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The pros and cons of polyelectrolyte capsules in drug delivery

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Polyelectrolyte multilayer microcapsules and nanocapsules are under review as multifunctional delivery systems. Tailoring functions in the entity of a single capsule is done by incorporation of functional polyelectrolytes or nanoparticles in between the layers during electrostatic self-assembly. The resulting capsules possess different properties such as controlled and triggered release, responsiveness to temperature, pH and light and could be navigated with a magnetic field. A variety of substances can be encapsulated and delivered to cells and tissues. Potential applications as well as in vivo experiments have recently been explored. Capsules made of biodegradable polymers showed low toxicity in vivo. Perspectives on and obstacles to a way of broader application are discussed.

Keywords: colloids, controlled release, encapsulation, layer-by-layer, nanoparticles

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1. Introduction

Since their advent in the later 1990s, polyelectrolyte capsules have undergone a remarkable evolution from study objects in a physicochemical context to promising drug delivery carriers [1-4]. Polyelectrolyte microcapsules are synthesized by layer-by-layer (LbL) [5-8] coating of a sacrificial template of size ranging from 0.1 to 10 µm [9,10], eventually followed by the dissolution of this template, resulting in a hollow capsule surrounded by a polyelectrolyte multilayer membrane [11,12]. **Figure 1** represents this procedure schematically. Generally speaking, these microcapsules are permeable for low-molecular-mass substances but impermeable for macromolecules [13]; however, numerous exceptions to this rule exist. For drug delivery purposes it is trivial that the capsules are filled with biologically active substances. The most obvious route is direct coating of the drug substance itself, leading to drug particles covered by a polyelectrolyte membrane [14]. Capsules filled with soluble macromolecules were initially developed using a post-loading procedure [15]. Therefore, the capsule membrane was reversibly permeabilized by shifting the pH [15-19] or changing the solvent polarity [20], allowing the inward diffusion of macromolecular drugs. Next, the capsule membrane was closed and the macromolecules remained trapped. Another approach involves the use of porous inorganic templates that are preloaded with the macromolecular drug substances of interest before being coated with polyelectrolytes [21-29]. Dissolution of the template yielding low-molecular-mass ions results in hollow capsules filled with the macromolecules of interest, as ions can freely diffuse through the multilayer membrane but the macromolecular drugs remain entrapped.

In this paper, recent contributions made in the field of drug delivery applications of polyelectrolyte capsules are reviewed. Further, in the Expert opinion section, it is discussed whether these capsules hold potential and which future directions could be taken to reach the stage of clinical applications.

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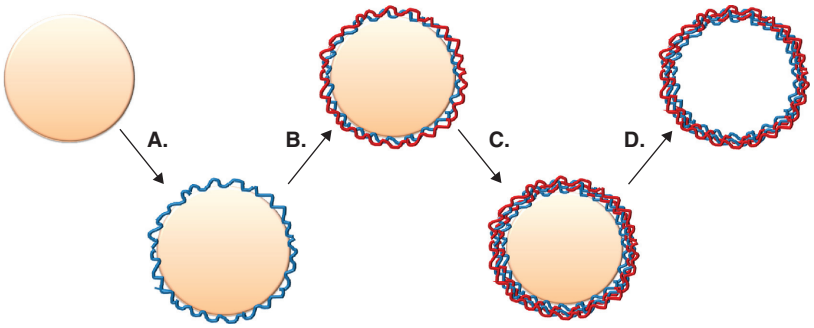

Figure 1. Schematic representation of the synthesis of polyelectrolyte capsules. A. In a first step a charged colloidal template is covered with a polyelectrolyte layer of an opposite charge using electrostatics as the driving force. **B.** In a second step the non-adsorbed polyelectrolytes are removed and a second polyelectrolyte layer with charge opposite to the first one in adsorbed. **C.** In the following steps these first two steps are repeated until the desired number of layers is deposited. **D.** In a final step the colloidal template can be dissolved and a hollow capsule remains.

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2. Encapsulation of drug crystals

Several groups have used layer-by-layer coating to modify the surface of drug crystals. Crystals of water-soluble drugs were suspended at a pH where they were no longer water-soluble and subsequently coated with several polyelectrolyte layers. The basic study on this issue was performed by Antipov et al. by coating fluorescein crystals, as the model drug, with polyelectrolyte bilayers composed of polyallylamine hydrochloride (PAH) and polystyrene sulfonate (PSS) [18]. Fluorescein was obtained in particulate form by precipitation in acidic (i.e., pH 2) medium followed by performing all the process steps at the same pH. On incubation of the LbL-coated crystals in aqueous medium at pH 8 the fluorescein solubilized, leading to an increase in fluorescence resulting from dequenching. It was observed that the dissolution profile of the dye could be modified towards longer release rates by increasing the number of polyelectrolyte layers. Following this study others have described the LbL coating of ibuprofen, insulin, vitamin K3, biotin and naproxen crystals using biodegradable polyelectrolytes as coating materials [30-34]. All these reports indicated that the presence of a polyelectrolyte coating decreases the drug release rate, resulting in a prolonged release time. This is illustrated by **Figure 2A – C**, which shows the dissolution of ibuprofen crystals coated with 15 bilayers of chitosan/dextran sulfate, yielding hollow capsules that released their payload. The corresponding drug release curves at pH 7.4 (the pH of the extracellular tissue, which is mostly encountered after parenteral injection) and pH 1.4 (the pH in the human stomach) are shown in **Figure 2D**, E.

3. Stimuli responsive release

For structures bonded through electrostatics, pH is an evident trigger to cause structural alterations [17,19]. When polyelectrolyte capsules are placed in a medium with a pH close to the apparent pK_a of one of the polyelectrolytes, the charge density of that polyelectrolyte is lowered and the multilayers loosen their intermolecular binding [35]. This leads to permeabilization of the membrane and further membrane decomposition when the repulsive forces between like-charged polyelectrolytes are no longer compensated by the attraction force of the oppositely charged polyelectrolytes. **Figure 3** illustrates this phenomenon schematically. However, although very straightforward from the conceptual point of view, it is less obvious to apply such pH triggered release under physiological conditions. The most well-known pH shift occurring in the human body is the acidification that takes place in the gastrointestinal tract [36]. However, many other less complex drug delivery systems have been developed to release their payload in this region of the body after oral administration. A second field of application is that of intracellular drug delivery. On phagocytosis, capsules end up in phagosomal/endosomal/lysosomal compartments that are known to have a slightly acid pH [37]. This was demonstrated recently by Parak and co-workers using dye-coupled-dextran loaded capsules [38]. It is a pH-sensitive dye emitting red fluorescence at basic pH and green fluorescence at acidic pH. The relative ratios of red and green fluorescence allowed determination of the pH of the capsules' intracellular environment as 5.2. Taking this into consideration, it would potentially be interesting to develop capsules that decompose on transition of the extracellular pH of 7.4 to the intracellular pH of 5.2. However, such capsules have not yet been reported and it is not that straightforward to predict the apparent pK_a of polyelectrolytes within a multilayer structure [35].

Besides a drop in pH in the cellular phagosomal/endosomal/lysosomal compartments, there is also a shift to a more reductive environment compared with the extracellular space [39]. This phenomenon was exploited by Haynie and co-workers to develop disulfide-stabilized polyelectrolyte capsules that could be decomposed by disulfide reduction [40,41]. Peptides containing thiol-bearing cystein moieties were synthesized and multilayers were constructed by

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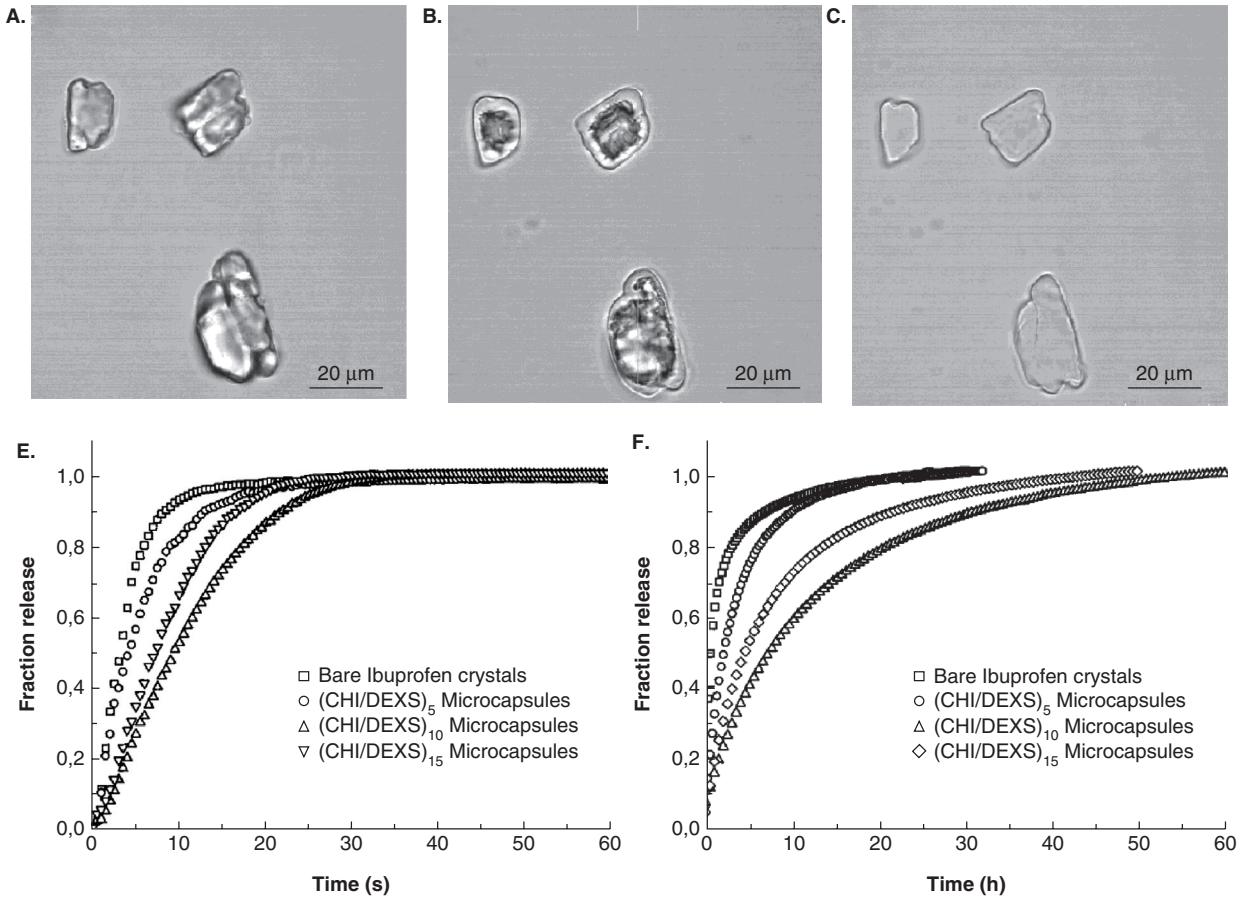

Figure 2. Transmission CLSM images of the drug release process from the $(CHI/DEXS)_{15}$ microcapsules. A. Morphologies of ibuprofen microcrystal before dissolution. **B.** Images of ibuprofen microcrystal in dissolution. **C.** Images of polysaccharide capsules after removal of the crystal cores. The mean size of the encapsulated ibuprofen microcrystals is 15.3 µm. Release profiles of ibuprofen from (CHI/DEXS) microcapsules with 0, 10, 20 and 30 polysaccharide layers at (**D**) pH 7.4 and (**E**) pH 1.4.

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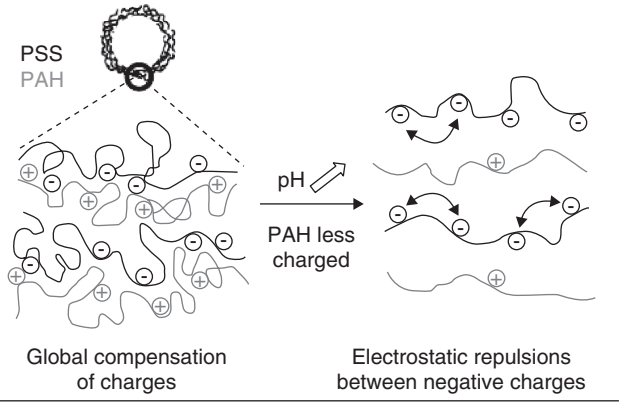

Figure 3. Swelling of the capsule in basic conditions owing to electrostatic repulsion between negative charges of PSS.

Adapted from Sukhorukov GB, Antipov AA, Voigt A, *et al.* pH-controlled macromolecule encapsulation in and release from polyelectrolyte multilayer nanocapsules. Macromol Rapid Commun 2001;22(1):44-6 [15].

PAH: polyallylamine hydrochloride; PSS: polystyrene sulfonate.

electrostatic interaction between peptides with an opposite net charge followed by an oxidative step to stabilize the multilayer by disulfide crosslinking. The pH of the multilayer build-up was chosen in such a way that the respective peptides carried an opposite net charge at that pH value, allowing multilayer build-up. However, at physiological pH (i.e., pH 7.4) the capsules were no longer stable unless they were crosslinked through oxidative disulfide formation of the thiol moieties. Further, the authors showed that on incubation of the capsules with a reducing agent (such as DTT or glutathione), the disulfide crosslinked capsules decomposed. This system was shown only in a so-called test tube situation, and no in vitro cellular experiments have been reported yet. Also, Zelikin *et al.* have explored the potential of disulfide-stabilized multilayers for intracellular delivery [42-45]. For this purpose they focused on capsules constructed from hydrogen-bonded layers instead of using electrostatic interactions [46]. At low pH polymethacrylic acid

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and polyvinylpyrolidone form hydrogen bonds, whereas at physiological pH they disassemble owing to the repulsive forces between the carboxylic acid groups of the polymethacrylic acid, which become charged at that pH. Similar to the Haynie approach, the multilayers were stabilized by the introduction of disulfide bonds using polymethacrylic acid modified with thiol groups through amide bond formation between cystein and the carboxylic acid groups of the polymethacrylic acid.

Besides drug release when a desired target in the body is reached, also drug release when a certain metabolite passes a critical level can be of interest. This is, for example, the case of diabetes mellitus, where elevated glucose levels in the blood are treated by administration of insulin. Glucose-responsive capsules were reported separately by De Geest et al. [47] and Levy et al. [48], making use of the glucose binding capacity of phenylboronic acid. Phenylboronic acid forms under slightly acid conditions, forming a covalent bond with vicinal diols such as glucose, leading to a shift in pK_a of the complex with approximately one unit [49]. A co-polymer containing both ternary amine groups and phenylboronic acid groups would thus lower its net charge in the presence of glucose. Such a co-polymer was synthesized by De Geest et al. and used as polycation in combination with polystyrene sulfonate for the fabrication of polyelectrolyte capsules. On addition of glucose, the charge balance within the multilayers became disturbed through a combination of intramolecular attraction forces between anionic boronic acid moieties and cationic amines, respectively, and intermolecular repulsion forces between anionic boronic acids and sulfonate moieties. These phenomena induced the disassembly of the polyelectrolyte capsules. The approach presented by Levy et al. was based on higher affinity of glucose for phenylboronic acid compared with mannan. Multilayers based on boronic ester formation of phenylboronic acid-substituted polyacrylic acid and mannan were deposited on a sacrificial template followed by decomposition of the template. The resulting hollow capsules appeared to be stable. However, in the presence of glucose, mannan is replaced by glucose, resulting in the decomposition of the capsules as glucose was no longer able to stabilize the multilayers.

For several applications, such as, for example, vaccination, it can be of interest to deliver therapeutic molecules after a certain incubation time with no or triggered-only slow release [50-53]. This leads to the concept of exploding capsules. Two types of exploding capsule have been reported so far. One type consists of polyelectrolyte capsules doped with infrared (IR) dyes [54] or metal nanoparticles [54-59], which render them susceptible to remote activation. Remote activation by a physical source, such as laser light [39,54-61], magnetic fields [62] or ultrasound [63,64], is an attractive approach in drug delivery as it allows a non-invasive opening of the capsules at a desired time point or when a specific target site is reached. A major parameter with respect to this concept is the penetration depth of the applied physical force. Although radio frequency and magnetic force fields can reach deep into the body, the research groups of Sukhorukov [54] and Caruso [55] have reported on remote IR laser activation of polyelectrolyte capsules. Therefore, the capsule wall was doped with an IR dye or metal (i.e., silver or gold) nanoparticles. On irradiation with an IR laser, the capsule shell is locally heated, resulting in capsule explosion and leading to the release of the encapsulated compounds. Recently, this concept of photoactivated release has also been applied for intracellular release. Initially Skirtach et al. demonstrated that on cellular uptake capsules could still be opened by IR laser irradiation without impairing the cell viability [57]. Further, Muñoz-Javier et al. assessed the fate of the released compounds [65]. As shown, ultrasound is more limited and IR laser light can only penetrate as deep as 1 cm. **Figure 4** demonstrates that opening of the capsules at high laser power leads to cell death, whereas opening of the capsules at low laser power leads to release of the capsules' payload into the cell cytosol, without causing cell death.

The second type of exploding capsule is the so-called self-exploding capsule developed by De Geest et al. [66-78]. These capsules consist of a degradable microgel core surrounded by a semipermeable membrane. When the microgel core degrades the swelling pressure increases and at a certain moment when the swelling pressure exceeds the tensile strength of the membrane the capsule explodes and the encapsulated content is released. **Figure 5** shows a series of confocal microscopy snapshots during the degradation of the microgel core. The degradation rate of the microgels is governed by the crosslink density of the microgels, which thus offers a tool for varying the capsules' time of explosion. The most straightforward application of these capsules is single shot vaccination where an injection of several populations of microcapsules, each exploding after a different time point, would lead to several antigen pulses, which could replace the booster injections that are often required to generate adequate immunity.

4. Capsule biocompatibility and degradation

For the purpose of drug delivery, biocompatibility and often biodegradability are mandatory. Once in contact with body tissues, polyelectrolyte capsules should be taken up by cells and degraded intracellularly or should degrade and release their content into the extracellular space. Enzymatic degradation and chemical hydrolysis of planar polyelectrolyte multilayers were pioneered, respectively, by Picart et al. (polypeptide and polysaccharide-based multilayers) [79] and Lynn and co-workers (multilayers based on ester containing polycations and polyanions) [80-88]. Degradable capsules were developed by De Geest et al. [89]. Poly-l-arginine and dextran sulfate were alternately deposited on calcium carbonate microparticles followed by the dissolution of the calcium carbonate in an EDTA solution. **Figure 6** shows a series of confocal microscopy snapshots of the

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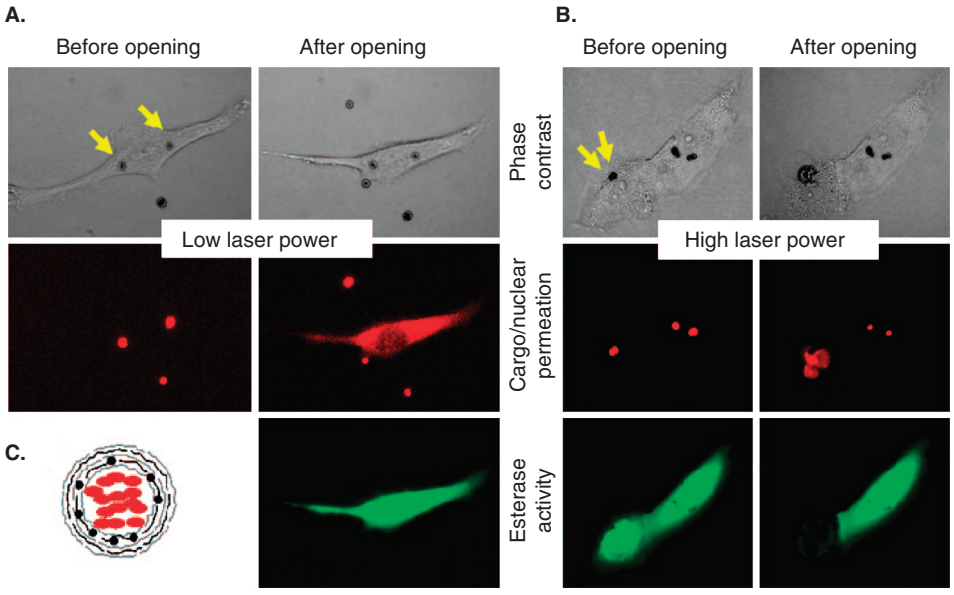

Figure 4. Cargo release and viability/cytotoxicity experiments with capsules filled with red Alexa Fluor 594 dextran as cargo and AuS2 particles embedded in their walls. Capsules were illuminated with (**A**) low laser power (2.3 mW), the minimum power needed to open the capsules, and (**B**) high laser power (31 mW), the maximum power output reachable with the laser diode used in these experiments. Phase contrast images show cells that have incorporated capsules (yellow arrows) before and after laser illumination. Red fluorescence images show the cargo release and the nuclear permeation (Ethd-1) in cases where capsules trapped in cells were excited with low laser power and high laser power, respectively. In the case of high power illumination, permeation of the cell membrane leads to loss of fluorescent cargo by diffusion out of the cell. Green fluorescence images indicate decrease of esterase activity in cells where capsules were excited with high and low laser power, respectively. **C.** Sketch of the geometry of capsules with Alexa Fluor 594 dextran (red ellipsoids) in their cavity and AuS2 particles (black circles) embedded in their walls.

Reprinted with permission from Muñoz-Javier A, Del Pino P, Bedard MF, *et al*. Photoactivated release of cargo from the cavity of polyelectrolyte capsules to the cytosol of cells. Langmuir 2008;24:12517-20 [65]. Copyright 2009 American Chemical Society.

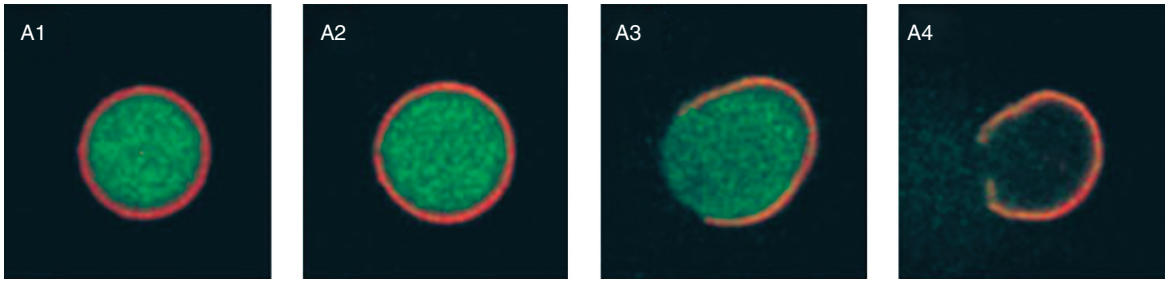

Figure 5. Confocal microscopy snapshots of self-exploding capsules during degradation of the microgel core. The microgel core is green fluorescently labeled whereas the polyelectrolyte membrane is labeled with a red fluorescent dye.

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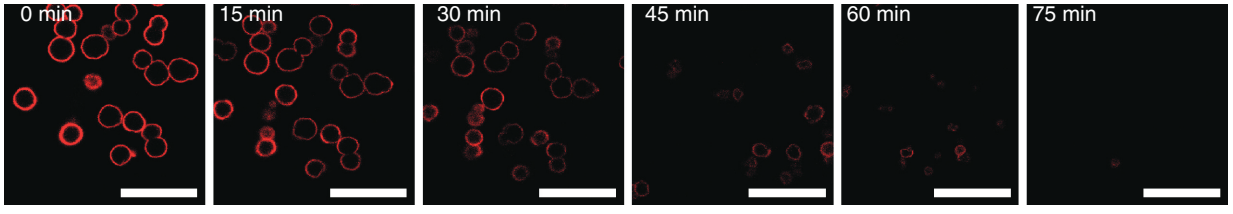

Figure 6. Confocal microscopy snapshots taken during the enzymatic degradation of biopolymer polyelectrolyte capsules in the presence of pronase, incubated at physiological conditions. The scale bar represents 10 μm.

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microcapsules incubated in a pronase solution at 37°C. Pronase is a mixture of enzymes able to quasi-cleave every peptide bond. As a function of time, the capsules slightly shrink, crumple and disassemble. Similar observations were reported by Borodina et al. using poly-l-arginine and poly-l-aspartic acid-based capsules templated on calcium carbonate microparticles containing both DNA (as model drug) and pronase, which digested the capsules from their interior [90]. Cellular uptake of polyelectrolyte capsules was first demonstrated by Sukhorukov *et al.* using a cancer cell line [91] followed by a thorough study of capsule phagocytosis by the Parak group [92-97]. These studies were performed using non-degradable capsules and aimed to gather fundamental insight into the kinetics and processing of the capsules. *In vitro* intracellular degradation was demonstrated further by De Geest *et al.* [89] by incubating biopolyelectrolyte capsules with VERO cells. On cellular uptake the capsules deform and become digested over several days.

The in vivo behavior of these capsules was assessed by the same group, injecting them subcutaneously in mice followed by dissection of the injection place at several time points [98]. Hematoxylin and eosin stainings of paraffin sections taken from the injection spot allowed the fate of the whole injected capsule population to be monitored. The injected mass behaved as a porous implant in which phagocyting cells gradually migrated as a function of time. The first day after injection, cells are attracted to the periphery of the injection spot, while after several days the whole spot becomes infiltrated with cells, which start to take up and degrade the capsules. The fate of the individual capsules was followed using capsules with a fluorescently labeled membrane as shown in **Figure** 7. Two days after injection some cells (visualized by DAPI (blue fluorescence) staining of the cell nuclei) have infiltrated the injected capsules and this infiltration continues further, as observed on the tissue section representing day 8. At both of these time points the cells appear to be scattered through the capsule mass without having taken up capsules. However, at 16 and 30 days after injection, the tissue sections clearly demonstrate capsule uptake and 30 days after injection intact capsules can no longer be distinguished as only capsule debris is visible within the infiltrated cells. Generally speaking, a moderate immune reaction was observed, including an acute phase comprising the recruitment of polymorphonuclear cells followed by a more chronic phase during which the capsules become phagocyted and degraded along with the appearance of fibroblasts, which start to surround the injection site.

5. DNA encapsulation and release

For the purpose of gene therapy where one aims to replace or repair defect genes, DNA has to be delivered intracellularly to the nuclei of living cells [51,99-102]. As several groups have already demonstrated that polyelectrolyte capsules are taken up very efficiently by cells both *in vitro* and *in vivo*, gene therapy can indeed be envisioned as a potential field of application for polyelectrolyte capsules. Several papers during the past year have dealt with the encapsulation of DNA in polyelectrolyte capsules. Owing to its polyionic nature, DNA is a naturally occurring polyelectrolyte and can be used as polyanion in LbL assemblies as pioneered by Sukhorukov and co-workers in the mid-1990s [103-105]. Schüler and Caruso incorporated DNA within the capsule membrane, using it as a polyanion in conjunction with spermidine, an oligoamine able to condense DNA [106]. Owing to the molecularly short interaction length of the respective polyelectrolytes, the multilayer construct showed very low stability in salt solution, which would probably impair their use in a physiological setting. This approach was modified by Shchukin *et al.* by precipitating DNA with spermidine onto the surface of a decomposable core template followed by the deposition of more polyelectrolyte layers of chondroitin sulfate and poly-l-arginine [107]. On decomposition of the core template the spermidine/DNA complex loosened and the DNA was distributed through the volume of the hollow capsules while retaining its double helix structure, as confirmed by circular dichroism measurements.

In gene therapy several hurdles have to be overcome. On cellular internalization, the capsules have to leave the phagosomal/lysosomal/endosomal compartments, reach the cell cytoplasm and finally enter the cell nucleus. These are huge challenges and polyelectrolyte capsules find themselves in a very early stage of development. The uptake and intracellular fate of polyelectrolyte capsules was first addressed by De Geest *et al.* [89] and assessed further by the Parak group [38,92-94,96,97], and evidence was gathered that polyelectrolyte capsules enter the cell through lipid raft-mediated endocytosis, become mechanically deformed through the pressure of the cell's cytosol and end up in phagosomal compartments without releasing their content into the cell cytosol. These findings point out the necessity of appropriate mechanisms to release the capsules' payload into the cytosol of the cell. As mentioned earlier in this review, release into the cytosol can be achieved by IR laser-activated capsules. Another approach has been proposed recently by Hartmann *et al.* using polyelectrolyte capsules containing so-called oligoamine patches [108]. These oligomers, based on basic amino acids, were able to switch from cationic to anionic in the physiologically relevant pH range from 5.5 to 7.5 by complexation with CO_2 and carbamante formation. As a result the capsule membrane became permeable and should thus be able to release encapsulated species. However, it still has to be demonstrated that the released species can escape from the phagosomal compartment to the cell cytosol. The method of proton pumping, which is often applied in delivery issues of gene therapy and leads to bursting of the endosomal compartment, has not yet been applied in the context of polyelectrolyte capsules and might offer interesting possibilities. The disulfide-stabilized hydrogen bond-based multilayer capsules of Caruso and co-workers have also been used for the encapsulation of nucleic acid such as oligonucleotides, single-stranded DNA, double-stranded DNA and plasmid DNA [44,45,109,110]. However, so far no functional biological

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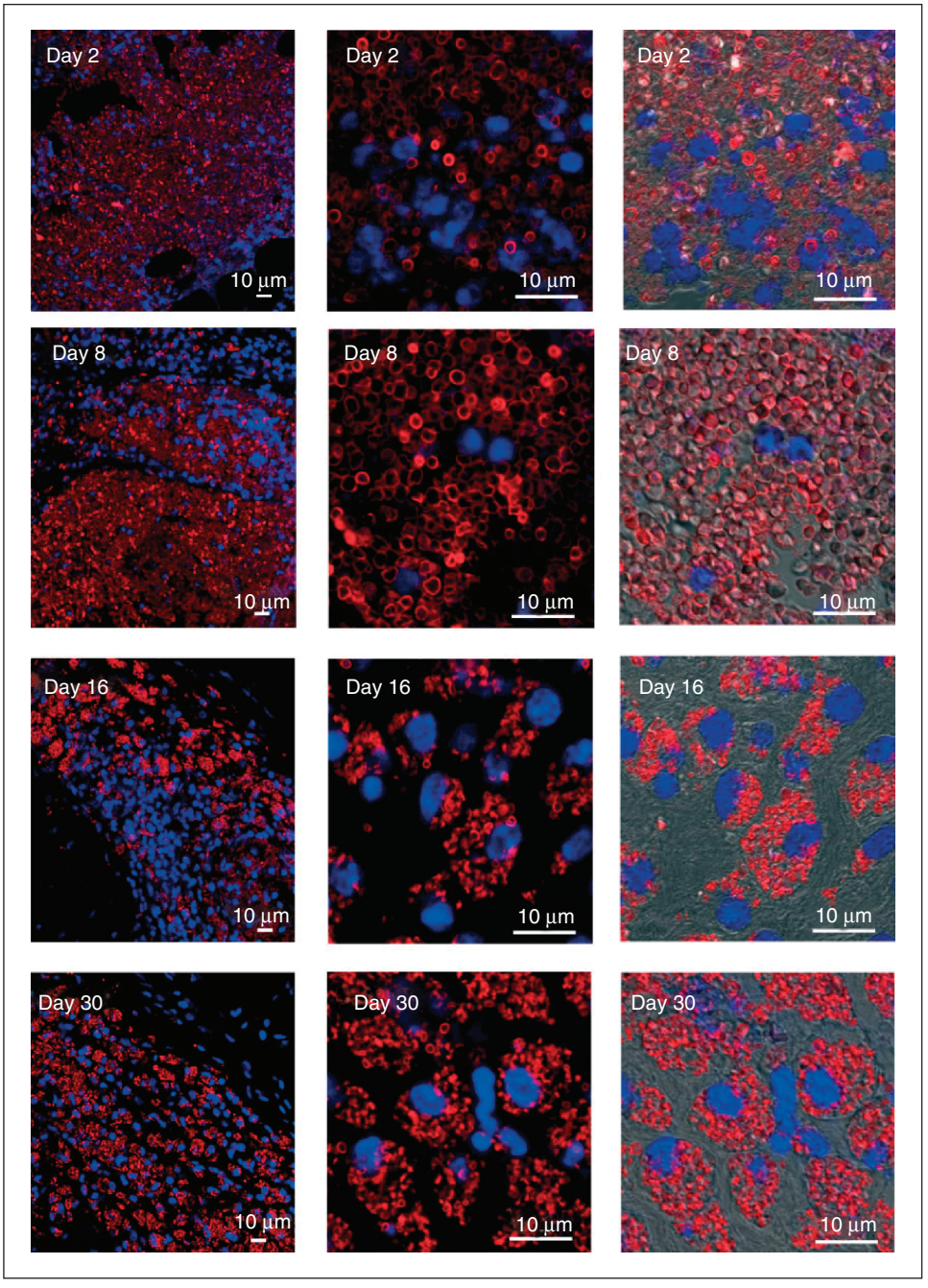

Figure 7. Confocal microscopy images of tissue sections taken at different time points after subcutaneous injection of microcapsules consisting of two bilayers of dextran sulfate/poly-l-arginine. The left column shows a large area of the injection site as an overlay of red fluorescence (due to rhodamin-labeled poly-l-arginine) and blue fluorescence (due to staining of nuclei with DAPI). The middle and right columns show a more detailed view of the injection spot. Middle: the red and blue fluorescence overlay at a higher magnification where individual cells and capsules can clearly be distinguished. Right: an extra DIC overlay for the right column to visualize cellular contours.

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DAPI: Diamidino-phenylindole; DIC: Differential interference contrast.

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experiments have been performed. Thus far, the only study dealing with successful gene transfection using polyelectrolyte capsules was reported by Reibetanz et al. using polyelectrolyte capsules with functional plasmid DNA in their wall [111]. Colloids were coated with dextran sulfate and protamine incorporated plasmids of, respectively, eGFP and dsRED. On cellular uptake the authors observed that these plasmid DNA were expressed by the cells. However, the mechanism responsible for these observations remains unclear.

6. Conclusions

In this paper, recent progress in the field of polyelectrolyte capsules for application in drug delivery has been reviewed. It has been shown that different functionalities that can be incorporated within the multilayer coating can lead to a variety of applications with potential for drug delivery. Coating drug crystals with polyelectrolytes can extend their release time. Incorporation of stimuli-responsive species such as weak polyelectrolytes, affinity centers or metal nanoparticles can render the capsules sensitive to external stimuli such as pH, glucose, CO_2 and laser illumination. Most of the systems are still at the conceptual stage; however, some are already developing towards the delivery of therapeutic active molecules. Cytotoxicity of capsules in vitro and in vivo has been assessed as well as their ability to degrade in living tissue. Further developments are expected and will open new avenues to polyelectrolyte capsule development for drug delivery.

7. Expert opinion

Polyelectrolyte capsules are a fairly new type of delivery system that has gathered increasing interest in the last decade from scientists active in different fields. The main advantage of these capsules is without doubt their multifunctionality and modularity. Owing to the electrostatic driving force for multilayer build-up, a wide variety of constituents can be chosen, such as synthetic polyelectrolytes, enzymes [112], lipids [113], nanoparticles [114], viruses [115-118], and so on. Further, both mechanical and physicochemical properties of the capsules can be tailored by varying these constituents or by varying the capsule thickness. The high modularity and versatility in material selection affords the advantage that there is a principal solution for any problem, but the difficulty remains of having a solution for a set of problems with a selected set of materials. Moreover, encapsulation within the empty void of polyelectrolyte capsules can easily be achieved under mild conditions avoiding the use of organic solvents or mechanical stress, which is often applied during the synthesis of 'traditional' drug delivery particles such as, for example, liposomes or PLGA microspheres. Taking into consideration all these aspects, such properties would lead directly to a hype in drug delivery. On the other hand, some realism must be applied, owing to the fact that the most commonly used building blocks of layer-by-layer assemblies have not yet been approved by the FDA. The first biocompatibility screening of De Koker *et al*. [98] has demonstrated a light tissue inflammation reaction on subcutaneous injection which is comparable with that of other types of degradable microsphere. Taking into account the fact that polyelectrolyte capsules are readily phagocyted by cells, it is no doubt worthwhile to investigate further the potential of polyelectrolyte capsules for intracellular delivery of therapeutic drugs. It has further to be established for which drug delivery applications polyelectrolyte capsules will have distinct benefits compared with other materials. So far few therapeutic molecules have been delivered *in vitro* using these capsules. Small cytotoxic compounds have been loaded through charge interaction in the capsules and demonstrated to kill *in vitro* cultured tumor cells [119]. DNA was used in the coating of polyelectrolyte-coated colloids [111] and shown to be able to transfect the genome of cultured cells as well as be used for DNA-induced vaccination *in vivo* on mice [120], and peptide-loaded capsules have been shown to induce antigen presentation in an *in vitro* cultured DC model [121]. These are promising steps and we are looking forward to new developments in the field that would further stimulate research in this exciting field. Finally, the fact that within the first decade of research in the area there has not emerged any clearly visible product should be commented on. This is probably because of the disadvantages mentioned above paired with a rather tedious preparation procedure. It should be noted here that capsule circulation and targeting through the bloodstream are hardly possible owing to the fact that the prevailing size that can be produced reliably without aggregation is > 1 μm and is not acceptable for intravenous injections. Other obstacles are relevant to the fact that in the area of drug delivery there is a tendency to stay with existing materials and improve their properties according to a specific purpose. In this case a procedure requiring qualitative change of a formulation is difficult to establish. What is required is a paradigm change where one first defines an application profiles and then conceptually studies ways to achieve this before discussing economic and ecological constraints. The latter are of course important, but the strength of these systems rests on the potential for solving problems that were previously not imagined to be solvable. We have shown here various attempts to arrive at a designed capsule and surface engineering and also look forward to new and simple ways to achieve this.

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Declaration of interests

The authors state no conflict of interest and have received no payment in the preparation of this manuscript.

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