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Designing LbL Capsules for Drug Loading and Release
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31.1 Introduction

Layer-by-layer (LbL) [1] assembly is a powerful tool for engineering microparticulate structures. On the one hand it allows one to tailor the surface chemistry of microparticles, rendering them responsive to physicochemical stimuli such as pH, ionic strength, light, and so on, to allow bio-specific recognition or just to prevent adsorption of unwanted species [2]. On the other hand, using microparticles as sacrificial templates, one can fabricate spherically-shaped free-standing polymeric multilayer films, forming hollow capsules [3–5]. These capsules are formed in multiple steps. First, alternating polymeric layers are deposited onto core microparticles. Typically electrostatics or H-bonding [6–8] between the successive layers is used as the driving force for this multilayer build-up. Secondly, the core microparticles are decomposed into low molecular weight degradation products which can freely diffuse through the LbL membrane. The resulting hollow capsules have walls with a thickness of typically a few tens of nanometers and surround an aqueous void.

From this conceptual point of view, LbL capsules form a binary system in which both the LbL membrane and the hollow void can be exploited to perform a specific function. As the primary focus of our research laboratories lies in the field of drug delivery, we will present in this chapter several approaches that we have developed in applying LbL technology to the design of drug delivery systems. For drug delivery purposes, two aspects are crucial: (i) something should be encapsulated inside the capsules and (ii) the encapsulated content should be released. The most evident route for encapsulation is without doubt the incorporation of drug molecules within the hollow void of LbL capsules, while engineering the LbL membrane to be responsive to specific physicochemical stimuli looks a straightforward way to release encapsulated material. In collaboration with the Sukhorukov group we developed several strategies that allowed encapsulation of macromolecular drugs into capsules using pre-loaded microparticulate templates. Furthermore, we explored several possibilities to design LbL capsules that could release their payload in a controlled fashion, not only by engineering the LbL membrane, but also by engineering the core templates.
Engineering the capsule core templates allows one to incorporate drug molecules and provides opportunities to equip the capsules with a drug releasing mechanism. Hydrogel microspheres are a well established class of materials used in drug delivery. For example, calcium alginate microspheres, produced by pouring an aqueous alginate solution into a solution of divalent calcium ions, causing ionic gelation of the glucuronic and mannuronic acid residues by the Ca\(^{2+}\) ions, has been used widely for drug and cell encapsulation. Furthermore, in order to stabilize these calcium alginate beads, poly-l-lysine coatings have been applied onto their surface to prevent the beads from dissolving when the Ca\(^{2+}\) ions become exchanged by monovalent Na\(^{+}\) ions in physiological media [9]. These coatings were also observed to form a diffusional barrier against diffusion of macromolecules into or out of the gel beads. These reports appeared in the early 1980s and calcium alginate beads were also among the first non-spherical substrates to be LbL coated. In 1994 Pommersheim et al. reported on the deposition of a multilayer coating onto calcium alginate beads with a diameter of several hundred micrometers [10]. By varying the number of deposited layers, the authors observed that, upon dissolution of the calcium alginate beads in the presence of Na\(^{+}\) ions, either stable capsules were obtained or the capsule membrane ruptured due to the osmotic pressure of the dissolving hydrogel cores. The McShane group elaborated further on the use of calcium alginate as core templates from drug loaded LbL capsules [11]. As calcium alginate bears an anionic charge at physiological pH, it can absorb relatively high amounts of oppositely charged molecules and serve as a drug reservoir. Subsequent LbL coating of these drug-loaded alginate beads allowed stabilization of the beads and could also play a role in controlling subsequent drug release.

This concept of electrostatic loading was first described by Mohwald and coworkers using melamine formaldehyde microparticles as the sacrificial template [12]. Upon decomposition of melamine formaldehyde (Figure 31.2b) in acidic media, not all melamine oligomers diffused through the capsules' LbL membrane and a cationic gel-like structure that could be loaded with oppositely charged molecules remained within the capsule membrane. Just as observed by Pommersheim et al., these authors also observed that decomposition of the core templates could lead to capsule rupturing due to an osmotic shock of dissolved core template components [13]. De Geest et al. elaborated on this phenomenon to equip LbL capsules with a

![Figure 31.1 Molecular structure of (a) alginate, (b) melamine formaldehyde and (c) dex-HEMA.](image-url)
Figure 31.2  (a) Confocal microscopy snapshots of self-exploding microcapsules. Dex-HEMA microgels were coated with a (PSS/PAH)$_3$ multilayer membrane and the degradation of the microgel core was accelerated by elevating the pH of the medium to 9 and heating to 37°C. (b) Confocal microscopy images and fluorescence intensity profiles of bare dex-HEMA microgels, dex-HEMA microgels coated with (PSS/PAH)$_4$, and dex-HEMA microgels coated with (PSS/DAR)$_2$ incubated in a 1 mg mL$^{-1}$ solution of FITC-dex. (c) Confocal microscopy snapshots taken at regular time intervals (overlay of green fluorescence channel and transmission channel) of (PSS/DAR)$_2$-coated microgels containing FITC-NP during the degradation of the microgel core triggered by the addition of sodium hydroxide. (d) Confocal microscopy snapshots of exploding capsules triggered by the addition of sodium hydroxide. The corresponding cumulative release curves of encapsulated 50 nm green fluorescent latex beads show that by varying the DS of the dex-HEMA (i.e., a DS of respectively 2.5 (red curve) and 5 (blue curve)) the onset of release upon incubation at physiological conditions can be tailored.
time-controlled release mechanism [14]. Figure 31.1c shows the molecular structure of these “dex-HEMA” hydrogels. Dextran was substituted with methacrylate groups that are connected to the dextran backbone by a carbonate ester. Polymerization of the methacrylates allows the formation of a crosslinked 3D network while hydrolysis of the carbonate esters allows this network to degrade into dextran and methacrylate oligomers. The use of dex-HEMA hydrogels offers several advantages: (i) the net charge can be tailored by incorporation of acidic (e.g., methacrylic acid) or basic (e.g., dimethylaminoethyl methacrylate (DMAEMA)), (ii) the degradation rate of the hydrogels can be tailored by varying the amount of crosslinks, and (iii) encapsulation of proteins into spherical dex-HEMA microgels with diameters ranging from 1 to 1000 μm is easily achieved using a water-in-water emulsion method based on the immiscibility of a poly(ethylene glycol) (PEG) and an aqueous dextran phase. This approach is of particular interest for the encapsulation of proteins as these often show enhanced affinity for a dextran phase compared to a PEG phase, in addition to the fact that organic solvents which might cause protein denaturation are avoided. The first paper in a series on this topic reported on the use of cationic microgels obtained by copolymerization of dex-HEMA with DMAEMA followed by coating of these microgels with three PSS/PAH polyelectrolyte bilayers. To prove the concept that the swelling pressure exerted by the degrading hydrogel core could be used as a trigger to rupture the (PSS/PAH)_3 membrane, the capsules were incubated at elevated pH (i.e., pH 9) and physiological temperature in order to accelerate the degradation of the dex-HEMA hydrogels. As shown in Figure 31.2a, at a certain moment, when the swelling pressure exceeds the tensile strength of the LbL membrane, the capsule suddenly ruptures and releases its payload.

In a number of subsequent papers, De Geest et al. further elaborated on this concept and elucidated that both the LbL membrane and the size and composition of the microgel templates played a critical role in controlling the release properties of these so-called “self-exploding capsules” [15]. An important observation was that, depending on the type of polyelectrolyte, either exploding or intact hollow capsules were obtained upon degradation of the microgel core. Furthermore, using FITC-labeled albumin or FITC-labeled dextran as a model drug, it was found that a significant fraction of the encapsulated payload was able to diffuse through the capsule membrane prior to capsule explosion [16]. These observations indicated the need to reinforce the capsule membrane to avoid premature leakage. This was tackled by applying a covalently stabilized LbL membrane, comprising PSS and diazoresin (DAR), that formed a covalent bond with the PSS’s sulfonate groups [17]. The resulting capsules exhibited a dramatic decrease in permeability (Figure 31.2b) but, in order to allow rupturing of the capsule membrane upon degradation of the microgel core, it was necessary to synthesize microgels with a diameter larger than 100 μm to reduce the pressure required to overcome the capsules’ tensile strength. As shown in Figure 31.2c, (PSS/DAR)_2-coated microgels are literally slashed prior to releasing their payload. By encapsulating fluorescent latex beads, it was possible to follow the trajectory of the released payload. Interestingly, it was observed that this type of “ejecting capsule” gives the latex beads such a momentum that they are propelled with an 800-fold increase in speed compared to mere Brownian motion.
Besides reinforcing the LbL membrane, another strategy to reduce drug diffusion is to use nano- or microparticles as the model drug rather than soluble macromolecules, as it could be hypothesized that the mesh size of an LbL membrane would be too small to allow premature release of particle-like materials. Furthermore, this also allowed the use of bio-polyelectrolytes, such as polysaccharides and polypeptides, instead of synthetic polymers such as PSS, PAH or DAR. Figure 31.2d shows confocal microscopy images of exploding capsules containing 50-nm sized latex beads [18]. An LbL membrane consisting of four layer pairs of dextran sulfate and poly-l-arginine was used to coat the dex-HEMA microgels. Upon dissolution of the microgel core, these capsules exploded and released their payload. Importantly, it was also demonstrated that by varying the crosslink density of the microgels (Figure 31.2d; DS: degree of substitution, that is, the amount of methacrylate groups per dextran backbone), it is possible to tailor the onset of burst release from the capsules. To further assess the versatility of this approach, LbL-coated 3-μm sized calcium carbonate microparticles and hollow LbL capsules were also demonstrated to be encapsulated and released from self-exploping capsules [19]. This allowed the construction of multi-compartment particles with the potential to load and release a wide variety of substances.

31.3 Engineering the Shell to Design LbL Capsules for Controlled Drug Release

Due to their polyionict nature, polyelectrolytes are inherently stimuli-responsive. In an aqueous medium at low ionic strength, in the absence of salt, polyelectrolytes adopt an elongated “rod-like” conformation, while addition of salt leads to a more compact “coiled” conformation. It had already been observed in the early days of LbL research that salt had a tremendous effect on both polyelectrolyte multilayer assembly and on pre-formed polyelectrolyte multilayers. Salt ions are capable of screening electrostatic charges and inducing swelling of the multilayers, increasing their permeability [20]. This also holds true for LbL capsules, and the Mohwald group demonstrated that LbL empty capsules could be loaded with macromolecules at elevated salt concentration, be “closed” at low ionic strength, and subsequently release their payload by again raising the salt concentration [21]. Besides responsiveness to salt, pH is also often an inherent trigger to change the behavior of a polyelectrolyte [22]. Especially, weak polyelectrolytes, such as PAA and PAH, exhibit a pronounced charge-shifting behavior which allows them to be uncharged, partly charged or fully charged, depending on their apparent pKₐ and the pH of the surrounding medium. Capsules consisting of one or more weak polyelectrolytes have also been demonstrated to exhibit reversible swelling/shrinking and loading/unloading by cycling the pH around the apparent pKₐ of the polyelectrolyte complexes [23].

However, although both of these mechanisms, that is, varying ionic strength and pH, clearly allow controlled release from LbL capsules, therapeutic applications of these concepts are scarce as large variations in pH or ionic strength are
predominantly encountered in the gastro-intestinal tract where competition with other established drug delivery systems intended for oral intake is difficult. In order to find their way in the field of drug delivery it is most likely that LbL capsules will have to be administered through parenteral injection, where they could act as a depot that releases its content after a specific stimulus, or after cellular uptake. Keeping this in mind our research laboratories, in collaboration with the Sukhorukov group, have attempted to work towards the design of LbL capsules that could release their payload under physiologically relevant conditions.

Glucose is a common metabolite and patients suffering from diabetes mellitus fail to secrete sufficient levels of insulin to lower glucose levels in the blood stream. Rather than injecting fixed doses of insulin at fixed time intervals, it could be advantageous to design drug delivery systems that release insulin on demand, that is, when glucose levels pass a certain threshold. This inspired us to synthesize polymers that could shift their overall charge and their charge density depending on the concentration of glucose in the medium. Phenylboronic acids are known to form anionic complexes with glucose and copolymerization of a phenylboronic acid containing monomer with a basic monomer yielded a polyelectrolyte which had a net positive charge in the absence of glucose, while addition of glucose induced anionic charges on the polymer backbone, which lowered the net charge density and changed the conformation of the polyelectrolyte. Assembling this polymer with PSS onto sacrificial polystyrene microtemplates, followed by decomposition of the polystyrene in THF, resulted in hollow capsules that contained glucose responsive moieties. Addition of glucose effectively induced disassembly of the capsules [24]. This concept could potentially be used for glucose-induced insulin release. However, the type of phenyl boronic acid used to construct these capsules has a $pK_a$ between 8 and 9, which means that glucose induced charge-shifting only takes place in this pH range. Recently, several groups have reported on the synthesis of phenylboronic acids that are responsive under physiological conditions, which could be of interest for application in our concept of glucose responsive capsules.

Another common stimulus that can be provided by the human body, and which is not restricted to diseased patients, is enzymatic hydrolysis. Enzymes are omnipresent in body fluids and actively phagocytizing cells contain an abundance of proteases in their lysosomes. Pioneering work by Picart et al. on planar films composed of hyaluronic acid and poly- L-lysine has demonstrated that living cells could attach to these LbL films, invade and gradually digest them [25]. Therefore, multilayer capsules built from polypeptides in their shell should also be prone to enzymatic hydrolysis and could thus serve as carriers for intracellular release of encapsulated therapeutics. This concept was explored by De Geest and coworkers using calcium carbonate (CaCO$_3$) coated with a polyelectrolyte multilayer film of dextran sulfate and poly- L-arginine as a sacrificial template [26]. The use of porous microparticles such as CaCO$_3$, which was introduced by the Sukhorukov group [27], as well as the use of mesoporous silica particles, which was introduced by the Caruso group [28], offers tremendous potential for the encapsulation of macromolecular drugs such as proteins and polynucleic acids. CaCO$_3$ is cheap, non-toxic and biocompatible. It is synthesized under ambient conditions by mixing aqueous solutions of sodium
carbonate and calcium chloride, and the resulting precipitate forms fairly monodisperse particles with a diameter of, typically, 3 μm and a high surface to volume ratio. By adding proteins during the precipitation reaction, these become incorporated within the pores with a nearly 100% encapsulation efficiency. Moreover, due to their porous nature, exhibiting a much higher surface roughness than typically “smooth” particles, such as PS, MF or silica, significantly higher amounts of polyelectrolytes are adsorbed during each deposition cycle, creating thick walled capsules which are more robust and less prone to buckling instabilities. This is of particular interest for intracellular drug delivery following parenteral administration, as the surrounding tissue will cause a certain mechanical pressure which should be withstood by the capsules prior to cellular internalization. Finally, CaCO₃ is dissolved under mild conditions in water by complexation with EDTA, leading to non-toxic low molecular weight degradation products, such as CO₂ and Ca²⁺. As an alternative to enzymatic hydrolysis, De Geest and coworkers also explored the use of degradable charge-shifting polycations (i.e., poly(hydroxypropyl methacrylamide-dimethylaminoethyl) (poly(HPMA-DMAE)) developed by the Hennink group [29]. These polycations were based on a polymethacrylamide backbone which was substituted with tertiary amine groups that were linked to the polymer backbone through a hydrolyzable carbonate ester. The use of degradable polycations – based on polyamines synthesized by Michael addition of dimethacrylates to diamines – to construct “erodable” LbL films was pioneered by Lynn and coworkers, and has been shown to be an effective approach for surface-mediated drug delivery [30]. As shown in Figure 31.3, two types of degradable capsules, as well as non-degradable synthetic PSS/PAH capsules were incubated with an *in vitro* cultured cell line (i.e., VERO cells). All three types of capsules were efficiently internalized by this cell line and through co-localization with “LysoTracker” (a fluorescent marker which stains intracellular acidic vesicles) and several endocytotic inhibitors it was found that these LbL capsules enter the cell through caveolae-mediated endocytosis and end up in endo/lyso/phago-somal vesicles. Whereas PSS/PAH capsules remaine intact over several days within lysosomal compartments of the cells, capsules based on dextran sulfate poly-l-arginine, or capsules containing the degradable polycation poly(HPMA-DMAE) exhibited intracellular degradation and, after several days of incubation, only debris of degraded capsules could be observed.

Besides enzymatic hydrolysis, another intracellular stimulus is the reductive environment which is encountered upon cellular internalization. This offers the possibility for redox-responsive capsules to deliver their payload selectively inside living cells. The Caruso group developed an elegant approach to the construction of capsules that could disassemble through reduction of disulfides in the presence of physiologically relevant glutathione concentrations [31]. First, poly(methacrylic acid) was substituted with thiol groups (PMA-SH) and assembled onto sacrificial silica microtemplates with PVP through hydrogel bonding. Subsequently, the PMA-SH layers were crosslinked by oxidative disulphide formation and the silica microparticles were dissolved in diluted HF solution. The resulting capsules were stable under normal physiological conditions but decomposed in an oxidative medium. The introduction of both redox-sensitive and enzymatically degradable capsules has
paved the road for the use of LbL capsules in a therapeutic setting and they are currently being evaluated in a number of drug delivery applications.

An alternative strategy to the use of physiological stimuli to induce drug release from LbL capsules, is the use of external triggers, such as light, ultrasound, magnetism or radiofrequency fields. Multilayer capsules susceptible to one of these triggers might be used as a drug depot — either extracellular or intracellular — and only release their payload after application of the specific physico-chemical stimulus. Light-triggered release from LbL capsules was elaborated on by both the Caruso and Sukhorukov groups by incorporating gold nanoparticles within the LbL shell [32, 33]. Upon irradiation with IR light, the gold nanoparticles absorb the energy and transform it into thermal energy. As a consequence, the capsules are heated far above their glass transition temperature ($T_g$) and break, releasing their encapsulated payload. This process has been shown to be well tolerated by living cells, and it was even shown that triggered release from capsules that were first fagocyted by living cells ruptured the lysosomal compartment, and released the capsules’ payload within the cellular cytoplasm [34]. Preliminary experiments showed no effect on cell viability and still allowed intracellular processes such as MHC-I presentation of peptides, released from the capsules, to take place.

Our research laboratories have, in collaboration with the Sukhorukov group, also contributed to the field of triggered release, focusing on the release of encapsulated macromolecules from calcium carbonate template capsules. As mentioned earlier,
due to its high porosity, CaCO₃ tends to adsorb higher amounts of polyelectrolyte than other template particles. This leads to thicker shells that exhibit enhanced mechanical stability and which will render the capsules less prone to small distortions caused by external triggers, such as light and ultrasound. To cope with these issues, hybrid nanoparticle/polyelectrolyte capsules were constructed. The rationale behind this was to reduce the capsule elasticity to render the capsules more susceptible to fracture. Mercaptosuccinic acid stabilized 1 nm gold nanoparticles with an anionic surface charge were assembled with the polycation PAH onto CaCO₃ microparticles, without any additional polyanion [35]. As shown in Figure 31.4a, this leads to capsules with a high content of gold nanoparticles which are literally glued together by PAH. These capsules were evaluated for their responsiveness to IR laser
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irradiation and ultrasound. Exposure to a focused 30 mW laser beam caused a whole agglomerate of capsules to explode and release their fluorescent payload (Figure 31.4b). A similar result was obtained when a capsule suspension was subjected to 10 s of a 20 W ultrasonic treatment with a frequency of 20 kHz (Figure 31.4c) [36]. These data clearly demonstrated the potential of laser and ultrasound irradiation for on-demand drug release from LbL capsules. However, there is still a long way to go for these systems towards clinical applications. Several issues regarding the penetration depth of light and ultrasound required to address the capsules have to be resolved, as well as the tissue reaction to injected capsules.

31.4 Interaction of LbL Capsules with Living Cells In Vitro and In Vivo

For applications in drug delivery, it is of the utmost importance that LbL capsules can be designed in such a way that they are non-toxic to living cells. This issue has been addressed by several groups, so far in vitro, and a general consensus is that at moderate capsule to cell ratios no acute cytotoxicity is observed [37, 38]. LbL capsules could be of particular interest for intracellular drug delivery. Several cancer cell lines, as well as immune cells, such as macrophages and dendritic cells, have been shown to be capable of internalizing LbL capsules. The Caruso group is currently performing pioneering work on engineering LbL capsules to load both hydrophilic and hydrophobic low molecular weight anticancer drugs. Recently, this group was able to demonstrate highly specific targeting and uptake of antibody functionalized LbL capsules by receptor recognition with extreme precision [39].

Our research laboratories have been active in evaluating LbL capsules for vaccine delivery to dendritic cells, which are the most potent antigen presenting cells. As mentioned earlier, upon cellular uptake, LbL capsules end up in intracellular acidic vesicles. The mechanism through which dendritic cells internalize LbL capsules composed of dextran sulfate and poly-L-arginine was investigated using various inhibitors of different endocytotic pathways. Blocking of actin polymerization appeared to completely abolish capsule uptake, suggesting an important role for...
cytoplasmic engulfment [40]. This was confirmed by transmission electron microscopy, and actin staining with fluorescence microscopy proved the role of cytoplasmic protrusions in the process of capsule internalization. Transmission electron microscopy was further used to assess the intracellular fate of the internalized capsules, and it was observed that the capsules remained surrounded by a lipid membrane. However, over time, the capsule shell ruptured and cytoplasmic content protruded into the capsule core (Figure 31.5a), which can most likely be attributed to a combination of enzymatic degradation by endo/lysosomal proteases and mechanical force exerted by the surrounding cytoplasm. Furthermore, several cellular organelles, such as lysosomes, mitochondria and endoplasmatic reticulum, were recruited towards the ruptured capsules, which will likely play a role in the processing and presentation of peptide fragments from encapsulated vaccine antigens.

To assess the intracellular fate of encapsulated antigens, ovalbumin (OVA) was encapsulated as model protein antigen. Antigen processing was investigated using a fluorogenic substrate of OVA (i.e., DQ-OVA); comprising OVA that is oversaturated with BODIPY dyes, thereby forcing the fluorescence in a quenched state. When DQ-OVA is degraded into small peptide fragments, the quenching is relieved and a bright green fluorescence emerges. This technique demonstrated that LbL capsules consisting of degradable polyelectrolytes (i.e., dextran sulfate and poly-l-arginine) allowed ready processing of the encapsulated proteins, as confocal microscopy and flow cytometry showed that antigen processing started in less than 4 h after cellular uptake (Figure 31.5b). As a control, DQ-OVA was encapsulated in non-degradable PSS/PAH capsules and found not to be processed upon cellular internalization. These observations indicated the crucial influence of capsule design in order to grant access of proteases to encapsulated protein antigens. To assess whether this fast antigen processing was accompanied with enhanced presentation of the OVA CD4 and CD8 peptide fragments to CD4, respectively CD8 T-cells, dendritic cells that were pulsed with OVA-loaded capsules were co-cultured with OT-I, respectively OT-II cells. OT-I cells are CD8 T-cells with a transgenic T-cell receptor that specifically recognizes the OVA peptide SIINFEKL presented by MHC-I, whereas OTII cells are transgenic CD4 T cells that specifically recognize the OVA peptide LSQAVHAAHAEINEAGR presented by MHC-II. As shown in Figure 31.5c, LbL capsule-mediated OVA delivery dramatically induces T-cell proliferation – as a measure of antigen presentation of dendritic cells to T-cells – compared to soluble OVA. This was especially found to be the case for presentation to CD8 T-cells, which is referred to as cross-presentation and believed to be a crucial step in the induction of cellular immunity against insidious intracellular pathogens, as well as cancer.

So far, few studies on the in vivo performance of LbL capsules have been reported. De Koker and coworkers have assessed the in vivo fate of LbL capsules composed of dextran sulfate and poly-l-arginine after subcutaneous injection and pulmonary delivery [41, 42]. Both studies were performed in mice. The pro-inflammatory response to subcutaneously injected capsules was characterized by the recruitment of polymorphonuclear cells and monocytes, and found to be within the same range as FDA approved vaccine adjuvants such as aluminum hydroxide. The injected capsules behaved as a porous implant with cellular infiltration emerging from the periphery.
and proceeding over time over the whole injected volume [41]. No ulceration was observed and the inflammatory response remained confined to the injection site, which became surrounded by several layers of fibroblasts. Tissue sections obtained from mice that were injected with fluorescently labeled capsules revealed that the capsules remained intact before becoming phagocyted by infiltrating cells. Two weeks post injection, all capsules were found to be inside cells and to have lost their spherical shape. One month post injection, only capsule debris could be observed within the cells. Taken together, these experiments demonstrate that LbL capsules fabricated from degradable polyelectrolytes are well tolerated in vivo and could serve as a drug carrier towards phagocyting cells.

Instillation of OVA-loaded capsules into the lungs of mice revealed a transient inflammation and promoted strong humoral and cellular immune responses [42]. This was attributed to the ability of LbL capsules to restrict the antigen to actively phagocyting cells, such as dendritic cells, whereas non-encapsulated soluble antigen would readily diffuse into the surrounding tissue. Moreover, capsule-mediated antigen delivery also resulted in an increased activation state of antigen presenting cells, through complement activation.

31.5 Conclusions

In the early years of LbL technology, since it was introduced by Gero Decher in 1991, and extended to hollow LbL capsules by the Mohwald group in 1998, a first objective has been to explore the potential of LbL technology for a wide range of drug delivery applications and to assess whether there was potential to compete with existing technologies, or even if there was an opportunity for LbL technology to offer an advantage. In this context, several concepts have been developed and evaluated, mainly in chemistry labs without direct applications being readily at hand. Nowadays, the field has moved more and more towards the development of LbL capsules specifically engineered for a well defined drug delivery purpose, for example, the delivery of cancer therapeutics, vaccine delivery, and so on. Furthermore, another emerging trend is simplification of the fabrication procedure. Whereas LbL technology inherently suffers from a multistep assembly, involving many time- and product consuming batch operations, more and more groups, both in the fields of planar LbL films as well as LbL capsules, are making efforts to drastically reduce the number of steps needed to generate capsules while aiming to keep the versatility of the LbL approach.

References


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