used as models to study the importance of shape in biological functions of organisms, such as bacteria and viruses, since the film stretching method can efficiently mimic many peculiar shapes exhibited by biological entities.

To go back to our strategy to use high intensity ultrasound as prospective for the formation of “surface” encapsulation systems, not just for the modification of individual materials (Figure 2), but simultaneous formation of advanced hybrid systems on example of formation special metal-polymer interaction by sonochemical intelligent nanoengineering.

Since the early work of Lord Rayleigh it is known that ultrasound may form cavitation bubbles inside liquids. Upon bubble collapse transiently temperatures more than 5000 K, pressures higher than 1000 atm with cooling rates above 10^8 K/sec are created.[99–101] Hence there is the potential of performing high temperature and high pressure chemistry, but with a reactor near room temperature and ambient pressure. Structures may also be formed and quenched far from equilibrium. The most pronounced effects of ultrasound on liquid–solid systems are mechanical and chemical, and these effects are attributed to symmetric and asymmetric cavitation collapses. Recent modelling has confirmed that symmetric bubble collapse in a liquid medium causes shock waves with high pressures in addition to high gas temperatures in the collapsed cavities. These high-pressure, high-temperature conditions exist for short time, however being enough for active surface modification. Such extreme conditions can be effectively used for active surface construction.[13,14,100]

Shock waves also potentially create microscopic turbulences.[101] This phenomenon increases the transfer of mass across the solid, thus increasing the intrinsic mass-transfer

coefficient, as well as possibly creating or modifying existing coatings, such as thick hybrid metal/polymer coatings.[102] Alternatively, this phenomenon may result in thinning/pitting of the film.[103] When the bubble collapses occur near a solid surface that is several orders of magnitude more extended than the cavitation bubbles,[104] the collapses occur asymmetrically[105] and solvent microjets are formed perpendicular to the solid surface. These microjets have an estimated speed of ca. several hundreds of m/s and lead to pitting and erosion of the surface.[106] Moreover, this behaviour leads to an enhancement in heterogeneous reactions (secondary cavitation-assisted processes) with active species formed in the reactor. Thus, a part of the vaporised molecules from the surrounding medium can be dissociated to form radical species, such as OH• and H•, for water sonolysis.[107] The radicals form by the hydrogen abstraction of RH additive molecules to form R• and/or by the pyrolysis of RH molecules during bubble collapse.[108] Recent studies[109] have suggested scenarios and provided prospective defined cavitation pathways for surface modifications based on their responses to ultrasound. Different responses result from differences in the surfaces' hydrophilic/hydrophobic properties or chemical reactivity. Thus, comparison of bubble formation on hydrophobic and hydrophilic surfaces with those formed in the bulk reveals a stronger response on the hydrophobic part of a patterned surface than on the hydrophilic part. If a surface changes its hydrophilicity/hydrophobicity during a sonochemical process, it is clear that the surface response to ultrasound becomes nonlinear.

The presence of monomer or polymer molecules in the sonochemical reactor can influence the cavitation process. Organic molecules are able to accumulate at the gas/liquid interface of cavitation microbubbles. The centre of the bubble exhibits high temperatures and pressures, whereas the bulk liquid remains under normal conditions. A transition zone also exists between these two states.[102]

Molecules are present in both the transition zone and the outer liquid phase. The time required for the orientation of long-chain molecules in the gas/liquid interface is longer than that required for short-chain molecules and longer than the bubble lifetime.[110] However, organic molecules near the bubble interface influence the cavitation process, which increases surface pressure, decreases the lifetime of the cavitation bubble, and leaves the molecule in the correct orientation and chemical state for transport and attachment to the surface.[111] Five main effects of cavitation are known for monomers and polymers: the formation of free radicals during the cavitation process,[112] possible polymerisation,[113] possible chain reorientation,[114] polymer decomposition[115] and the possible involvement of organics in chemical processes, such as oxidation and bond breakage.[24]

Despite the great interest in the prospective field of controlling the metal–polymer interactions by high-intensity ultrasound through cavitation-assisted processes, a general lack of knowledge persists about such processes. A few reports have concentrated on the characterisation of the chemical interactions between metals and untreated polymer surfaces, and a few others have concentrated on plasma-treated polymer surfaces. From the studies on untreated polymer surfaces, several general observations can be made. Typically, for polymers that do not contain carbon–oxygen or carbon–nitrogen functionalities, little to no chemical interaction is observed, irrespective of the reactivity with metal.[116] For reactive metals, such as Al, Mg, Cr, and Ni, extensive chemical interactions can occur, typically with oxygen atoms in oxygen-containing polymers.[117] For metals with moderate chemical reactivity, such as Cu, Ti and Ag, chemical interactions were found to be polymer dependent.[118] Thus, for example, titanium is interesting to study because its moderate chemical reactivity allows discrimination between weakly and strongly interacting nucleation sites on the polymer surface.

Figure 10 shows a schematic representation of the main initial surfaces and some hypothesised consequences of sonochemical surface modification. Three main possible methods of metal-polymer interaction have been postulated: 1) the attachment of polymer molecules to metal surfaces or thin metal-oxide layers on the metal; 2) the formation of a hybrid, which simultaneously interacts with and modifies the metal, and polymer or monomer attachment with subsequent polymerisation, or monomer polymerisation and subsequent polymer attachment; 3) the formation of a thin hybrid layer on the metal surface and the subsequent attachment of the polymer (either initially present or formed from the monomer during the process of sonication).

Many fundamental aspects of cavitation-assisted processes during surface modification are still unclear, and in situ investigations, together with a detailed study of each type of material and the prospects for their combinations, are necessary to elucidate the details of these reactions. The following central problems have been identified:

- To arrive at a mechanistic model of cavitation-assisted processes on solid surfaces. Physico-chemical properties of the surface are relevant for the surface's response to ultrasound-assisted modification. Only a few authors have suggested models for a given type of material and its combination with other materials.
- To distinguish relationships between the primary and secondary effects of ultrasound, depending on the mechanical material properties and crystallinity. One might expect (and some results have already shown) that hard and soft metals exhibit different visible responses to ultrasonic exposure and can be building blocks for novel materials. Polymers are expected to exhibit a stronger response than hard materials such as Ti. For soft materials with low thermal conductivities, local heating during ultrasonic processing may lead to a decrease or, oppositely, an increase in surface roughness because high local mobility may enable surface tension to flatten the surface. The bubble collapse causes hot spots, and the pressure pulses are also converted into heat; these effects may induce local melting. Thus, a crystalline surface may locally melt and become amorphous after cooling, as has been observed for biopolymers. Reactive species may be created in the solution and in the solid, which may cause a metal to oxidise deeper inside the solid or a polymer to be destroyed or cross-linked. Concerning the influence of polymer surfaces, we have observed that ultrasonic treatment may render a surface hydrophobic/hydrophilic.
- To localize the effect of ultrasound. Thus, bubble nucleation may be controlled through patterning. A pressure pulse on

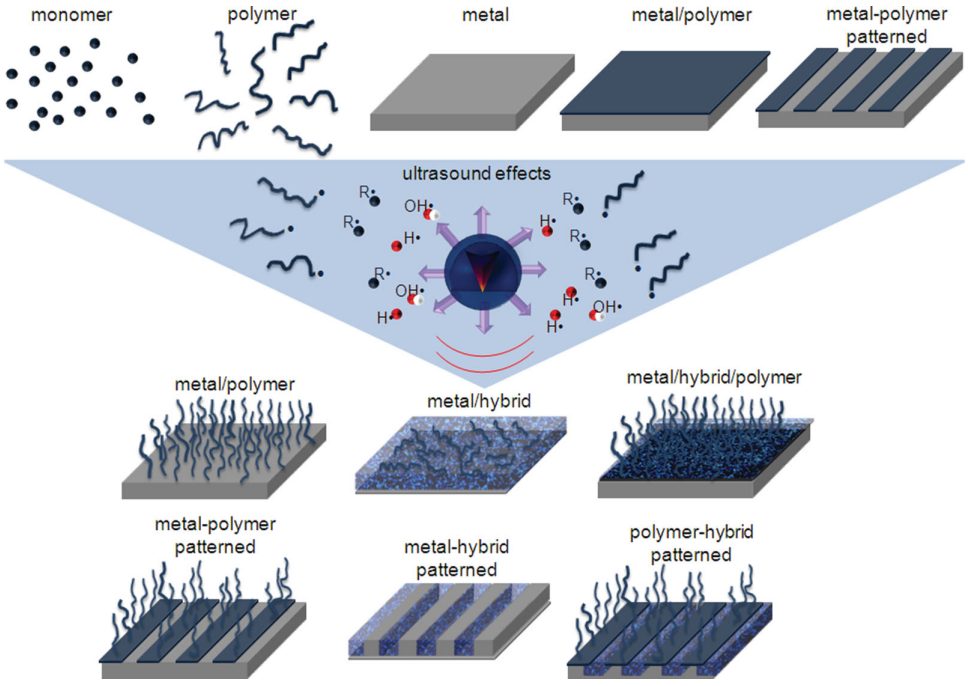

Figure 10. Schematic presentation of the research objects containing the material combination (individual not shown): initial materials – monomer, polymer, metal, metal/polymer, and metal-polymer-patterned surface – UPPER part; possible ultrasonic effects in the reactor – physical (shock waves and liquid jets) and chemical (formation of radicals from monomer and polymer and sonolysis of the liquid (here, water shown)) – MIDDLE part; and some examples of systems which could be expected after applying ultrasonic exposure: polymers could be attached to the metal (here shown as a brush formation on the surface); the metal and polymer could form a porous hybrid system; on the surface of a metal, a thin hybrid (metal/polymer) layer could be formed with subsequent polymer attachment to the hybrid (here, brush formation is shown); and in the case of an initial patterned surface, the combination of approaches is possible – LOWER part of the scheme.

a material may be focused on defects or grain boundaries. This fact necessitates the study of solids with a defined microstructure. Whether destruction proceeds along patterns, defects and grains is also relevant.

– To follow the kinetics of sonochemistry in complex multicomponent systems. A solution to this issue is still unclear, but a solution is necessary because materials can be obtained with drastically varying hydrophilic/hydrophobic properties, roughness, porosity, crystallinity and, in the case of hybrids of metals and biopolymers, different nonlinear acoustic responses. The facts that the surface is made more hydrophobic or hydrophilic by ultrasound and that this further influences bubble nucleation may have interesting consequences for the time and space dependence of the treatment: the dose dependence becomes nonlinear and surface and gas specific and patterns can be reproduced with enhanced contrast to have, for example, defined protein/surface adhesion.
– To control the modification of the surfaces via the concentrations of additives in the system (monomer, polymer) and to establish the role of initial cavitation in acoustic droplet vaporisation in different solutions.
– To define intermediate steps of the process. If intermediate states of destruction resembling a porous solid can be produced, then new active surfaces may also be produced.
– To provide scenarios of active surface construction based on pronounced responses of the metals and polymers to ultrasound. These are required for implants connected to bone, metals (alloys of titanium and magnesium), and they therefore must be investigated for the possibility of controlling their structure and influencing the treatment (with or without additives in the system) of their surfaces. Protein and cell adhesion must also be investigated with respect to their interactions with a surface. Implants with the possible ability of sustained drug delivery due to the use of metals or hybrids with defined porosity for active chemical (such as drugs) storage and release by an internal (such as Mg dissolution) or external stimuli (pH, temperature, light) need further study. This research area is obviously very promising with respect to stem cell research.

In summary, ultrasonic chemistry carries many exciting prospects but is in its infancy with respect to our understanding and control of the process, which necessitates a multidisciplinary approach that combines interface and colloid science, acoustics, inorganic, physical and polymer chemistry, and other disciplines for specific applications. Concerning the latter, the focus in the following is laid on biomaterials and construction of hybrid materials. Moreover, to have real progress in fabricating intelligent materials, e.g., capsules, design by certain methodology (high intensity ultrasonic one), it is of high priority to have strong collaboration between different scientific fields. Thus after enough data concerning the effect different materials is collected, this might stimulate theoretical treatment and simulations. In **Table 1** are presented some possible starting points[119] for future simulations of high intensity

Table 1. Hierarchical-multiscale: examples of simulations of interaction between cavitation bubble and metal / metal-polymer / polymer / hybrid surface.

Hierarchical-multiscale	Electronic state	Atomic scale	Pseudo-particles	Continuum theory
Possible calculation methods	– quantum mechanics chemical reactions thermodynamic properties	– kinetic Monte Carlo molecular dynamic	– lattice Boltzmann method	– constitutive electric-plastic metal deformation –FEM –FFT
Some important parameters	Reaction products, chemistry of cavitation-assisted processes	Orientation of crystal, anisotropy, kinetics of defect, nucleation, roughness, porous formation	Penetration of liquid and gases inside-outside the formed porous structures, density and viscosity of liquid	Roughness (R), temperature, pressure, nature of metal / metal-polymer/polymer/hybrid (lattice parameters, phase diagram, nature of local bonds, elastic properties, patterns, defects)

ultrasonic treatment for metal surface modification needed to design hybrid materials by different pathways, such as presented in **Figure 11**. In particular hierarchical-multiscale examples are presented of simulations of interaction between cavitation bubbles and metal/metal-polymer/polymer/hybrid surfaces. Thus for each hierarchy level different theories can be applied: electronic state; atomic scale; pseudo-particles and continuum theory. Possible calculation methods are shown as well as some important process parameters are pointed out. One could imagine the very high level of cooperation which is needed between different groups to establish real progress in intelligent materials design with deep understanding of the process of construction of intelligent materials.

5. Materials for Capsules

Nowadays a wide variety of available materials are suitable for use as delivery devices. One must take into account the needed application to select one of the systems for encapsulation. In some cases polymer capsules are needed: synthetic or natural polymers for encapsulation systems. However in other cases, e.g., "free" capsules to be introduced into anticorrosion coatings, long term mechanical stability of capsules is needed and either mesoporous inorganic materials are used as main component to deliver active chemicals or hybrids of inorganic/polymeric materials are used for capsule construction. Oxides, calcium carbonate and other ceramics are known to be used as capsule cores to store in their porous interior active chemicals and deliver active chemicals to a desired area. Silicon formation and modification for encapsulation systems are known especially for systems where advanced properties of luminescent silicon are needed. Carbon based structures are used as mechanically stable light weight material. Metal based structures are developed for delivery devices. More often, as was already mentioned above, to have intellectual encapsulation systems post functionalization of individual materials is needed, for example to provide pore closure. After modification the final capsules in most cases consist of a hybrid mixture of components used for capsule formation. A separate topic for cell related application is cell encapsulation or bio-production of capsules by cells. In the following chapter we will mention some specific examples of different systems.

5.1. Polymer Capsules

Polymers as materials for the formation of "free" hollow polymer capsules are the most established class of materials.The variation of known and available systems is amazing: at least one paper was published every day during last year with mentioning the keyword "polymer capsule". This is because different applications, e.g., different drugs delivery, sensors, reactors, templates, catalysts, are besides need in require variations of size, composition, morphology and, specific polymers. The use of synthetic polymers offers the opportunity to fine tune their chemical structure to achieve a modular release, which is an advantage for the intelligent encapsulation systems. Natural polymer networks can be also tailored, but just to some extent by changing polymer concentration and crosslink density. Development of hybrid networks in which natural polymers are synthetically modified or combined with synthetic polymers, has been proposed to combine beneficial properties of both kinds of polymers with respect to mechanical properties, tailorability in terms of biodegradability as well as biocompatibility and cytocompatibility.

Very powerful and an increased area of scientific interest, for example for "surface" capsules, are hydrogels to be used for encapsulation systems. The possibility to tailor the release kinetics of proteins from hydrogels can be achieved through the use of excipients or by changing the crosslinking density of the polymer network. The geometry of the hydrogel-based depot also affects the release rate and the duration. Generally, the bigger the device, the longer the diffusion distances and the longer the release consequently lasts.

5.1.1. Synthetic Polymers Systems

Interesting as capsule materials are advanced nanoengineered polymers which can provide capsules with advanced additional functionality via their structuring and functional characteristics. Examples are in the area of conductive polymers, such as e.g., polypyrrole, polyaniline. Electrically conducting polymers have been the subject of continuous research and development due to their potential applications in many technological areas such as rechargeable batteries, sensors, electromagnetic interference shielding, electrochromic display devices, smart windows, molecular devices, energy storage systems, membrane gas separation, and so on.[120]

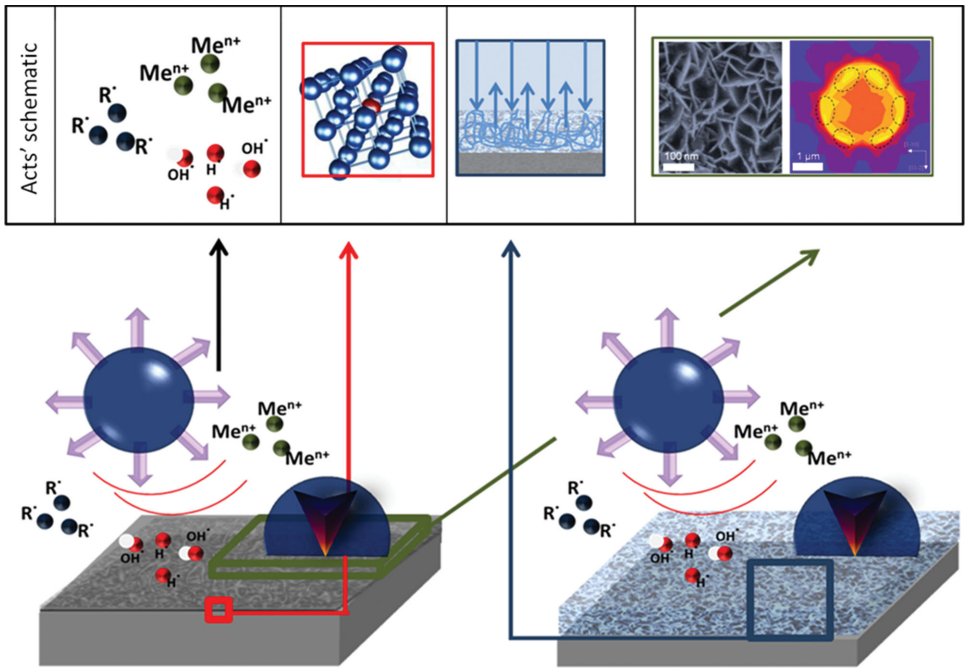

Figure 11. Schematic presentation of the possible objects for simulation. The ultrasound affects the initial and modified materials differently, i.e., nonlinear response to cavitation assisted processes is observed. Upper part shows examples of possible to simulations systems in hierarchical-multiscale. Start point (upper row, right images) can be continuum theory as comparison of R experimental (obtained with in situ setup) with R simulated; and on the origin of deformation-induced rotation patterns below cavitation jets as indents.

Polypyrrole microcapsules were successfully prepared by electrochemical polymerization of pyrrole on the surface of stainless steel electrodes.[121] The size of the capsules and the thickness of the polypyrrole shell (up to complete filling of the capsule with grown polypyrrole) can be varied by changing both the scan speed of the electrode potential and potential range. The polypyrrole shell of the microcapsule exhibits very strong barrier properties in acidic media at $2 < pH < 7$ and a high permeability at $pH > 7$, providing effective encapsulation of low molecular weight species at low pH values. The capsules can be used on the surface of "steel" providing a "surface" encapsulation system or being detached from the steel as "free" capsules.

Intensive works with some other polymers are known due to their unique properties providing in the following capsule functionality and stimuli response. Poly(N-isopropylacrylamide) (PNIPAM)[122] is known to open capsules in response to several stimuli: pH, T. Among the various synthetic polymers studied for the delivery of growth factors in tissue repair, PEG-based networks play a prominent role.[123] Mostly studied for LbL systems are such synthetic polymers as poly(styrene sulfonate) sodium salt (PSS), poly(ethyleneimine) (PEI), poly(allylamine) (PAH), poly(diallyldimethylammonium) chloride (PDADMAC), poly(meth)acrylic acid (PMA/PAA). The synthetic polymers are used in their different combination to achieve the needed functionality. Here the detailed work on the combination of "week-week", "week-strong", "strong-strong" polyelectrolytes for self-healing LbL can be mentioned.[124]

Microgels/nanogels possess high water content, biocompatibility, and desirable mechanical properties.[125] They are crosslinked polymeric particles, which can be considered as hydrogels if they are composed of water soluble/swellable polymer chains. They offer unique advantages for polymer-based drug delivery systems: a tunable size from nanometers to micrometers, a large surface area for multivalent bioconjugation, and an interior network for the incorporation of biomolecules. Present and future microgel applications require a high degree of control over properties. They include stability for prolonged circulation in the blood stream, novel functionality for further bioconjugation, controlled particle size with uniform diameter, and biodegradability for sustained release of drugs for a desired period of time and facile removal of empty devices. Nowadays various synthetic strategies for the preparation of microgels/nanogels are known, including photolithographic and micromolding methods, continuous microfluidics, modification of biopolymers, and heterogeneous free radical and controlled/living radical polymerizations.

In all it is important to know that for a particular application a particular system should be chosen and adapted, for example allowing to go from in vitro to in vivo study.

5.1.2. Natural Polymers for Encapsulation Systems

Natural polymers offer a degree of functionality not available for many synthetic polymers, such as tailorability in terms of biodegradability as well as biocompatibility and cytocompatibility. There is a large number of systems based on natural polymers available today. Some examples are presented below. The main classes of natural polymers studied formulations are polysaccharides, proteins/polypeptides, DNA, liposomes.[126] Examples of polysaccharides used for capsule formation are chitosan,[127] dextran,[128] alginate,[129] hyaluronic acid.[130]

Chemistry offers tools to modulate the structure of natural polymers without a negative effect on their advanced properties. Thus even after extraction and some modification one can use, e.g., silk protein, for advanced encapsulation systems with bio-fuctionality.[131]

Natural polymers are especially prospective for tissue engineering and other bio-applications, e.g., for the physical encapsulation of growth factors. Taking hydrogels as example, hydrogels designed with natural polymers as building blocks display multiple advantages over synthetic polymer networks with respect to their biocompatibility, biodegradability and good cell adhesion properties. Therefore, extensive work is available on biopolymer-based hydrogels for cell and growth factor encapsulation in regenerative medicine.[132]

Lipids and lipopolymers self-assembled into biocompatible nano- and mesostructured functional capsules offer many potential applications in medicine and diagnostics.[133]

5.2. Inorganic Materials

Inorganic materials are extensively used to provide encapsulation systems: from hollow particles to, which is mostly the case, porous substances to encapsulate and store active chemicals. Here again functionality of the inorganic material and its following nanostructuring, e.g., SAM or LbL, provide space for capsule optimization taking into account needed properties and functionalities. Thus capsules can be controlled in vivo, which is very important for material circulation in the body, by loading of mesoporous luminescent Si with the drug.[134] Capsules can be dissolved without negative effect to the body: $CaCO_3$ for delivery of insulin,[135] magnesium[24] biodegradable implants.

5.2.1. Oxides, Calcium Carbonate and Other Ceramics

Oxides are extensively used for formation of delivery devices. Thus mesoporous silica provides an excellent matrix for guest molecules, due to several attractive features among their textural and chemical properties, which play an important role in the loading and release of molecules, i.e., they govern the host-guest interactions between the bio-ceramic matrix and organic guest.[44] The SiO_2 for capsules provides a combination of structural, mechanical, chemical and optical features that might both overcome challenges associated with conventional delivery of therapeutic agents and have advantages over existing delivery systems. Among the important characteristics, these materials present high surface area (ca. 1000 m^2g^{-1}), large pore volume (ca. 1 cm^3g^{-1}), regular and tunable mesopore diameter (2–50 nm) and pore channel systems homogeneously organized in 2D and 3D mesostructures,[136] biocompatibility and biodegradability of silica based capsules make them a promising biomaterial for drug-delivery applications. They can be easily functionalized, protected and designed for controlled drug release through nanosized pores or by embedment in the silica.[137] The preparation of ultra-high-purity and fraction-free silica capsules from raw material is possible using simple separation procedures. These microcapsules are proposed as excellent natural porous materials for delivery applications.

Magnetic particles such as iron oxide nanoparticles find many applications as contrast agents, in magnetic cell sorting, and immunoassays in pathology laboratories.[138] For example recently it was shown to use polymer-shelled magnetic microbubbles on the interplay of shell structure with low- and high-frequency mechanics of multifunctional magnetic microbubbles.[139] Efforts are underway to develop magnetic particles for controlled and directed transport of therapeutics as well as hyperthermia treatment for cancerous tumors.[140]

5.2.2. Silicon Formation and Modification for Encapsulation Systems

Porous Si exhibits a number of properties that make it an attractive material for controlled drug delivery applications. Subsequently, porous Si or porous SiO_2 (prepared from porous Si by oxidation) host matrices have been employed to demonstrate in vitro release of the steroid dexamethasone, ibuprofen, cis-platin, doxorubicin, and many other drugs.[141] With a free volume that can be in excess of 80%, porous Si can carry cargo such as proteins, enzymes, drugs or genes. It can also carry nanoparticles, which can be equipped with additional homing devices, sensors, or cargoes. The tailored pore sizes and volumes that are controllable from the scale of microns to nanometers; a number of convenient chemistries exist for the modification of porous Si surfaces that can be used to control the amount, identity, and in vivo release rate of drug payloads and the resorption rate of the porous host matrix; the material can be used as a template for organic and biopolymers, to prepare composites with a designed nanostructure; and finally, the optical properties of photonic structures prepared from this material provide a self-reporting feature that can be monitored in vivo.

Usually porous Si is prepared by electrochemical etching. Thus porous Si is a product of an electrochemical anodization of single crystalline Si wafers in an aggressive hydrofluoric acid electrolyte solution. Pore morphology and pore size can be varied by controlling the current density, the type and concentration of dopant, the crystalline orientation of the wafer, and the electrolyte concentration in order to form macro-, meso-, and micropores. Pore sizes ranging from 1 nm to a few microns can be prepared.

The group of Sailor with co-workers[142] showed the prospects of post-anodization ultrasonic treatment of silicon to provide detachment of mesoporous luminescent layers/microparticles with their following use for drug delivery. A procedure for generating colloidal suspensions of Si that exhibit luminescence, attributed to quantum confinement effects, was described. Samples of n- or p-type Si that have been electrochemically etched to form porous Si can be ultrasonically dispersed into methylene chloride, acetonitrile, methanol, toluene, or water solvents, forming a suspension of fine Si particles that luminesce. Transmission electron microscopy analyses show that the Si particles have irregular shapes, with diameters ranging from many micrometers to nanometers. Luminescent, composite polystyrene/Si films can be made by the addition of polystyrene to a toluene suspension of the Si nanoparticles and casting of the resulting solution onto a glass

slide. Simultaneously the prospects of sonochemical treatment of luminescent microparticles in different solvents to change their luminescent nature were shown.

Recently a concept of sonochemically regulated construction of submicron and micron porous silicon with unique mechanical, optical and drug delivery properties as initial material micron-Si particles, crystalline, or amorphous, p- or n- type, were suggested.[143] An experiment on ~100 μm particles of silicon proved the formation of nanocrystalline Si and its subsequent phase transitions (crystalline–amorphous–crystalline) without oxidation in water solution in the presence of hydrogen donor material. Thus the 10-min-sonicated particles exhibit a pronounced crystalline structure, and their size decreases to the submicron scale. The amorphisation of the particles is observed within 20 min of modification. Further exposure (>30 min) causes well-pronounced crystal growth from the amorphous phase in addition to a further size decrease. The observed phase transition (crystalline ↔ amorphous) is probably the main factor responsible for ultrasound-assisted modification of silicon. Special conditions provided by high-intensity ultrasound could affect the melting and growth of the silicon crystals. The form of a solidified microstructure can be controlled by fast local heating and cooling cycles provided by cavitation. The crystal formation depends upon the difference between the rates of attachment and detachment of atoms at the interface. The rate of attachment depends on the rate of diffusion in the liquid and is, therefore, affected by sonication.

5.2.3. Carbon Based Structures

Carbon-based encapsulation systems attract particular interest, since they are chemically inert, but can be surface-functionalized for the grafting of active chemicals: nucleic acids, peptides, and proteins. Moreover such systems can be loaded with other active chemical, providing multi-loading capacity. Thus, carbon nanotubes,[144] fullerenes,[145] graphene[146] and nanodiamonds[147] have been studied for drug delivery.

The size, geometry, and surface characteristics of single-wall nanotubes (SWNTs), multiwall nanotubes (MWNTs), and C_{60} fullerenes makes them appealing for drug carrier usage. SWNTs and C_{60} fullerenes have diameters on the order of 1 nm, about half the diameter of the average DNA helix. MWNTs have diameters ranging from several nanometers to tens of nanometers depending on the number of walls in the structure. Fullerenes and carbon nanotubes are typically fabricated using electric arc discharge, laser ablation, chemical vapor deposition, or combustion processes. The application of these nanomaterials in the fields of vaccine delivery, gene delivery, small molecule transporters, and targeted delivery is being explored.

5.2.4. Metal Based Structures

"Surface" encapsulation systems, mentioned above, are built on the surface of mesoporous sonochemically treated metals[13,14] or anodized structures[41] and are prospective for such applications as implants, lab-on-chip and organ-on-chip growth, formation of anticorrosion and antifouling surfaces.

Moreover when linked to or embedded within polymeric drug carriers, metal nanoparticles can be used as thermal release triggers when irradiated with infrared light or excited by an alternating magnetic field.[148] Biomolecular conjugation methods of metals include bifunctional linkages, lipophilic interaction, silanization, electrostatic attraction, and nanobead interactions.[108]

Gold nanoparticles have received great attention in the synthesis of multifunctional drug delivery carriers due to the unique capability of attachment of thiol-derivatized molecules.[48] Not only can gold nanoparticles be decorated with a targeting ligand, hydrophilic polymers such as PEG for imparting stealth properties and therapeutics (drug or nucleic acids), but they can also be imaged using contrast imaging techniques. Moreover, once the gold nanoparticles are targeted to the diseased site, such as tumor, hyperthermia treatment can be used for tumor destruction.

5.3. Composites and Hybrids

It is clear that a variety of particle platforms have been developed for a wide spectrum of applications, and they have unique advantages and limitations. Combinations of materials have also been developed to benefit from the advantages of various materials while addressing the limitations of these materials. For example, inorganic nanoparticles possess unique optical and magnetic properties, but lack favorable bulk mechanical properties and surface processing characteristics. In contrast, polymeric particles offer flexibility with respect to manipulation of surface chemistry, bulk mechanical properties, and particle geometry.

Core@shell particles with an inorganic core (quantum dots, iron oxide nanoparticles) and polymeric shell have been developed, which can be used for therapeutic delivery and imaging.[149] Additional functionalities, such as luminescence of the core, can be easily introduced. Similarly, $CaCO_3$-polystyrene composites have been developed where $CaCO_3$ provides required strength and polystyrene provides compatibility.

Liposomes and polymeric nanoparticles are the two most widely researched drug delivery platforms. Attempts have been made to combine the advantages of both systems. For example, polymeric nanoparticles have been encapsulated within fusogenic liposomes to regulate the intracellular pharmacokinetics of gene-based drugs by protecting them from enzymatic and hydrolytic degradation.[150]

The group of Zhitomirsky[151] has made progress in constructing effective chitosan composite encapsulation systems. They use electrophoretic deposition for the fabrication of chitosan-carbon nanotube-hydroxyapatite and hydroxyapatite-$CaSiO_3$-chitosan composite encapsulation systems. The use of chitosan enabled the co-deposition of hydroxyapatite and carbon nanotubes or $CaSiO_3$ particles and offered the advantage of room temperature processing of composite materials. The thickness of the individual layers was varied in the range of 0.1–20 μm. A layered composite chitosan – multiwalled carbon nanotube surface encapsulation system was in the range of 0.5–10 μm which could be manipulated by variation of the deposition voltage and deposition time.

Intelligent design of "smart" encapsulation systems based on inorganic materials is required nowadays following functionalization. Thus silica based capsules provide flexibility for the design of complex drug-delivery vehicles through functionalization with sensing biomolecules or immunotargeting bioreceptors, optically active dyes (for imaging) and/or magnetic nanoparticles (for controlled movement to target diseased tissue or cancer cells).[84] There is interest in nanorobotic delivery systems. In regards to their physical and structural properties, porous silica capsules are ideal microscale bodies for designing these future robotic devices for delivery, e.g., biomedical applications. However, the self-propelled function is missing here, and to introduce mobility, one could attach bacteria to the diatom in addition to, or instead of, the gliding motility of diatoms themselves. Many bacteria propel themselves along in a fluid by rotating their corkscrew-like tails, called flagella, at relatively high speeds, and as robust machines. These flagellae can easily be integrated with other microscopic components and do not need to be purified or reconstituted. The bacteria motors work using a simple chemical energy source (glucose) and are naturally sensitive to the environment (e.g., metal ions, ethylene diamine tetraacetic acid [EDTA]), which means that nanobot movement can be controlled. Of course, in the dark parts of our bodies, we might want to use motile apochlorotic diatoms.

5.4. Biological Objects: Cell Encapsulation and Capsule Formation by Cells

Live cell encapsulation technologies are in trend. Several major important features for cell encapsulation can be mentioned: complete encapsulation, mechanical stability, selective permeability, e.g., for immune isolation, suitable extracellular microenvironment for optimal cellular functions. One should be aware that enhancement of one advantage does not decrease the other function. For example, a thick membrane with good immune isolation and mechanical stability often leads to poor nutrient/oxygen supply for cellular functions.

There are numbers of techniques for cell encapsulation: ionic gelation, complex coacervation, interfacial precipitation. Methods have been developed to encapsulate various primary cells or cell lines for different tissue engineering or therapeutic applications.

The materials used for cell encapsulation have to be biocompatible. Cross-linked chitosan, collagen, agarose microspheres, ceramic-based materials and their combination with polymers, e.g., polyethylenimine, poly-acrylic acid, different compositions of methacrylates, polylysin, sodium alginate, hydrogels and polyelectrolytes.

Preferably material for cell encapsulation should be not only biocompatible but also biodegradable. For example biodegradable self-reporting nanocomposite films of poly(lactic acid) nanoparticles engineered by layer-by-layer assembly were suggested.[152] In particular, multilayer assemblies of biodegradable poly(lactic acid) (PLA) nanoparticles based on hydrogen-bonding or electrostatic interactions were designed and fabricated. Moreover, gold nanoparticles can be effectivly grown within the PLA nanoparticle assemblies either through UV-irradiation or under mild reducing conditions to create biodegradable nanocomposites with distinct optical response, which allows monitoring biodegradation of the films. The nanocomposite coatings of PLA nanoparticles were enzymatically degraded by a-chymotrypsin. The biodegradation process can be colorimetrically monitored with UV-vis spectroscopy thus opening the way for facile and real-time monitoring useful for biotechnology applications.

The material used for cell encapsulation is selected according to the following application for a specific cell line and can have advanced functionality, e.g., be stimuli responsive. Thus encapsulation of liver microsomes into a thermosensitive hydrogel for characterization of drug metabolism and toxicity was demonstrated.[153] The thermosensitivity of the hydrogel (Pluronic F127-acrylamide-bisacrylamide hydrogel) was studied using a swelling ratio and protein release assay to verify its ability to encapsulate microsomes. The metabolic activity of microsomes encapsulated in gels was investigated by detecting the metabolites of hydrogel-compatible substrates, including dextromethorphan, chloroxazone and testosterone. The classical anticancer prodrug cyclophosphamide was chosen as a model drug for the study of drug metabolism and the prediction of drug effects. When the microsomes encapsulated in the hydrogel were used in the cell culture system, the drug induced a higher level of apoptosis in MCF-7 cells compared with traditional microsomes.

Hydrogel functionalization and its variety provides space for optimization of the material used for cell encapsulation. There are studies how synthetic materials affect a natural cell and its metabolism. An example of such a research can be the analysis of the influence of encapsulation of cardiac stem cells (CSCs) within matrix enriched hydrogel capsules on cell survival, post-ischemic cell retention and cardiac function.[154] Transplantation of ex vivo proliferated CSCs is an emerging therapy for ischemic cardiomyopathy but outcomes are limited by modest engraftment and poor long-term survival. The effect of single cell microencapsulation to increase CSC engraftment and survival after myocardial injection was explored. Transcript and protein profiling of human atrial appendage sourced CSCs revealed strong expression the pro-survival integrin dimers – thus rationalizing the integration of fibronectin and fibrinogen into a supportive intra-capsular matrix. Encapsulation maintained CSC viability under hypoxic stress conditions and, when compared to standard suspended CSC, media conditioned by encapsulated CSCs demonstrated superior production of pro-angiogenic/cardioprotective cytokines, angiogenesis and recruitment of circulating angiogenic cells. Intra-myocardial injection of encapsulated CSCs after experimental myocardial infarction favorably affected long-term retention of CSCs, cardiac structure and function. Single cell encapsulation prevents detachment induced cell death while boosting the mechanical retention of CSCs to enhance repair of damaged myocardium.

There are numbers of studies to induce regeneration of organs by cell injection. However mostly cells are difficult to inject without their damage. Thus cells are encapsulated before being injected. For example, injectable calcium phosphate–alginate–chitosan microencapsulated MC3T3-E1 cell paste for bone tissue engineering in vivo was suggested.[155] The study aimed to develop alginate–chitosan microencapsulated mouse

osteoblast MC3T3-E1 cells to evaluate the osteogenic potential of a calcium phosphate cement complex with these cells, and trace the implanted MC3T3-E1 cells in vivo. MC3T3-E1 cells were embedded in alginate microcapsules, cultured in osteogenic medium for some days, and then covered with chitosan before mixing with a paste of calcium phosphate cement. The construct was injected into the dorsal subcutaneous area of nude mice. Lamellar-bone-like mineralization, newly formed collagen and angiogenesis were observed after 4 weeks. After 8 weeks, areas of newly formed collagen expanded with further absorption of osteoid-like structures. Cell tracing in vivo showed that implanted MC3T3-E1 cells were clearly visible after 2 weeks. The in vivo results indicate that the injectable encapsulated cells are promising for bone tissue engineering applications.

R. Grass' group in Zurich suggested an effective method of reversible DNA encapsulation in silica to produce radical oxygen species (ROS)-resistant and heat-resistant synthetic DNA 'fossils'.[156] In particular, the protocol describes a method for encapsulating DNA into amorphous silica (glass) spheres, mimicking the protection of nucleic acids within ancient fossils. In the approach, DNA encapsulation is achieved after the ammonium functionalization of silica nanoparticles. Within the glass spheres, the nucleic acid molecules are hermetically sealed and protected from chemical attack, thereby withstanding high temperatures and aggressive ROS. The encapsulates can be used as inert taggants to trace chemical and biological entities. The protocol is applicable to short double-stranded and single-stranded DNA fragments, genomic DNA and plasmids. The nucleic acids can be recovered from the glass spheres without harm by using fluoride-containing buffered oxide etch solutions. Special emphasis is placed on a protocol of the safe handling of the buffered hydrogen fluoride solutions. After dissolution of the spheres and subsequent purification, the nucleic acids can be analyzed by standard techniques (gel electrophoresis, quantitative PCR and sequencing).

An important issue is the development of encapsulation devices as an effective platform for implantation of genetically engineered cells in allogeneic conditions, which could be adapted to the chronic administration of recombinant proteins. An example of a successful device is a high-capacity cell encapsulation system suggested for the implantation of allogeneic myoblasts, which survive at high density for at least one year.[157] The system is developed as flat sheet device. It is based on permeable polypropylene membranes sealed to a mechanically resistant frame which confines cells seeded in a tailored biomimetic hydrogel matrix. In order to quantify the number of cells surviving in the device and optimize initial conditions leading to high-density survival, devices containing C2C12 mouse myoblasts expressing a luciferase reporter in the mouse subcutaneous tissue were implanted. It was shown that the initial cell load, hydrogel stiffness and permeable membrane porosity are critical parameters to achieve long-term implant survival and efficacy. Optimization of these parameters leads to the survival of encapsulated myogenic cells at high density for several months, with minimal inflammatory response and dense neovascularization in the adjacent host tissue.

One cell can be a capsule for the other one. Thus bacteria are effective capsules for bacteriophages. When a stimulus is applied the bacteriophage can be released from the bacteria. It was shown for example that titania and ROS generated on it under actinic irradiation provide release of bacteriophages from *Lactic* bacteria.[158]

Capsules can be formed by cells. Vesicles released by eukaryotic cells act as capsule used by cells to exchange biomolecules as transmembrane receptors and genetic information.[159]

Cell-derived vesicles as a bio-platform for the encapsulation of theranostic nanomaterials.[160] Endothelial cells were loaded with different types of nanoparticles solely or in combination. The cells were then incubated to form in the cell vesicles around the nanoparticles. Then the release of biogenic vesicles loaded with nanoparticles was triggered. Functional nanoparticles were encapsulated in a cell-camouflaged nanoplatform. A cell-camouflaged nanoplatform enclosing such nanoparticles represents the concept of cell-released vesicles as a universal nanoencapsulation platform.

6. Stimuli Response of Capsules

Materials science and chemical biology provide a variety of choices for stimuli triggered capsule behavior. Materials with "dynamicity" whereby surface properties can be modulated by an internal and external stimulus on user demand have been actively exploited for the past decade. These switchable materials with dynamic properties are widely used for a number of applications such as micro/nanoarrays, biomolecule immobilization, basic cell studies, and tissue engineering on a variety of materials. Stimuli to control capsule opening are physical (temperature, laser light, electric and magnetic field, ultrasound, and mechanical action), chemical (ionic strength, pH, electrochemical and solvent) and biological ones (enzymes and receptors).

In the past years, design of novel bio-responsive capsules that release drugs in response to an intracellular signal, in particular acidic pH and redox potential due to enzymatic reactions, has received great interest.[161] pH controls the linear charge density of an adsorbing polymer as well as the charge density of the previously adsorbed polymer layer. Bio-capsules which are pH sensitive, are usually designed to destabilize vehicles and to release drugs in endosomal and/or lysosomal compartments, which have pH values typically as low as 5.5 and 4.5, respectively. In comparison, redox-responsive capsules are mostly intended to disassemble and release drugs in the cytosol which contains 2 to 3 orders higher levels of glutathione (GSH) tripeptide (approximately 2–10 mM) than the extracellular fluids (approximately 2–20 μM).[162] Glutathione (GSH)-responsive systems were suggested as effective nano-vehicles for targeted intracellular drug and gene delivery.[163] GSH/glutathione disulfide (GSSG) is the major redox couple in animal cells that determines the anti-oxidative capacity of cells.[164] GSH/GSSG is kept reduced by nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione reductase. The intracellular level of GSH is also dependent on other redox couples such as NADH/NAD+, NADPH/NADP+ and thioredoxin$_{red}$/thioredoxin$_{ox}$. This significant difference in GSH level has rendered GSH-responsive submicron capsules most appealing for targeted intracellular drug delivery. It should further be noted that

the endosomal compartment is also redox-active, and the redox potential is modulated by a specific reducing enzyme gamma-interferon-inducible lysosomal thiol reductase in the copresence of a reducing agent such as cysteine (but not GSH).[165]

Moreover, the redox-active lysosome contains also low-mass iron that is kept in a reduced state (Fe^{2+}) by the acidic interior and high concentrations of thiols such as cysteine within lysosome.[166] GSH-responsive encaspsulation systems such as micelles, nanoparticles, polymersomes, nanogels, dendrimers, and nano-sized nucleic acid complexes for controlled delivery of anti-cancer drugs (e.g., doxorubicin and paclitaxel), photosensitizers, anti-oxidants, peptide and protein drugs, or nucleic acids (e.g., DNA, siRNA, and antisense oligodeoxynucleotide) were suggested. The unique disulfide chemistry has enabled novel and versatile design of multifunctional delivery systems to overcome both extracellular and intracellular barriers. It is anticipated that GSH-responsive nano-vehicles have enormous potential in targeted cancer therapy.

The encapsulation systems based on reduction-sensitive polymers have attracted a lot of attention for diverse biomedical applications including controlled drug delivery, gene delivery and diagnostic imaging.[167] It has to be noted, however, that only in the last couple of years exploding progress has been made in the capsule design for triggered intracellular drug release It should further be noted that many of the reported systems are not based on biodegradable and/or biocompatible materials, which are nevertheless the first requirement for most biomedical applications. In the future, more efforts should be directed to development of novel cell-sensitive degradable polymers and copolymers including polyesters, polycarbonates, polypeptides, poly(ester amide)s and poly(ester urethane)s. Notably, recently there have appeared interesting reports on the synthesis of reduction-sensitive stepwise cleavable star polymers,[168] biodegradable polyurethanes derived from L-arabinitol,[169] and cascade degradable linear polymers.[170]

Lipids and lipopolymers self-assembled into biocompatible nano- and mesostructured functional capsules offer many potential applications in medicine and diagnostics due to their stimuli response. Thus recently it was demonstrated[171] how high-resolution structural investigations of bicontinuous cubic templates made from lyotropic thermosensitive liquid-crystalline materials have initiated the development of innovative lipidopolymeric self-assembled nanocarriers. Such structures have tunable nanochannel sizes, morphologies, and hierarchical inner organizations and provide capsules for the predictable loading and release of therapeutic proteins, peptides, or nucleic acids. It was shown that structural studies of swelling of bicontinuous cubic lipid/water phases are essential for overcoming the nanoscale constraints for encapsulation of large therapeutic molecules in multicompartment lipid carriers. The findings were generalized to control the stability and the hydration of the water nanochannels in liquid crystalline lipid capsules to confine therapeutic biomolecules within these structures. It was done by analyzing the influence of amphiphilic and soluble

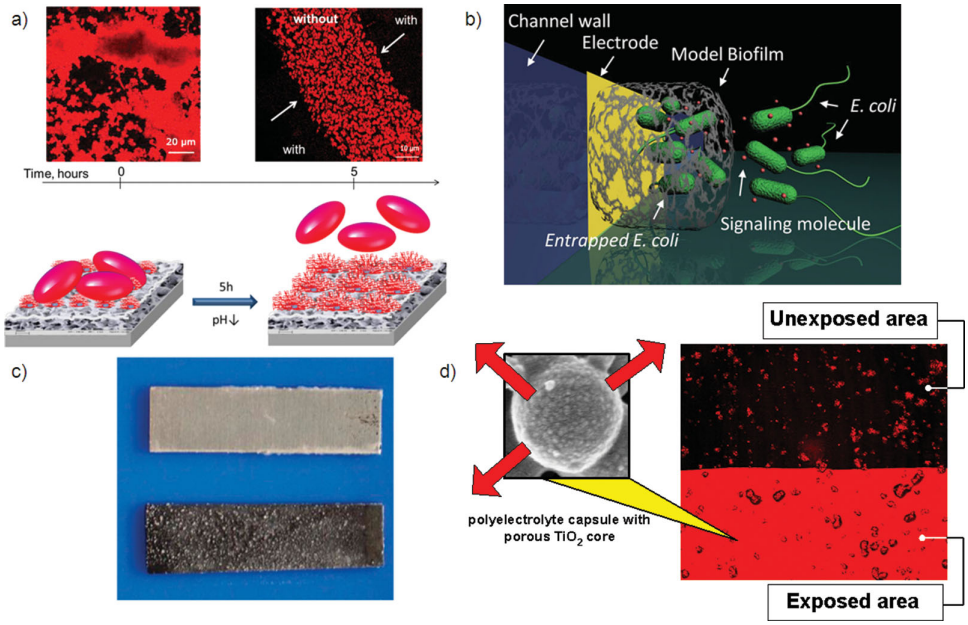

Figure 12. Examples of application of surface encapsulation systems. a) Self-controllable system of biocide coating: confocal kinetic study (fluorescence mode) and schematic illustration of pH triggered self-cleaning behavior of the porous metal surface covered with pH responsive micelles. As model cells *Lactococcus Lactis 411* bacteria (loaded with Rh6G) were used. Bacteria decrease pH, micelles respond to change and increase in size, bacteria detach from the surface. Reproduced with permission.[14d] Copyright 2012, Wiley. b) The functionality of stimuli-responsive polysaccharide alginate is demonstrated by biofabricating 3D cell-gel biocomposites: mimicking the formation of biofilms, for interrogating phenotypes of *E. coli* bacterial populations. Reproduced with permission.[172] Copyright 2012, Wiley. c) Long-term corrosion test: aluminum alloy covered by the LbL hybrid of PE/inhibitor coating (above) and unmodified aluminum plate (below). Reproduced with permission.[124a] Copyrights 2009, Wiley. d) Micrograph of the edge of the laser beam trace at the surface of LbL surface hybrid system which is polyelectrolyte capsules containing titania in silica-zirconia film. The red area corresponds to the release of the Rhodamine 6G from the capsules. Reproduced with permission.[43c] Copyrights 2009, Royal Chemical Society.

additives (e.g., poly(ethylene glycol)monooleate, octyl glucoside, proteins) on the nanochannels' size in a diamond (D)-type bicontinuous cubic phase of the lipid glycerol monooleate. At body temperature, the long-living stability of swollen states, corresponding to a diamond cubic phase with large water channels was shown. With the application of a thermal stimulus, the system becomes progressively more ordered into a double-diamond cubic lattice formed by a bicontinuous lipid membrane. High-resolution freeze-fracture electron microscopy indicates that nanodomains are induced by the inclusion of proteins into nanopockets of the supramolecular cubosomic assemblies. These results contribute to the understanding of the structure and dynamics of functionalized self-assembled lipid nanosystems during stimuli-triggered liquid crystal based capsule phase transformations.

Enzymes, as an external stimulus for inducing capsule switching, can offer unprecedented opportunities for applications including tissue engineering, drug delivery, and biosensors.

7. Conclusion

Over the past several years, significant progress has been made with regards to structural engineering of capsules. Much of this progress has been application driven. Examples of some advanced applications are presented in **Figure 12**. In this review, we have pointed out some important aspects for "smart" surface capsule design of different materials with attention to capsules with various stimuli sensitivities, multifunctionality and -loading capacity. Fabrication of complex encapsulation systems in surface nanostructures combined with control over surface functionality is expected to lead to unique nanostructures and nanodevices with unprecedented functional properties for the next generation devices including the exploration of their application with a focus on the different research area ranging from medicine to material science and electronics. Access to complex structures is achieved by available advanced modern methodologies of synthesis of capsule cores or the following capsule modification with, e.g., polymer grafting, SAM, LbL, sol-gel methodology. Examples of innovative surface modification approaches and their impact on properties of the resulting materials as well as applications enabled by these surface modifications have been highlighted. As one powerful and prospective methodology for both formation of encapsulation systems and the following nanostructuring, the sonochemical approach is highlighted throughout the review. This approach can be effective for the design of various materials: oxides, metals, silicon, polymers, hybrids, etc. It is an instructive example to highlight the importance of cooperation between synthetic chemistry with theoretic modeling to design process regulation and effective use of a powerful methodology for design of various types of effective encapsulation systems.

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