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Release from polyelectrolyte multilayer capsules in solution and on polymeric surfaces

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Release from polyelectrolyte multilayer microcapsules represents one of the most important steps enabling practical use of the microcapsules. A number of biological and non-biological applications are envisaged by proper encapsulation of molecules of interest and their release performance. Since the invention of the microcapsules at the Max-Planck Institute of Colloids and Interfaces in 1998 the work towards microcapsule assistant release has undergone tremendous progress. Almost simultaneously with development of release approaches an extensive base of applications has been advanced. In this progress report the release from the capsules in a solution and those immobilized on the surface of polymeric films is addressed.

1. Introduction

The progress in engineering layer-by-layer (LbL) assembled polyelectrolyte multilayer capsules[1],[2]showed an strong research activities which enabled, on one hand, investigation of underlying principles, which govern molecular and polymeric interactions, while on the other hand spurred many interesting applications, many of which are directed to drug delivery.

The capsules are fabricated by consecutive deposition of positively and negatively charged polyelectrolytes[3]onto liquids, cells or colloidal particles, also referred as templates.[4] Upon dissolution of the template by a suitable solvent, the polymeric shell remains intact, thus producing a hollow capsule. Flexibility of the capsule structural design, a large number of polymers and also organic molecules or inorganic particles used as multilayer constituents stimulated developments in this field. This variety of materials suitable for incorporation into polymeric shells determines a broad range of functionalities and tailor-made characteristics of the shell.

Early research on polyelectrolyte multilayer capsules concerned understanding the properties of polymers comprising the shell, employment of different sacrificial templates, investigation of capsule response to various stimuli and development of drug delivery carriers using the microcapsules.[5]Recent developments in the area of polyelectrolyte multilayer capsules were mainly concentrated on: a) understanding physico-chemical aspects of the capsule fabrication (e.g. an influence of polyelectrolyte charge,[6] an interplay between hydrophilic and hydrophobic interactions, synthesis of the templates) which promoted essential functionalities such as encapsulation and release performance,[7] and b) applying this knowledge for development of a broad range of applications, most notably in the bio-medical area.[8]

In this progress report, we describe the basics of encapsulation and release, and present an update on the recently developed applications. We elaborate on future trends in the area and provide an outlook. Two main trends, which should shape future developments can be clearly identified in this research area. One of these directions concerns in depth elaboration of physico-

chemical principles which would make broader the capsule functionalities. Another trend, which partially depends on novel functionalities, is subsequent development of new applications, particularly bio-medical and drug delivery applications. These applications should stimulate development of not only applied aspects for the capsule use, but also help to understand fundamental principles behind polyelectrolyte self-assembly and release mechanisms. We first briefly describe main principles used for capsule assistant molecule encapsulation and release and then highlight capsules applications including catalysis, drug delivery, theranostics.

2. Diversity of polyelectrolyte multilayer capsules and encapsulation methods

2.1. Capsule assembled based on electrostatic interactions

First and foremost polyelectrolyte multilayer capsules were fabricated using electrostatic interactions between self-assembled polyelectrolytes.[9] Consecutive deposition of oppositely (positively and negatively) charges polymers is applied to assemble multilayer shell. The strength of the interaction as well as multilayer response to chemical stimuli can be controlled by the structure of the used polymers, the state of polymers upon adsorption, their isoelectric point, grafting and charge density.

2.2. Capsule assembled using hydrogen bonding

Hydrogen bonding has been identified as a promising interaction for LbL assembly.[10] Microcapsules made of polymethacrylic acid (PMA) and polyvinylpyrrolidone (PVPON) were made by Sukhishvili and co-authors.[11] Such microcapsules swell at acidic and basic pH and the pH-sensitive loading of dextran and its release was reported.[6] The capsules were also sensitive to changes in ionic strength. Addition of high concentration of salt can be used for promoting the capsule cargo release.

It is important to highlight that adsorption of polycations while building the shells induces the release. It was shown that microcapsules prepared similarly using different poly(carboxylic acids) exhibited different pH thresholds for shell swelling. Recently, Tsukruk and co-workers[12] have prepared tannic acid based multilayer microcapsules through hydrogen bonding with acceptor polymers such as PVPON, poly(N-vinylcaprolactam), and poly(N-isopropylacrylamide). These microcapsules were stable over a wide pH range from 2 to 10 and exhibit pH-sensitive permeability changes to dextran. In addition, gold nano-particles (AuNP) were grown in the tannic acid-containing capsule wall under mild conditions, which suggests the possible use of AuNP as a scaffold for the introduction of proteins or DNA in the capsule through electrostatic or covalent modification.

2.3. Cross-linked and ion cross-linked capsules

Another interesting method to produce polymeric capsules is the crosslinking of hydrogels[13] by metal ions. Both polyelectrolyte multilayer shells[14],[15] and templates[16],[17] can be cross-linked. In the latter case a possibility of using Ca^{2+} ions represents an interesting step because it can be removed by EDTA during the dissolution similarly to dissolving $CaCO_3$ template. Availability of silver nanoparticles is particularly interesting for release application, especially if their distribution can be controlled.[18] Further development was conducted by adsorption of the alginate onto the porous colloids templates followed by jellification with silver ions. After the calcium carbonate dissolution, the stable silver alginate capsules were formed.

2.3. Diversity of capsule shapes tuned by choice of a sacrificial template

2.3.1. Anisotropic shapes

The properties of microcapsules depend also on templates on which they are assembled,[4] while two main types of templates can be distinguished - non-porous templates possessing smooth surface and porous templates. One classical example of such smooth non-porous templates is silica or polystyrene particles. Such templates are often commercially available and possess

good monodispersity and uniform multilayer shell thickness. Due to a complete dissolution of silica templates, microcapsules produced on them are very reproducible.

In the case of porous templates such as calcium carbonate vaterite crystals, the significant advantages includes relatively low cost of production and the possibility to use pores for encapsulation of molecules into the formed capsule. Calcium carbonate particles[19] have been extensively used as easy produced porous sacrificial templates, which were shown to target cancer cells.[20] Release mechanisms based on crystal recrystallization has been elaborated.[21] Recent findings have revealed that the geometry of the templates could affect their uptake into cells by phagocytosis.[22] Attachment of particles to the specific site of cells can be tuned not only via surface chemistry but also by changing the geometry of the particles even at the nanoscale.[23],[24],[25] Thus, future trends in particle assisted drug delivery are seen towards novel methods of synthesis and elaboration of anisotropic particles which in some cases may even resemble such natural entities as bacteria.[26],[27]

The flexibility of polyelectrolytes allows keeping different shapes of the formed multilayer capsules after decomposition of the sacrificial solid templates.[28] Shchepelina *et al* compared morphology, mechanical properties, and permeability of hydrogen-bonded LbL microcapsule shells assembled on square cadmium carbonate against the same shells assembled on spherical silica.[23] The patterned template-assisted assembly of the cubic micro-particles driven by the competing capillary, Coulombic, and van der Waals forces in comparison with the traditional spherical colloidal microparticles had been studied by Lisunova *et al*.[29]

Doxorubicin cubes have been identified as effective carriers of doxorubicin in cells,[30]while cubic shape has been reported to be effective for the interaction of LbL polymeric particles with breast cancer cells.[31] Transformation of capsules of different shapes has been reported by the group of Kharlampieva.[32] Such pH shell shape dependence of was used by Kozlovskaya et al[27] for pH triggered intercellular response and release by the capsules degradability or swelling mechanisms.

Recent developments in the area of design of new sacrificial templates for microcapsules include anisotropic shapes.[33] A set of differently shaped (spherical, elliptical, and squared) $CaCO_3$ particles was synthesized through changing the stirring speed, time, pH value, and salt ratio and the loading capacity of such capsules was studied.[34] These particles were further used for the build-up of polyelectrolyte multilayer capsules loaded with dextran molecules which replicate the initial shape of the $CaCO_3$ templates after their decomposition with EDTA. Template size control[21] as well as their porosity[35] are of high interest for biological applications and stimulates further works towards synthesis of the calcium carbonate templates.

2.3.2. Isotropic shape, anisotropic shell composition – Janus capsules

Janus capsules represent a special class of anisotropic carriers – their shape is uniform, but their shell would have two distinct parts. They have been the subject of extensive research,[36],[37],[38] geared by possibilities of improved targeting and uptake. In the case of Janus capsules, a widely used approach for their fabrication is partial embedding and partial protection of the shell for subsequent modification of the unprotected part of the shell.[36] Using such a protection, Kohler *et al* has demonstrated that the degree of protection or the degree of patchiness can be controlled by adjusting of softness of the polymeric multilayer films working as matrices for trap of capsules to be modified to produce Janus capsules.[39]An innovative method of assembling Janus capsules is based on fusion of capsules, carried out either by salt or temperature.[40] Microcapsules with anisotropic shell composition are best suited for targeting specific cells or even cellular compartments.[41]

2.3.3. Anisotropic shape, Janus capsules – multicompartment anisotropic capsules

Fabrication of Janus capsules was reported by using partial masking in thick, biocompatible, hydrogel-like poly-L-lysine)/hyaluronic acid or (HA/PLL) films.[42],[43] Capsules and particles

with two half-shell patches were demonstrated. Peculiarly, the unprotected part of capsules was modified with smaller capsules creating thus anisotropic, multicompartment, Janus capsules.

2.4 Multicompartmentalization

A carrier which is capable of carrying several molecules in one entity, but in different subcompartments, a multicompartment vehicle, is often sought in the field of drug delivery.[44] An analog with small lipid vesicles has also been reported.[45] Recently, multicompartmentalization has been shown for polymersomes.[46] The capsule analogues of such multicompartment carrier are capsosomes.[47],[48] They represent polyelectrolyte capsules containing structurally intact liposomes with a payload. Poly(styrene sulfonate) (PSS) and poly(allylamine hydrochloride) (PAH) were used for assembling polymeric capsules and 50 nm zwitterionic 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) liposomes were used as a cargo. The advantage of such type of the multicompartments is the stability against chemical degradation allowing repetitive function over an extended period of time. The further assemblies of capsosomes were performed by using biodegradable poly(N-vinyl pyrrolidone) (PVP) and thiol-modified poly(methacrylic acid) (PMASH).[49] They achieved high retention of luciferase and b-lactamase within sub-compartment liposomes during 14 days.

Hierarchy of multicompartment capsules include concentric and pericentric as some of the most widely used carriers. The preparation of pericentric carriers can be achieved when situating multiple subcompartments concentrically around the larger inner core or compartment. Porous calcium carbonate particles is one of good promising examples as sacrificial template material. These particles were used as inner core bearing large (enzyme horseradish peroxidase (HRP)) molecules while small molecules (Amplex Red) have been loaded into liposomes subsequently attached via electrostatic interaction to the $CaCO_3$ particles. First, the inner particle or larger inner core is synthesized. The enzyme-catalyzed reaction was observed during disruption of the outer compartments by ultrasound by confocal microscope.[50] Not only inorganic particles are

useful for the assembly of complex carriers, but also polymer hydrogel microcapsules with tens of 300 nm subcompartments with permeable shell have been demonstrated. By applying chemical stimuli these multicompartments have been degraded in a selective manner.[51] Recent developments in the area of multicompartment microcapsules include functionalization with polymersomes.[52]

3. Encapsulation into and release from microcapsules

3.1. Encapsulation into microcapsules

Encapsulation strategies for loading of molecules of interest into polyelectrolyte multilayer capsules can be very diverse, but this step influences the release from microcapsules. Responsiveness of polyelectrolytes to various stimuli has been one of the main features, which enable control over properties of the capsules and different encapsulation strategies.[8] For example, changing the pH of the solution in which capsules are immersed can lead to protonation/deprotonation of weak polyelectrolytes - this affects the charge balance within the shell and can be used either for shrinking or swelling of the shell, thus changing its permeability and allowing for encapsulation of molecules.[6] Other distinct examples include incorporation of such polyelectrolytes, possessing hydrophobic moieties, as poly(styrene sulfonate) (PSS) or varying the charge compensation through the number of polyelectrolyte layers, which can be used for shrinking or swelling of capsules upon raising the temperature above the glass transition temperature of the polyelectrolyte multilayer complex[7],[53].

A distinct example of the latter approach is synthesis of calcium carbonate templates in the presence of molecules to be encapsulated, the so-called co-synthesis. Encapsulation can be conducted into already prepared capsules or carried out simultaneously with preparation of templates for microcapsules.[54] Advantages of such approach include high loading capacity and relatively fast fabrication of capsules (since molecules to be encapsulated are already

incorporated into the templates during capsule fabrication). Post-loading was also conducted for anticancer doxorubicin,[55] including emulsion templates.[56]

Another approach is based on already synthesized or commercially available templates. In this approach, the polyelectrolyte shell is first built around those templates, which are subsequently dissolved, and molecules to be encapsulated are incorporated afterwards, typically using external stimuli. The thermal and pH encapsulation methods were first developed on commercially available templates[4] (SiO_2, polystyrene, *etc*).

It can be noted that the principles discussed here polymeric microcapsules are also relevant for other nanocarriers.[57]

3.2. Release from polyelectrolyte multilayer capsules in solution

Release mechanisms are closely related to drug delivery applications. Indeed, just as the encapsulation, the release mechanisms are based on physical, chemical, or biological stimuli,[8] as shown in **Figure 1**. This functionality directly depends on molecules, particles or additives incorporated into polyelectrolyte multilayer shell. Approaches of initiating release from capsules depend on the type of external influence or stimulus.

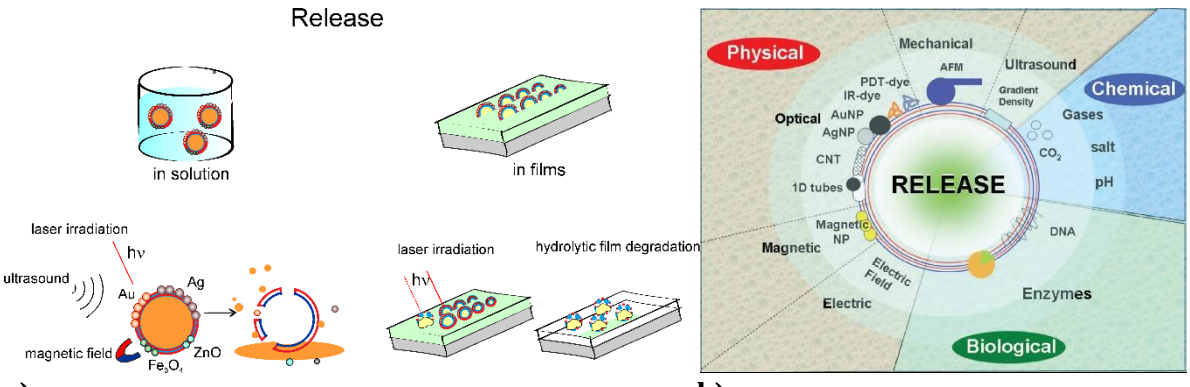

Figure 1. Release from microcapsules: a) in regard with the application point of view: in a solution versus immobilized in films; and b) in regard with mechanisms using physical, chemical, and biological stimuli. Image b) is reproduced from[3] with permission of the Royal Society of Chemistry.

We look further at biological, physical and chemical stimuli[8] for release from microcapsules. Biological stimuli, although often used for targeting, can be also used for release through biodegradability[58],[59] or specific linkage dependence, wherein disulfide linkages, described by the group of Caruso can be degraded intracellularly.[60] In the latter work, HeLa cells were incubated in vitro with PMA_{SH} capsules – capsules based on poly(methacrylic acid) (PMA)-modified with thiol groups (PMA_{SH}). Disulfide bonds were then cleaved, while thioesters remained stable. Using the lipophilic dye DiI (1,10-dioctadecyl-3,3,30,30-tetramethylindocarbocyanine perchlorate) it was found that redox-sensitive PMA_{SH} capsules allowed intracellular release of DiI as evidenced by the distribution of DiI through intracellular hydrophobic domains. The extracellular medium is known to be oxidative, while the cellular cytoplasm is a reductive environment. However, PMLC are commonly internalized in phagosomal compartments that are also oxidative and should therefore not favor decomposition of PMA_{SH} capsules. That reason is that PMA_{SH} capsules did allow release of their payload was attributed to the role of thiols associated with cell surface proteins. This so-called exofacial thiols catalyzed redox-activated release from the capsules and blocked exofacial thiols completely abolished intracellular release, although the capsules were still internalized.

Physical stimuli stand-out for their controllability and non-disruptiveness to the environment. Laser-nanoparticles interaction has been demonstrated as one of the first controllable release approaches. A laser can be easily coupled into a microscope, it can be non-invasive (by appropriate choice of the wavelength, i.e. near-IR for biomedical applications), and offers a high temporal and spatial control over light application to a sample. Polymers comprising the shell of microcapsules do not absorb in the visible and near-IR part of spectrum, so one needs to incorporate such active centers as light absorbing particles[61],[62],[63] or molecules[64],[61],[65]. Incorporating these active centers into the walls of the capsules can be used for controlling release of encapsulation materials or even release only a portion of encapsulated materials[66]

by modulating the permeability of the polymeric membrane. In this case, the modulation of the polymeric membrane took place by raising temperature on metal nanoparticles just slightly over the glass transition temperature of the polyelectrolyte multilayer complex. Peculiarly, a similar modulation on lipid membranes[67] or disruption of the membrane of other types of carriers, red blood cells,[68] was achieved, although the mechanism in that case is different. The role of metal nanoparticles here is to locally generate an increase of temperature by conversion of light energy into heat.[69] Such methods are extensively used for drug delivery because they do not alter the chemical composition of the environment, and, therefore, could be conducted under physiological conditions where changing pH or ionic strength is not a viable option. Advances in the area of release also include site-specific release, where nanoparticles are immobilized onto a specific place of the capsule shell or the laser is directed onto a very specific place even for an uniformly functionalized microcapsule.[70] For all of the above approaches, it is essential to control the concentration of nanoparticles upon adsorption and their distribution.[69],[18]

Ultrasound is an another method of inducing the release. Generally, it is widely used for the synthesis of various nanomaterials, such as coating carbon nanotubes and noble metals and in various biomedical applications: destruction and fragmentation of contrast agents, gas release, polymer destruction, and in drug delivery.[71] But ultrasound was also used for breaking the capsules for releasing of encapsulated materials.[72],[73] Nanoparticles were used here to increase the density of microcapsule shells, and it was found that nanoparticles adsorbed on microcapsules affect the action of ultrasound on their shells.[72] Powers in the range of 100-500 W at frequencies of 20 kHz were applied for capsule destruction. High-frequency ultrasound (1.2 MHz, 0.33 W cm-2) was applied to nanocomposite microcapsule with zinc oxide nanoparticles in polymeric shell and monitored in situ upon exposure of their aqueous suspension to ultrasound. Increasing the sensitivity of microcapsules to ultrasound represents one of the goals in this direction.[74]

Multilayered hollow capsules can also be functionalized with magnetic nanoparticles for release and targeted delivery. Ferromagnetic cobalt nanoparticles containing a layer of gold (Co/Au) were incorporated into the assembly of PSS and PAH polyelectrolyte multilayer shells. Subsequently, application of alternating magnetic fields resulted in increased shell permeability. Lu and co-workers showed that magnetic field affects the permeability of microcapsules by acting on aggregates of nanoparticles.[75] The permeability of the $(PSS/PAH)_4(PSS/Co@Au)_1(PSS/PAH)_6$ capsule for FITC-dextran before applying alternating magnetic fields is negligible; FITC-dextran is blocked from diffusion into the capsules. After applying an alternating electromagnetic field (1200 Oe, 150 Hz) to the capsule/FITC-dextran mixture for 30 min, the capsules became permeable for the dextran. Although the magnetic activation of microcontainers is a good candidate for controlled drug delivery, the long exposure time and the strong magnetic field are required to permeabilize the capsule shell leading to an increase in the temperature which is problematic for application of temperature sensitive biomolecules such as proteins.

Microcapsule rupture and release can also be achieved by disrupting the shell membrane by mechanical deformation. Mechanical properties are fundamentally important because they determine capsule stability and integrity. Design of mechanically stable capsules is of high interest since they are typically deformed upon intracellular uptake,[76],[77] leading to losses in the amount of delivered material. A new method consisting in release upon mechanical deformation of polyelectrolyte multilayer capsules has been developed by combining fluorescence microscopy with AFM force spectroscopy.[78] Such an approach has allowed to measure the details of release upon mechanical deformation and forces exerted by cells upon uptake.[79]

Chemical stimuli (such as pH, salt, solvents) are more often used for encapsulation than release, because they are more disruptive than biological and physical stimuli. Exceptions in this area

include a specific design of the polyelectrolyte multilayer shell to induce the release, for example, “click” chemistry.[80]

3.3. Release from polyelectrolyte multilayer capsules immobilized onto polymeric surfaces

Polyelectrolyte multilayer capsules in a solution target a variety of applications where particles or capsules can be used as carriers. Here we look at microcapsules immobilized onto polymeric films, where a different sort of application is targeted. The films themselves can be used as reservoirs of drugs, which can be subsequently delivered from the films.[81],[82],[83],[84] Enzyme encapsulation can be also performed with films.[85] Release of plasmid DNA from intravascular stents has been shown as an interesting application,[86] while controllable release directly from the surface of films by laser light has been identified as a potential trend-setting development.[87],[88] Hydrolytic degradation of films can be used as another mechanism promoting release from the polymeric films.[89] Release from phospholipid polymer and poly(vinyl alcohol) hydrogels connected by reversible covalent bonding on titanium demonstrates the versatility of surfaces as drug delivery reservoirs,[90] while polyarginine /hyaluronic acid films[91] exhibit antibacterial properties.[92]

Cell-surface interaction and delivery of biomolecules from the capsules into cells from the surfaces is also of high interest for extracellular delivery. In this case, microcapsules are immobilized or embedded on the surface of films, on which cells are subsequently grown. LbL films are good candidates in regard with the films, but it is the so-called exponentially grown films that play an important role here.

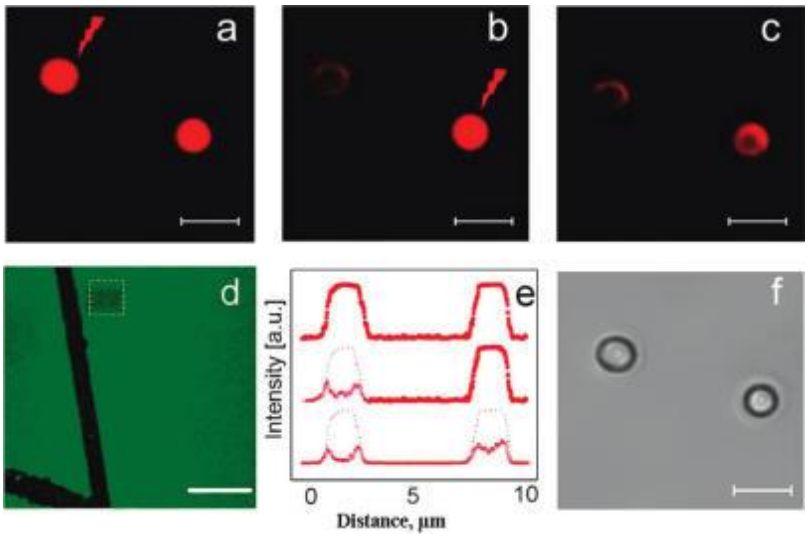

Figure 2. Adsorption of microcapsules onto the (PLL/HA)24/PLL films. (a-c) CLSM images of the capsules exposed to near-IR light irradiation. (d) CLSM image of the film surface (the film is prepared with PLL-FITC; black lines are scratches made by a needle for easier film imaging). (e) Cross-sectional profile of the capsules after step-by-step laser exposure (the sections from top to bottom correspond to the images a-c, respectively). The scale bar in parts a-c and f is 4 μm. (f) TEM images of the capsules after light irradiation. The scale bar in part d is 25 μm. Reproduced with permission from[93] the American Chemical Society.

The exponentially built multilayer films[94] are assembled into very thick (the thickness is on the order of micrometres), compared to normal LbL films (typically the thickness is on the order of nanometers). These thick LbL films allow immobilization of the microcapsules, which, once immobilized onto the surface of films, can release their cargo by the laser acting on nanoparticles in the shells of capsules.[93] One such example is shown in **Figure 2**, where the red channel (top row, red channel) shows sequential release of one capsule and then another capsule, Figure 2 (a-c). The surface of the films can be clearly seen in the green channel, Figure 2d, where two black lines are drawn for identification purposes. The red microcapsules are located in a slightly bleached area (white zoomed-in area). Further, we discuss various biomedical applications of microcapsules.[95]

4. Bio-medical and drug delivery applications

4.1.Intracellular delivery

Microcapsule delivery into living cells has seen early interest and underwent significant developments.[96] Microcapsules were shown to be effectively uptaken by cells. Subsequent studies reported intracellular delivery and controlled release inside cancer cells[97] as well as release through biodegradation. Fundamental processes relevant to immunology have been also investigated during the course of cell experiments. In such studies, microcapsules possessing light absorbing nanoparticles in their shells were incorporated inside living cells. Subsequent controlled release of encapsulated peptides led to peptide-MHC Class I protein complex formation and eventual surface presentation of such a complex at the cell surface.[98] That essentially confirmed a fundamental question of immunology – the surface presentation of small peptides – in an experiment, which allowed to measure the time scale of the surface presentation of peptides and mechanisms of its intracellular transport. Recently, release of anticancer agents, proteins and nucleic acids (mRNA), where plasmonic nanoparticles were used for remote release, was investigated.[99] Further application of this technique was conducted in regard with release of active enzymes.[100]

4.2.Moving the cargo on the surfaces

Efforts have been made to exploit microcapsules for the active transport of cargo, which is relevant for release around and functionalization of surfaces.[101] Special attention is paid to self-regulated and autonomous motion. For this purpose, the integration of chloroplastic ATPase into the microcapsule wall containing of a lipid bilayer has been demonstrated. This was used for the synthesis of ATP by such composite capsule. The driving force for ATP synthesis, catalyzed by ATPase, was provided by an acid–base transition between the interiors and exteriors of the capsules. Later on ATPase was also integrated into lipid-coated hemoglobin or glucose oxidase capsules. ATP could be synthesized in the protein microcapsules by utilizing proton gradients, which were produced from oxidation and hydrolysis of the glucose. This was catalyzed either by the added or immobilized glucose oxidase (GOD). The most recent advance

reported by the same group is the construction of a dynamic biomimetic system by bringing kinesin coated microcapsules close to microtubules. The multilayer capsules which can drive cargos such as vesicles, proteins, and organelles were functionalized with kinesin molecules and were put along microtubules. The microtubules act as tracks for the kinesins coated capsules and guide them to move directionally (**Figure 3**). Both hollow and filled capsules are transported by kinesin motors along microtubules. Further, the microcapsules were attached to microtubules through biotin–avidin interaction, which also act as a transport shuttle of the attached microcapsules.[102] These approaches provide a great promise to design complex self-regulated nanodevices by using biological motors for mimicking efficient intracellular transport.

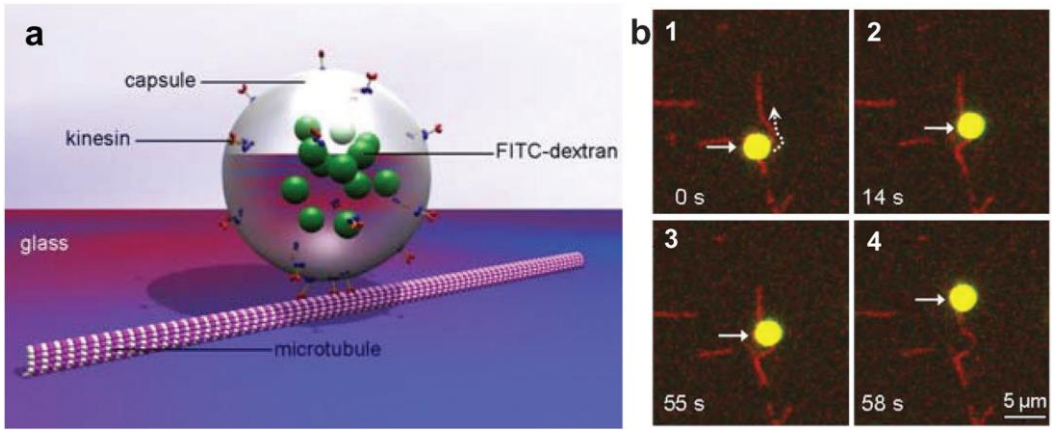

Figure 3. a) Schematic illustration of a multilayer capsule as a cargo driven by kinesin motors along a microtubule. (b) Time-lapse images of a capsule, coated with kinesin molecules, moving along a microtubule. Adapted with permission from ref.[102] Copyright 2009, Elsevier.

4.3. Biomimetic, biochemical and mechanical sensors

Although the size of microcapsules can vary in a broad range, most of the capsules have been made with diameters around several micrometers. That falls in the same size range as, for example, red blood cells (~ about 7 µm), and one might assume that the microcapsules would deform similarly to red blood cells. In-vitro experiment can be designed to investigate such deformability, where capsules encounter similar obstacles of passing through the blood

capillary vessel as the RBCs do, if they similarly circulate in the blood stream. Therefore, their deformability and recovery after passing through a thin capillary channel is of practical importance and highly demanded . Another biomimetic application has been shown to construct capsule-in-capsule assembly, which could resemble artificial cells.[103]

Biochemical sensing has been first shown by means of the example of monitoring intracellular pH. This approach was implemented through encapsulation of pH sensitive polymer inside capsules and incorporating such capsules inside living cells.[104] Fluorescence read-out has facilitated the signal recording. A next step in the area of biochemical sensing was taken in the direction of determining the concentration of oxygen in water.[105]

Mechanical sensing using microcapsules was demonstrated recently by measuring mechanical properties of microcapsules by colloidal probe AFM and subsequent correlation of these data to those obtained upon uptake of microcapsules. These studies revealed that upon uptake cells exert forces on the order of 0.2 μN. Mechanical properties can be also controlled by cross-comparison of microcapsules with red blood cells – some experiments were done by squeezing the microcapsules through a microfluidic channel.[106]

Enhancement of mechanical properties is a very relevant aspect, because early study revealed that microcapsules without chemical reinforcement of their walls cannot deliver encapsulated cargo. Additional layers can be used for enhancement of mechanical properties[107] and for tuning the release,[108] while organic molecules deposited in the polyelectrolyte multilayer shell can be used for inducing chemical cross-linking. It was reported that metal nanoparticles provide additional links between polymers and thus enhance mechanical properties.[109] This enhancement is concentration dependent and can be tuned by choosing an appropriate density of nanoparticle coverage. Carbon nanotubes can be used as an alternative for enhancement of mechanical properties upon deposition onto polyelectrolyte multilayers.[110]

4.4. Delivery relevant for gene therapy

A range of important applications stems from delivery of oligonucleotides as well as other biologically relevant molecules, such as DNA, siRNA. One particular area that could be singled out here is gene therapy, where the main goal is to introduce and replace genes. DNA itself could be either used as a building block of the capsule shell or as material to be delivered.

As an alternative to the use of electrostatic interactions, the Caruso group has elaborated on the use of hydrogen bonding to incorporate oligonucleotides either inside or in the wall of polyelectrolyte capsules.[111] In another study, oligonucleotides accumulated in the pores of amine modified mesoporous silica microspheres due to electrostatic interactions. Subsequent multilayer build-up of hydrogen bonded PMA and PVPON followed by etching of the silica core templates and yielded hollow capsules with stably encapsulated oligonucleotides.[60] In addition, DNA hybridization based on hydrogen bonding between homopolymeric oligonucleotide blocks has been explored to construct multilayered capsules. In spite of the feasibility to incorporate nucleic acid based biomacromolecules into polyelectrolyte capsules or to use them as wall constituent, there are only few reports of functional biological experiments showing polyelectrolyte capsule mediated gene delivery. Selina *et al* reported on the in-vivo use of a swine fever DNA vaccine by incorporating plasmid DNA into degradable biopolymer based dextran sulfate/carrageenan capsules.[112] Parak and co-workers demonstrated release from lysosomes by proton sponge effect.[113]

4.5. In-vivo drug delivery

Real experiments with animals represent yet another venue of extensive range of application of multilayer capsules. Up until now, most studies concerned targeting tissue or cell without circulation. Microcapsules were shown to promote treatment of colorectal cancer.[114],[115] The biomimetic polymeric microcapsules with the immunosuppressive and tumor-recognition functionalities of natural leukocytes have been developed for the improving the accumulation

of capsules in tumor site through the molecular recognition of membrane-bounded proteins of CLMVs in vitro and in vivo.[116] In-vivo studies represent an essential functionality,[117] so it is envisioned that more research will be conducted in this area in the nearest future.

4.6. Theranostics

Theranostics is an emerging and rapidly growing area, which deals with developing strategies for detecting or monitoring and simultaneously treating diseases. In the context of drug delivery and application of polyelectrolyte multilayer capsules, this can be achieved using multicompartment carriers. The most relevant functionality here is to be able to encapsulate sensing molecules in some compartments, and medicine necessary for treatment into other compartments.[118] If the molecules are small enough, then this molecule can freely diffuse through the polymeric shell of capsules. On the other hand, if the sensor molecule is sufficiently large, then small ions and salts can freely diffuse through the shell providing means for diagnostics. In either case, molecules necessary for treatment of diseases will need to be released, which can be achieved by methods described above. Another strategy of using microcapsules for theranostics is to explore a polymeric shell as an interrogating surface, for instance in surface enhanced Raman sensing (SERS)[119],[120] and photoacoustic imaging.[121] In SERS approach, molecules either are physically/chemically interacting with plasmonic shell of microcapsules or stand close (few nanometers) to the surface, thus molecules can be spectroscopically recognized both in liquids and in the living cells.[99-102] Photoacoustic imaging of microcapsules is expected to contribute to non-invasive carrier visualization for delivery of molecules with *in vivo* distribution as well as specific treatment for the release of a payload.

4.7 Corrosion protection

Another application where release prominently stands out is the corrosion protection. Here polyelectrolyte multilayer capsules were used to on-demand release of anticorrosion protective

agents.[122] Control over the release from microcapsules was achieved by laser light, making the microcapsules as a complementary release vehicles in comparison to halloysite clay nanotubes proposed by Lvov *et al*[123], silica containers,[124] and other polyelectrolyte based assemblies.[125]

4.8 Outlook

Microcapsules exhibit a high potential for interesting applications due to flexibility of their construction, diversity of functionalization with nanoparticles and molecules, and availability of a variety of forms, shapes and multicompartmentalized structures. Different methods have been developed for encapsulation and release – providing a platform for using microcapsules. Looking in future, additional encapsulation methods would always be useful providing desired loading of capsules. Release methods are particularly essential because they bring necessary control over availability of delivered molecules. Further extension of the range of techniques available for release as well as adjusting their parameters to suit for essential applications will certainly find their applications, and should spur further research activities.

5. Conclusion

In conclusion, polyelectrolyte multilayer capsules have seen a wave of extensive developments and increased interest in the past decade. That led to identification of physico-chemical principles underlying the interaction of polyelectrolytes in the shell. This review presents release methods from polyelectrolyte multilayer capsules including relevant encapsulation as essential features of the capsules. Subsequently, recent advances, particularly relevant for drug delivery, are presented. A large number of interesting applications has been demonstrated including catalysis, drug delivery, intracellular delivery, light-induced release. Some of these studies provided important applications of capsules in bio-medicine and drug delivery, while others aim to help investigating important key processes relevant to biology. It is expected that these applications will grow in numbers, thus contributing to understanding fundamental

aspects in biology, chemistry, and physics. The area of drug delivery without doubts stands to benefit from these developments.

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Andre Skirtach received MSc degree from Moscow State University of Lomonosov, Russia, and PhD degree from McGill University, Canada. Subsequently, he joined the National Research Council of Canada (NRC) in Ottawa. In 2000, Dr. Skirtach and colleagues were involved in establishing a prominent startup— Trillium Phot., Inc. He then moved to the Max-Planck Institute of Colloids and Interfaces, Golm, Germany, where he worked as a Group Leader. His scientific research interests include nanotechnology and nanobiotechnology, nanoparticles and their interactions, polymeric capsules and planar interfaces, self-assembly and its applications. Since 2011, Dr. Skirtach has joined the University of Ghent, Belgium.

The table of contents entry should be 50–60 words long, and the first phrase should be bold.

Progress report in molecular release from polyelectrolyte multilayer capsules addresses current achievements in encapsulation and release into/from the capsules. Multiple stimuli used for encapsulation and release are discussed. Subsequently, a number of applications such as drug delivery, catalysis, intracellular delivery are highlighted where the release and encapsulation are particularly important.

Keywords: polyelectrolyte multilayer capsules, release, laser, nanoparticles

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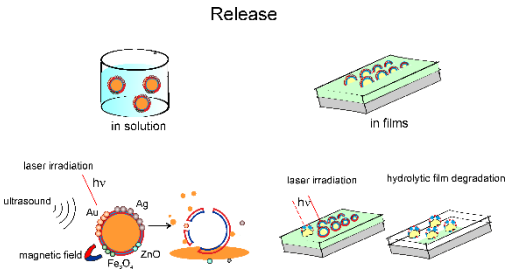
Release from polyelectrolyte multilayer capsules in a solution and on polymeric surfaces



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