Decade of developing applications exploiting properties of polyelectrolyte multilayer capsules

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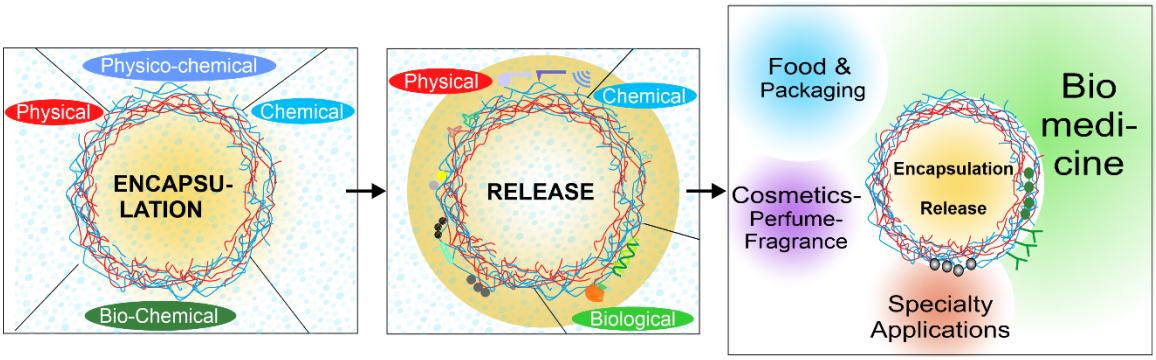
Abstract. Upon transferring the layer-by-layer (LbL) coating approach from planar surfaces to spherical templates and dissolving these templates resulted in fabrication of polyelectrolyte multilayer capsules. The versatility of the coatings of capsules and flexibility with bringing in virtually any material into the coatings – have quickly drawn substantial attention to them. Here, we provide an overview of main developments in the field, highlighting the trends of the last decade. At the beginning, various methods of encapsulation and release are discussed followed with a broad range of applications, which were developed and explored. We also outline current trends, where the range of applications is continuing to grow, including addition of whole new and different application areas.

Abstract graphic



Keywords: layer-by-layer, polyelectrolyte multilayer capsules, nanoparticles, templates

1. Introduction

Polyelectrolyte multilayer (PEM) capsules are containers used for encapsulation and possessing a distinct composition of the shell, which is composed by sequential application of oppositely charged polyelectrolyte polymers or particles. They were first reported in 1998 at Max-Planck Institute of Colloids and Interfaces, Potsdam, Germany. [1,2] Originally, the LbL assembly employing oppositely charged polyelectrolytes (PE) was developed for coating flat surfaces. [3,4] This approach drew attention of the scientific community due to extensive possibilities to control the properties of the surfaces. Not only the charges of the polyelectrolytes, but also the salt in which they are immersed, their concentration and molecular weight allow one to control desirable properties of the coatings, which can be applied on various surfaces.

Similarly to the flexibility of designing flat surface coatings, there is an extensive flexibility in designing capsules or specifically the capsule wall, which leads to various valuable properties. The actual development of multilayer capsules is associated with two steps: first, transfer of the LbL coating technology on spherical particles, and second, dissolution of the particles which are named sacrificial templates. In the first step, the layers are fabricated by alternative deposition of anionic and cationic PEs on a sacrificial colloidal template, followed by the dissolution of the core. An essential feature of the second step, the dissolution of the core, is that it leaves the polyelectrolyte shell intact thus allowing encapsulation of molecules in the cavity of capsules.

Polyelectrolyte multilayer capsules have been the subject of intensive studies in a large part because of possibilities of functionalization with different molecules and structures [5] as well as flexibility in tuning the permeability [6] of the polyelectrolyte multilayers. Besides polyelectrolyte multilayer capsules, different encapsulation approaches exist including biocompatible liposomes, high-throughput interfacial polymerization approaches, micelles, etc. But essential advantages exit: (1) responsiveness to different stimuli, which can be sorted into three main categories, including physical, chemical and biological factors. [7] The process used to entrap various substances such as drugs, bioactive enzymes, liquid crystal droplets, *etc*. in the hollow cavity of microcapsules under stimulus is referred to as encapsulation; (2) another attractive attributes of multilayer capsules is bringing new functions or controlling the internal structural by incorporating organic dyes, [8] inorganic nanoparticles, [9,10] magnetic nanoparticles, [11] carbon nanotubes, [12] antibodies, [13] *etc* during the multilayer fabrication process; (3) extensive controllability of the thickness, mechanical properties, functionality, and eventually targeting by molecules incorporated inside or attached to the outer layer of capsules; (4) precise control over the size of the capsules (from nano- to micro- and macro- meter range) due to: (a) the choice of templates and (b) applying physico-chemical treatment (for example, temperature) for shrinking or expanding the capsules; (5) controlling mechanical properties of capsules; and (6) controlling the encapsulation and release rate of molecules. All these properties promoted development of various applications. [14] And it is these attractive advantages prompted development of numerous publications on PEM capsules and put them under the spotlight for their wide use in many practical applications ranging from sensors, bioreactors, theranostics, cell engineering, antibiotics, and delivery carriers.

Over the past decade and since our last review, [15] which focused on polyelectrolyte multilayer capsules and more particularly on release mechanisms, micro- and nano- capsules have seen further growth, especially in the number of applications. Here, we provide an overview of recent development highlighting encapsulation and release methods. First, some significant and critical aspects of preparation of microcapsules, including the LbL method, the cores or templates and polyelectrolytes. This is followed by different approaches used for encapsulation and release, both classified according to respective stimuli

used for encapsulation and release. The choice of an appropriate encapsulation technique is mainly affected by physical and chemical properties of the core materials, shell polyelectrolytes, and to be encapsulated molecules. And these stimuli can be divided into four main categories: physical, chemical, physico-chemical, and bio-chemical. In addition, we present an updated overview of different applications of PME capsules, which continue to grow. Finally, an outlook into future research on novel microcapsules for diverse applications is also provided.

2. Preparation of capsules

2.1. LbL as a method of fabrication

As it was mentioned above, the LbL method was originally developed for films on flat substrates, [3] where sequential adsorption of alternatively charged polyelectrolytes takes place. The structure of polyelectrolyte multilayers (PEM) as well as polyelectrolyte complexes have been studied by different groups. [16–19] Multilayer assemblies fabricated using different interactions including electrostatic, hydrophobic, charge-transfer, host–guest, coordination chemistry, biologically specific interactions as well as hydrogen bonding, covalent bonding, stereo-complexation, and surface sol–gel process. [20–22] In addition, PEM can be cross-linked to control their properties. [23–25] Originally, sequential deposition by immersion was used but later several other deposition methods have been developed.

2.1.1. Methods of LbL deposition

a) Alternative adsorption of polyanions and polycations on a substrate such as glass in an aqueous solution followed by washing is most widely used LbL application method. [4,26] The first report on methods which can be related to LbL method was reported for nanoparticles in the mid-1960s. [27] Later on, adsorption of polymers was reported by Decher, [26] after which the LbL assembly has been a well-established protocol for molecules. [28–30]

b) In the spray-coating technique, sequential spraying of alternatively charged polyelectrolytes takes place. In 2000, Schlenoff and co-workers described this sprayed-based LBL buildup. [31] This spray-based method requires a relatively fast formation of strong interactions between the layers. [32] The fast-spraying process can be transformed to industry. [33] Driven by such an inspiration, Hammond et al [34] developed a fully automated system capable of depositing thin polymer films from atomized mists of solutions containing species of complementary functionality based on this spray-coating technique.

c) Spin-coating is another generally used and industrially relevant coating technique in which deposition of polymeric layers takes place on a spinning substrate. [35,36] In spin coating, the polymeric films are produced thinner than those in immersive coating, however this method is faster. [37–39] Integrating injection systems with rotating substrates allows spin assembly to be automated. [40]

d) Microfluidic-based assembly of LbL films and capsules, such as microfabrication and manipulation, are widely used in different platforms due to their advantages of uniform laminar flow, low cost, time-saving analysis, and effective control over the molecule concentration in space as well as time at microscale levels. [41,42] Studies combining microfluidic based LbL technologies have also gained numerous interests recently. [43–46]

2.1.2. Composition of LbL layers.

a) Polymers, biopolymers, and bio-based materials represent an important class of polyelectrolytes. Some polymers and biopolymers used for fabricating capsules are overviewed later in this review (in the section

2.3.2). Bio-based materials, for example, nanocellulose) are attractive not only due to their abundance and sustainability, but additionally they offer extraordinary chemical and mechanical properties have already opened further applications of LbL structures, including capsules. [47–49] LbL assembly of a range of polymers has been demonstrated as appropriate to form an enzymatically degradable film. The biocompatibility and non-toxicity of nanocellulose gives them possibility for various biomedical applications, such as sustained drug release. [50] In addition, by using nanocellulose, with rather polymers, it was possible to create nanocellulose capsules to withstand harsh environment due to their robustness in low pH, high ionic strength and at elevated temperatures. [51]

Self-assembled multilayers designed to interact via ionic bonding with cationic or anionic polyelectrolyte cannot be detached without significantly rupturing or degrading the film. More recently, the use of hydrophobic surfaces, dissolvable support layers, mandatory crosslinking, or cytotoxic solvents to assembly detachable and free-standing LBL multilayer were reported. [52–54]

b) Hybrid organic–inorganic coatings and capsules represent a sub-class of hybrid materials. [55] They consist of an organic polymeric layer and inorganic phase (for example, via sol-gel reactions). Inorganic nanoparticles play an increasingly important role in effectively leading to the construction of the so-called hybrid coatings. [55–58] A combination of both organic and inorganic materials adsorbed to each other at the one interaction of one complex system can benefit from the advantages of both phases and grant this hybrid system novel functions. [59–62]

c) Inorganic nanoparticles (for example, silver or gold) are merely incorporated into the already existing polymeric layer. And these were done as layer [63] or incorporating nanoparticles into a polymeric shell. [64] Multilayer capsules with the shell composed of purely inorganic component extent the range of shell materials. Recently, Jie and co-workers have assembled a new type of capsules employing solely nanoparticles in the walls. [65] X-ray diffraction analysis was used to verify the template (calcium carbonate) dissolution, while effective release by both ultrasound and laser was shown; the latter was also used to kill cancer cells.

Many of these methods can be also used for fabrication of PEM capsules, where polyelectrolytes are deposited onto spherical templates instead of flat substrates. [66,67] An important step of PEM capsule fabrication is that the spherical template or core is dissolved leaving the polyelectrolyte shell intact, Fig. 1.

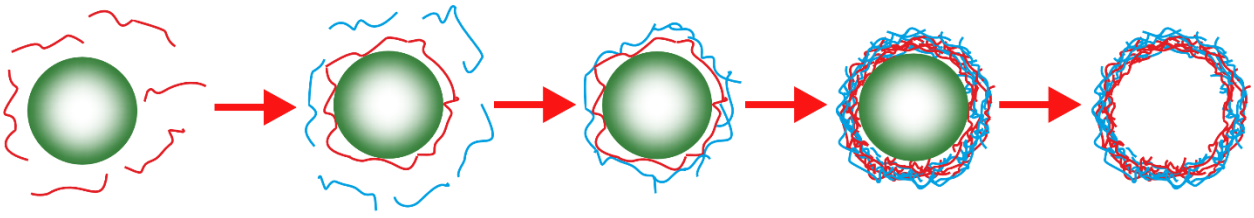


Fig. 1 Schematics showing major steps for fabricating microcapsules involving electrostatic interaction between polymers upon deposition onto a sacrificial template, followed with the dissolution of the template but leaving the polyelectrolyte shell intact.

2.2. Templates

Templates, also called cores, on which polyelectrolyte layers are deposited determine the morphology and properties of the PEM capsule shell. The choice of the template core for the preparation of these

capsules is an important part for developing applications. The advantages and disadvantages of different templates corresponding to the core dissolution, [68] the stability of the component shell and the aggregation influence the properties and application of polyelectrolyte multilayer capsules. [69] Various templates for fabrication of capsules are available including both nonporous and porous templates. [70]

2.2.1. Nonporous organic templates.

Melamine formaldehyde (MF) [71,72] and polystyrene (PS) [73–75] stand-out as prominent organic nonporous templates used early in research on capsules. Advantages of such templates is their high monodispersity and availability in different size ranges, but their disadvantages include necessity of a solvent for dissolution, higher prices, a potential effect on the polyelectrolyte shell, which may affect reproducibility of results. Extreme monodispersity and a good stability of them are helpful to produce monodisperse capsules.

2.2.2. Nonporous inorganic templates

Nonporous silica is an inorganic nonporous template, which was shown to lead to very reproducible results, thus removing potential difficulties in affecting the polyelectrolyte multilayer shell and difficulties with reproducibility. [76,77] But prices of the templates as well as requirement of application of a dangerous solvent which significantly affects bioactivity, hydrofluoric acid (HF), still represent essential disadvantages of silica. Gold nanoparticles were also used as a template. [78,79]

2.2.3. Porous organic templates

This type of template can be fabricated from nonporous inorganic cores and that would bring porosity for the template necessary for loading of molecules. But using porosity for loading molecules has been done more frequently for porous inorganic templates.

2.2. 4. Porous inorganic templates

An advantage of using such porous templates is that the highly porous interior of the particles can be exploited to embed various materials. Inorganic templates include mesoporous silica (MS) particles, [80] and calcium carbonate ($CaCO_3$) particles [81,82] that do not significantly affect the activity of biomaterials entrapped within the templates can be dissolved under mild condition. The high surface areas and nanopore volumes, and homogeneous nanopore structures of MS particles have been demonstrated to encapsulate a variety of species, such as proteins, [83–85] low-molecular-weight drugs, [86–89]and nanoparticles. [90–92] Calcium carbonate particles which are inexpensive to fabricate has shown increasing interests due to its biocompatibility, biodegradability, and a relatively easy production (Fig. 1 a-c). But the relatively poor control in size of these porous particles and their tricky aggregation behavior limit the application of this type of templates in some cases. [93–95]

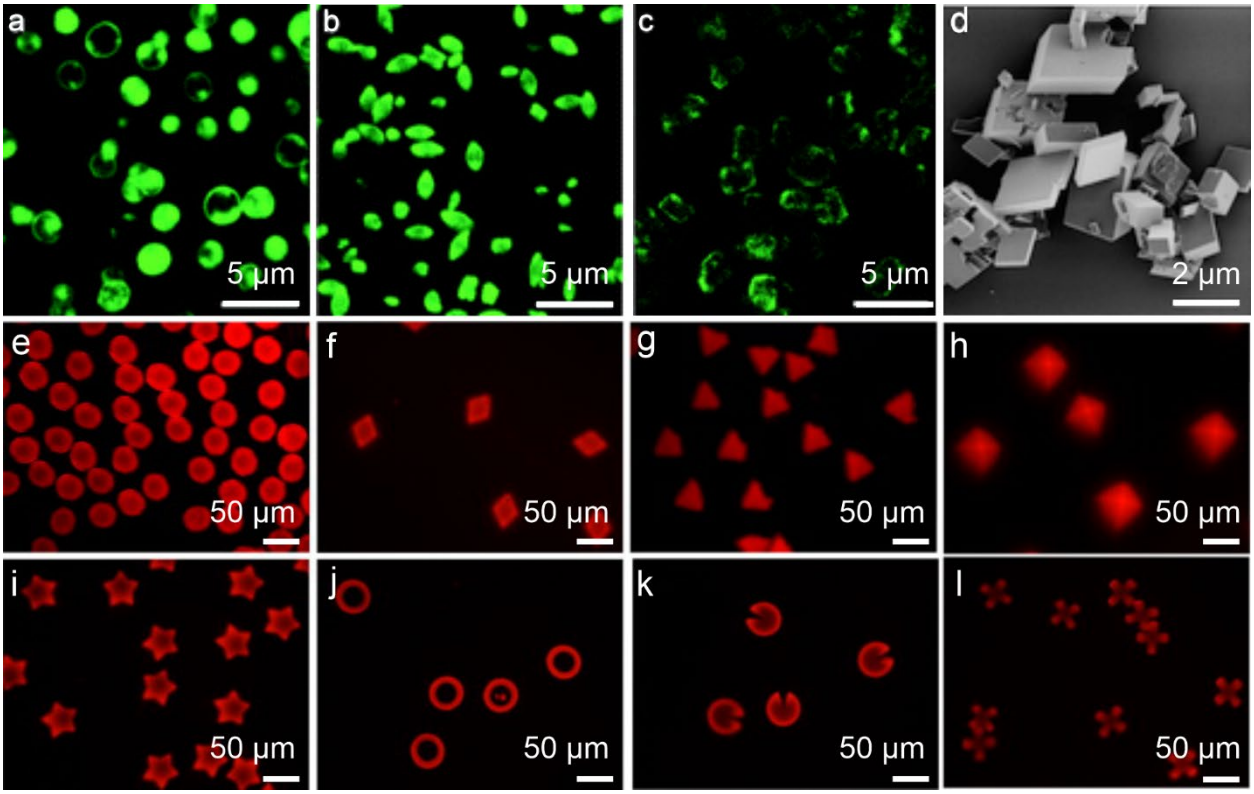


Fig. 1 Confocal laser scanning fluorescence images of spherical (a), ellipsoid-like (b) and square (c) $CaCO_3$ microparticles. The microparticles were embedded with FITC–dextran molecules by co-precipitation and subsequently covered by several oppositely charged polyelectrolyte layers through the LbL assembly; (d) SEM images of $CaCO_3$ rhombohedral microcrystals (calcite); (e-i) Fabrication of microparticles of different geometries by the hydrogel template approach. Modified with permission from ref. [96]. Published with permission of 2012 The Royal Society of Chemistry. Modified with permission from ref. [97]. Published with permission of 2010 Elsevier.

Different geometries of microcapsules were fabricated on various $CaCO_3$ polymorph templates synthesized by adjusting the intermixing speed, time, pH value, and the ratio of initial ingredients. [96] Other porous particles, for example, calcium phosphate, [98] manganese carbonate, [99] cadmium carbonate [100] and mesoporous silica [92] are also attractive as potential templates.

2.2.5. Anisotropic templates

Anisotropic particles attract high interest [101,102] in the field of polyelectrolyte multilayer capsules due to their advantages over spherical particulates, including bio-mimetic behavior, shaped-directed flow, deformation, surface adhesion, targeting, motion, and permeability. [103] The LBL assembly based on anisotropic templates allows the precise control with various colloid geometries over their physical and chemical properties. These polyelectrolyte capsules have been shown to copy the shapes of sacrificial cores on which the polymeric shell is deposited. [104,105] Shape shift of these anisotropic capsules can be achieved by drying, [106] changing pH, [107–109] and permeability. [110,111]

2.2.6. Biological templates: cells, viruses, lipid-based

Overview of these and additional organic and inorganic templates, including such biological templates as red blood cells, viruses and liposomes has been presented. [112] Indeed, compared with colloidal micro- and nano-particles, novel bio-based and hybrid templates, including: nanocellulose, [113] erythrocytes, [114] cells, [115] bacteria, [116] protein [117] and liposomes [118,119] have great potential for applications in the biomedicine, cosmetic, and food industries due to their biocompatibility, biodegradability and biosafety.

2.2.7. Gel, microgel and nanogel templates

Additionally, hydrogel, especially alginate hydrogel, can be used as an ideal template candidate which can predefine the form and enhance biodegradability of microcapsules. [120–122] Acharya et al. developed a new hydrogel template approach to produce polymeric microstructures of different geometries by creating a silicon wafer master template (Fig. 2 e-l). [97] Chen et al. fabricated custom-shape microcapsules using hydrogel templates with poly-L-lysine shell via a stop flow lithography. [123] By tuning the properties of both the dextran-based degradable microgel core and the LbL membrane swelling pressure which is evoked by the degradation of the microgel is indeed able to rupture the surrounding LbL membrane. [124] The hydrogel template approach presents a new strategy of preparing microcapsules of predefined size and shape with homogeneous size distribution for drug delivery applications. The simplicity and high precision in processing makes the hydrogel template method useful for scale-up manufacturing of microcapsules.

2.2.8. Emulsions like oil-in-water and hydrophobic templates

Oil-in-water emulsions (O/W) exhibit a great ability to carry large quantities of hydrophobic substances in the dispersed phase and protect them from degradation. Oil droplets produced by such emulsions can be coated by thin polyelectrolyte shells and suspended in an aqueous medium to fabricate microcapsules serving as carriers of various agents. [125–130] Lee et al. developed a method to fabricate stimuli-responsive polyelectrolyte microcapsules in one step based on nanoscale interfacial complexation in emulsions. This one step method extends the utility of polyelectrolyte microcapsules and overcomes the major challenges that are presented by conventional polymeric microcapsule preparation techniques.

2.2.9. Air-bubble based capsules

Based on the template of air microbubbles and LbL self-assembly, Shchukin and coworkers [132] successfully accomplished electrostatic LBL assembly of polyallylamine/poly(styrene sulfonate)(PAH/PSS) multilayers on the surface of an air microbubble (core) to structure microcapsules with sizes ranging from 1 to 20 µm. The method can prevent the negative affects brought by core decomposition. Inspired by this work, Ge and coworkers [133] fabricated giant polyelectrolyte microcapsules with sizes ranging approximately 100 µm by depositing poly (allylamine hydrochloride) and poly(styrene sulfonate) onto monodispersity bovine serum albumin or liposome (Lipo) microbubbles.

Some of above-mentioned templates were summarized by Parakhonskiy et al. [112] and recently updated by Kozlovskaya et al. [103] In addition to above mentioned templates, one can also add three other classes: gel-, emulsion-, and air-based ones.

2.3. Polyelectrolytes in planar LbL and capsules

2.3.1. LbL method for making capsules

Production of polyelectrolyte multilayer capsules is conducted in several steps. As it is shown in Fig. 1, polyelectrolytes are deposited onto a sacrificial template, which is later dissolved. Weak polyelectrolytes are frequently used in multilayer capsules because greater control over coating properties can be achieved by varying the ionization of the weakly charged groups through pH adjustments. Rubner and coworkers have shown that pH stimulus can lead to a substantial and irreversible transformation of the film morphology fabricated by a pair of two weak polyelectrolytes: poly(acrylic acid) (PAA) and poly(allylamine hydrochloride) (PAH). [134] Tjipto and coworkers also achieved film control by developing a route involving a weak-strong copolymer pairs polydimethyldiallylammonium chloride (PDADMAC) together wth PAH. [135] Sukhishvili reported a binding of metal ions with weak polyelectrolyte multilayers which were highly permeable to reagents and reaction products within hundreds of nanometers of the film bulk. [136] De Geest and coworkers applied 'click' chemistry for the preparation of polymeric microcapsules based on biodegradable 'click linkages'. [137] The influence of ions on polyelectrolytes has been investigated by Schlenoff *et al*. revealing ion-free assembling of layers. [138]

2.3.2. Polyelectrolyte polymers for microcapsule

Different polyelectrolytes have been used for microcapsule production. A variety of polyelectrolytes, Fig. 3, has been used for fabrication of capsules, where several phases of development can be seen. [139] Initially, polyallylamine hydrochloride (PAH), polystyrene sulfonate (PSS), polydimethyldiallylammonium chloride (PDADMAC) and later polyacrylic acid (PAA), polyvinyl siloxane (PVS), polyvinylpyrrolidone (PVP), poly(N-isopropylacrylamide) (PNIPAAm), polyethylene glycol (PEG), poly(vinyl caprolactam) (PVCL), poly(N,N-dimethylacrylamide) (PDMAAm)) *etc.* have been used, partially driven by knowledge accumulated in the area of LbL flat surfaces. These polyelectrolytes allowed to accumulated initial knowledge of capsule preparation and allowed to control their properties. [140–148]

In the next phase and driven by high interest in biological applications, more biocompatible and biodegradable polyelectrolytes were used, including poly-arginine (PARG), poly-L-lysine (PLL), polylactic acid (PLA), hyaluronic acid (HA), chitosan (CHT), dextran sulfate (DS). The first HA/PLL assembly was made on planar surfaces [149] and later applied to polyelectrolyte multilayer capsules. [150] Biocompatibility of synthesized by LBL assembly has been investigated by Zyuzin et al. [151] Recent addition of tannic acid and bovine serum albumin has brought this area closer to preclinical trials. The choice of biopolymers for polyelectrolyte multilayer shell has been recently discussed. [152–157]

Further, such special polyelectrolytes as nafion, MEPE, *etc* bring essential and specific properties (such as a control over the permeability of the polymeric shell) and thus complete a wide range of polyelectrolytes used for preparation of capsules.

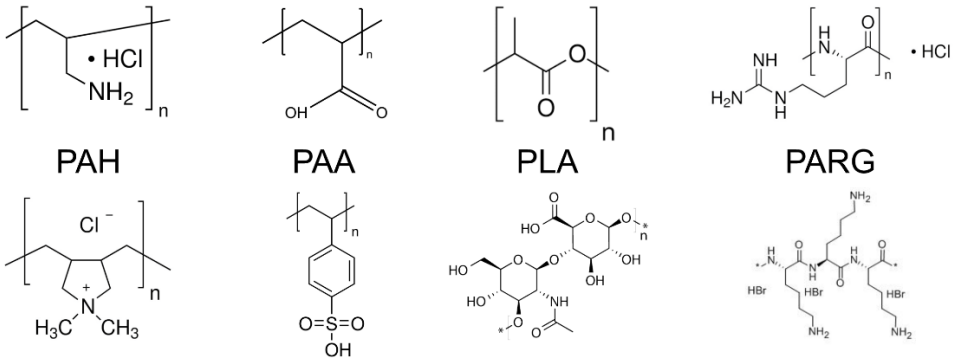


Fig. 3 Structure of some polyelectrolytes showing polyallylamine hydrochloride (PAH), polyacrylic acid (PAA), polylactic acid (PLA), poly-arginine (PARG), polydimethyldiallylammonium chloride (PDADMAC), polystyrene sulfonate (PSS), hyaluronic acid (HA) and poly-L-lysine (PLL).

2.3.3. Properties of PEM in microcapsules

Sukhorukov and co-workers have used a combination of weak and strong polyelectrolytes to investigate and exploit the effect of pH on a weak polyelectrolyte, while keeping the strong polyelectrolyte charged. Microcapsules allow to study the state of polymers, where mobility and intermixing of polyelectrolytes are important parameters. The degree of dissociation of polyelectrolytes in microcapsules has been investigated by Musin et al., [158] who studied the mixing of polyelectrolytes upon dissolution of calcium carbonate template (core): a partial intermixing of polyelectrolytes with encapsulated proteins. Directed electron transfer in the layers of microcapsules has been studied by Tedeschi et al., [159] who have doped polyelectrolyte multilayers by a dye, pyrene: an efficient electron transfer between the layers has been reported.

3. Encapsulation and release

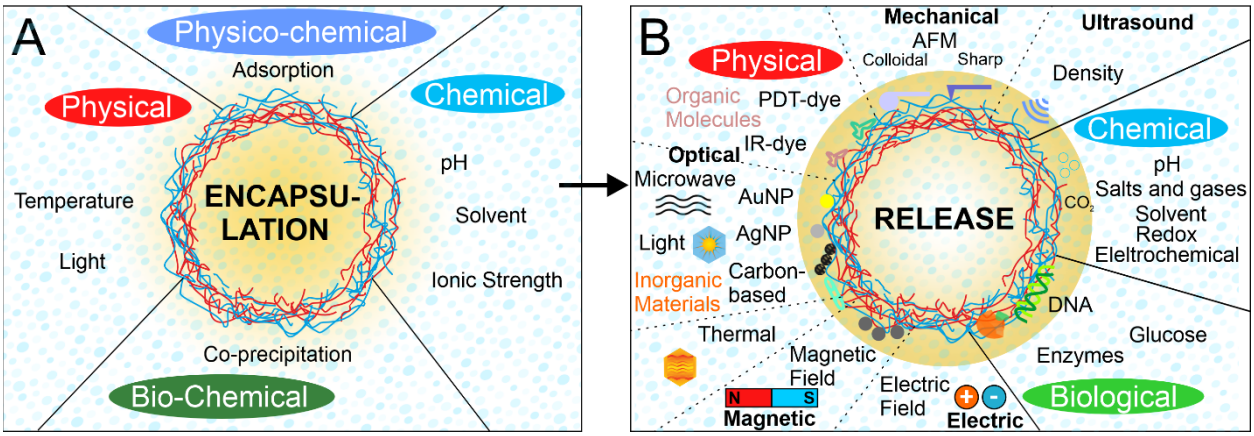


Fig. 4 Schematics showing diverse methods of encapsulation (a), release (b). The main categories and sub-divided details are shown with specific methods and examples of encapsulation, release.

3.1. Encapsulation

One of the most attractive properties of PEM capsules is a possibility of encapsulation of different molecules or compounds ranging from enzymes, nucleic acids, peptides, proteins, therapeutic drugs, biomolecules, fluorescent molecules, and nanoparticles in their hollow cavity. This can be carried out in many ways which can be sorted into two main strategies: direct and indirect. In the former case, encapsulation occurs during synthesis of the template core, such as coprecipitation or using the material itself as a template. In the latter cases, external triggers, for example, pH, temperature, light, and magnetic field which can control the permeability of the shell enable capsules to embed various substances.

3.1.1. Chemical stimuli

a) pH-based encapsulation

The pH-based encapsulation is achieved reversibly by adjusting the pH of the surrounding solution. The principle of this method is a change of electrostatic interaction between the polyelectrolytes.[160,161] Microcapsules swell, and the pores of the shell composition expand with the enhancement of permeability upon pH increasing. Molecules can penetrate inside the capsules smoothly. Decreasing pH can lead to a reverse process where the pores close and present a "pH-latch" equipped capsule interior loaded with cargo. [162]

b) Solvent

Another approach to achieve the incorporation of molecules into capsules is the so-called solvent-exchange strategy which based on different solubilities of molecules or ions in various solvents. [163] Loading into $CaCO_3$ particles (for encapsulation based on CaCO3 templates) can be done in pre-loading (upon incorporation) or post-loading (upon adsorption). [164]

c) Encapsulation of poorly water-soluble compounds

Generally, polyelectrolyte multilayers only allow small solutes such as ions, dyes, and drugs to penetrate while they prevent macromolecules. This semi-permeability can create a difference in physicochemical properties between substrate and microcapsules interior and make a chance to build up a polarity slope through shell component which can entrap poorly water-soluble compounds inside of microcapsules. [165]

3.1.2. Physical stimuli

a) Thermal-based encapsulation

Thermochemical responses of microcapsule assembly is another important tool to influence the morphology and mechanical properties of polymer shell. [166] This can assist the release of molecule in nano/microscale and control the size and mechanical properties [167,168] of such capsules in macroscale. [169–171] There is a temperature window (thermal range) for encapsulation and is just above the glass transition temperature of the polyelectrolyte pairs constituting the shell. [172,173] Beyond this threshold, irreversible shifting (shrinking or swelling) can occur due to the interplay of hydrophobic and electrostatic interactions. These heat treatment methods are very promising because they enable fabrication of mechanically stronger capsules. [174]

b) Light induced encapsulation

Analogous to other stimuli-responsive capsules, encapsulation could be achieved using the light-responsive capsules, for which their multilayer shell can be adjusted by shining to external light. [175] In particular, some interesting light sensitive molecules, for instance, azobenzene and photoacid play a critical role in light induced encapsulation. The transitions of azo-benzene molecules from *cis*- to *trans*-configuration upon illumination near the pores is a cooperative way thus embedding molecules inside capsules. [176,177] Photoacid generators (PAGS) was reported as another light-driven method can be used to modulate the permeability of polymersome membrane accomplishing encapsulation and release. [178]

3.1.3. Biochemical stimuli

Coprecipitation is a biochemical technique in which templates are synthesized by a direct precipitation strategy. Knowledge of biochemical properties of to be encapsulation materials is essential in this technique. [179] During the process of coprecipitation, [180] functional molecules are involved, and these molecules are entrapped into the interior of the template cores. Subsequently, the template is covered with polyelectrolyte multilayer shell, then deformed by producing hollow capsules.

3.1.4. Physco-chemical stimuli

Adsorption is an attractive physico-chemical approach due to its simplicity, [164] where molecules are added to already-prepared templates. Then, adsorption takes place due to various interactions, for example, electrostatic interaction, hydrogen bonding, or Van der Waals forces, *etc*. Most frequently employed templates were SiO_2 and $CaCO_3$. One of the biggest challenges of this method is a limited loading capacity. This loading capacity is determined by the porosity of template cores which surface absorb these molecules. In the case of non-porous templates, the loading can go to even worse situation.

3.2. Release from capsules

Once encapsulation and delivery for molecules inside are achieved the contents of the capsules need to be released at a particular site and time. The stimulus for trigged opening can be logically sort into three categories, including physics, chemistry and biology inspired methods. The release can be trigged by diverse individual stimulus and dual-stimuli, [181–183]even multi-stimuli. [184–186] Among these already used stimuli, pH variation, light irradiation, temperature changing, variation of the redox potential and the introduction of a magnetic field are the most widely used stimuli that can be used to induce the release of an active molecule in a medium. [187,188]

3.2.1. Physical stimuli

a) Mechanical deformation

Mechanical deformation is one of the oldest methods of triggering release since the first reports on carbonless paper. Quantification of release have been realized by incorporating with AFM technique. [189,190] Mechanically induced release of encapsulated content was simply triggered by a rotation, [191] where centrifugation-based method was used to quantify mechanical strength of the shell and mechanically induced release by plotting the pressure applied for release versus the shell thicknesses.

b) Optical

Light has been also applied as an external source, thus offering the capability to accomplish a precise and easily adjusted intensity, wavelength, and spatiotemporal control over the attachment of cells or biomolecules, biosensors, and diffusion of encapsulated molecules for controlled drug delivery purposes.

[192–194] The incorporation of various light-responsive materials, for example, metal nanoparticles (NPs), novel polymers, [195] light-absorbing dyes, [196–201] graphene [202] and carbon nanotubes [203,204] in LbL multilayer shell is the most widely used strategy. [131] Using near infrared (IR) light is attractive for carrying out release from microcapsules. Noble metal NPs or infrared (IR)-dyes that obtain high absorption in the near-infrared (NIR) range incorporated in polyelectrolyte multilayer structure are highly suitable for biomedical applications due to the low absorption of NIR radiation by skin and most of the tissues. Some metal NPs (gold nanoparticles) embedded in polymeric multilayer assemblies can adsorb the energy of laser which is shined on the structure and lead into localized temperature rise around noble metal nanoparticles and result in changes in the film permeability, morphology, composition, and structure. [205] Bedard et al. constructed polyelectrolyte microcapsules on dex-HEMA microgel as a sacrificial template and functionalized with gold nanoparticles, which were found to have the ability to release encapsulated material in a pre-determined direction by selectively irradiating a given region of a capsule's wall with an infrared laser. [206]

All these features benefit from the unique interaction of such metallic nanoparticles embedded within the component layers with light. Under the illumination of light, enormous electrons in these metallic materials are forced to collectively oscillate in phase, present generally as surface plasmon resonance adsorption of the NPs, whose adsorption cross-section is significantly more intense than normal dyes due to their surface-area-to-volume ratio. The local temperature increase caused by the metal NPs beyond the spinodal point of water and melting point of the metal, the different thermal expansion coefficients of materials could deform the assembly shell. [207]

Katagiri fabricated tunable UV-responsive microcapsules consisting of polyelectrolyte multilayers, lipid bilayers, and SiO_2–TiO_2. [208] Photocatalytic rupturing of the capsules upon UV irradiation triggered the release of loaded dye on demand. Yi et al. developed a new type of multilayer microcapsule composite of $(PDADMAC/PAZO)_4$-$(DAR/Nafion)_2$, which realized shell sealing and swelling upon same UV light exposure. [195] This strategy to fabricate such dual-function capsules triggered by single external stimulus inspired the development of multifunction capsules for further applications.

c) Temperature

Temperature changes can cause the melting of a microcapsule or can result in a phase transition, volume variations and transforming a hydrated state to a dehydrated state. This technique is to employ the inherent phase transition of polymer materials upon the change of temperature. Some temperature sensitive polymers which are used as wall materials can be categorized into heat-expandable polymers (e.g., PDMAAm/PAA) and heat-shrinkable polymers (e.g., PNIPAAm/ PVCL, poly(N-vinylcaprolactam)) based on the different temperature response. [209,210] Rising temperature can break hydrogen bonds in the heat-expandable polymers, then causing the expansion and loosening of the polymer network, thereby releasing encapsulated active agent. While heat-shrinkable polymers present on opposite way. In this route, the shell wall is comprised of a mixture of two polymers which repone differently to the change of temperature. One of the polymers shrinks when the microcapsule is heated, and another one remains physically intact, enable the creation of pores in the shell wall that allow core contents get through. [211] Meanwhile, temperature rapidly rises above the lower critical solution temperature (LCST), some heat-shrinkable polymeric microcapsules collapsed, thereby triggering the release of loaded cargo. [212,213]

The convenience of temperature stimulation makes these strategies particularly attractive for various applications,[214] since temperature affects, for example, softens polyelectrolyte multilayers. [215] In addition to directly heating a material, magnetic, [216] light, [217] microwave, [218,219] and electrical stimuli [220] can result

in temperature changes that ultimately lead to capsule triggering. It should be noted these stimuli leading localized heating of polymers to trigger release essentially still belongs to the thermal-induced release via external energy supply. [221]

d) Magnetic fields

Microcapsules with magnetic properties can be remotely triggered to release their payload by the magnetic field.[222–225] A common way to introduce a magnetic functionality is to adsorb magnetic nanoparticles into polyelectrolyte multilayers of the capsules. Alignment of magnetic particles entrapped in the composite shell structure along the direction of magnetic field creates driving forces inside the polyelectrolyte network which change penetration and desorption of macromolecules. [226,227] Another reason of the increased permeability can be the localized heating caused by magnetic nanoparticles serve as absorbing centers and inducing release.

e) Electric fields

Encapsulated cargo release of microcapsules with polyelectrolyte shells can be regulated by electric fields serving as sources of an electromagnetic irradiation. [228–232] A variety of electrically sensitive materials have been incorporated into microcapsule shells and cores. [233,234] The incorporation of molecules into shell walls that preferentially align in electric fields can be used to modify release rates of core materials. Kim and coworkers [235] fabricated electric field-response microcapsules with shell walls comprised of poly(vinyl alcohol) (PVA), poly(acrylic acid) (PAAc), and multiwalled carbon nanotubes. The release of loaded drug increased under higher applied voltages and with more efficient dispersion of carbon nanotubes throughout the capsule shell walls.

f) Ultrasound

The ultrasound waves applied in various processors and instruments has proven their efficiency to be used for release purposes both in vitro and in vivo without harming normal tissue.[236] The effect of ultrasound trigging a release benefit from acoustic cavitation in liquids created by ultrasonic waves. When the ultrasound waves is introduced, micro scaled air bubbles are formed immediately which was initially dissolved in the aqua solution and start oscillating in the surrounding fluid. Though the input power is low, these bubbles collapse cavitation and transit enormously concentrated energy in the fluid. Ultrasound-based release allows the capsule shell to tear into fragments leading to the release of molecules when the capsules are subjected to ultrasound stimuli. [237]

3.2.2. Chemical stimuli

a) pH-based release

Chemical stimulus, pH, was discussed in regard with encapsulation. But it as well as other chemistry-based stimuli such as salt and gases, can be also used as methods for triggering release. [24,238–241] pH dependent swelling behavior of polyelectrolytes multilayers architecture is the key property which induces the release of molecules. Such behavior was explained by the contribution of repulsive and attractive electrostatic interactions to the formation of collapsed and gel phases. [242–244]

b) Salts and gases

Salts, gases were also described as methods for inducing release. Electrochemical release from liposomes embedded into polyelectrolyte multilayers was demonstrated by Graf et al. [245] Salt is another key parameter, which can enable control the interaction of polyelectrolytes, their conformation in solution as well as glass transition temperature (Tg) of the polyelectrolyte complex. [246] Oligoamine patches on microcapsules induced release from capsules upon addition of CO_2 has been reported [247] Non-destructiveness of release in relation to microcapsules is certainly a significant advantage of such approaches. Their disadvantage is limited applicability in biomedicine.

Assembly capsules obtained by an emulsion-mediated process demonstrated unique plasmonic resonance responses, where release can be achieved by a solvent. The superior stabilizing power and unique self-assembly of nano-surfactants offer a possibility to encapsulate diverse payloads including nanoparticles for instance, quantum dots (QDs) Au, Fe_3O_4, and Fe as well as small molecules including Nile red, pyrene, and Doxorubicin (DOX) without adding any molecular surfactants. [248]

c) Redox reactions

The basic principle of redox-responsive microcapsules is to trigger the release of encapsulated molecules utilizing redox reaction upon addition of oxidants or reductants. [249,250] Redox-responsive microcapsules broadly involved disulfide linkage which is reduced by different reductive agents, including NaBH4, glutathione (GSH) and folic acid (FA). [251–253] Following this principle, Caruso et al. [254] developed a novel polymer hydrogel microcapsule based on disulfide cross-linked poly(methacrylic acid) (PMA_{SH})and poly(vinylpyrrolidone) (PVPON) on silica particle templates. A cellular concentration of GSH triggered degradation of microcapsules by inducing disulfide bonds on the walls. Vansco et al. [255] fabricated redox-controllable permeability of polyelectrolyte microcapsules by repeatedly depositing both the positively and negatively charged polymers contained ferrocene repeat units (PFS–/PFS+). The oxidation of ferrocene units triggered capsule swelling and allowed to increase the permeability of microcapsule shell walls.

d) Electrochemical stimulus

Electrochemical stimulus was used to induce release from microcapsules functionalized with liposomes, [245] where electrochemical stimulus was reported to induce locally confined pH values. That would induce protonation of the phospho-L-serine lipids leading to release of their contents.

3.2.3. Biological stimuli

Different biological stimuli are available for biodegradation-based release, including glucose responsiveness and enzyme degradation. [256–259]

a) Glucose

Glucose responsive capsules using acid as a glucose-sensitive moiety have been reported first by De Geest et al. [260], who described phenylboronic acid-based glucose-responsive polymeric capsules disassembled in less than 5 min in the presence of glucose; then, other groups have reported additional studies. [261,262] These polyelectrolyte capsules are the first polyelectrolyte capsules able to respond to a stimulus that can be provided by the human body which would accelerate the process of applying capsules in the biomedical field for the controlled delivery.

b) Enzymes

Enzyme-based degradation and biodegradability are increasing significant in biology and drug delivery field. [263,264] Destruction by disulfide bonding deconstruction and enzymatic reaction have been widely used in such applications. Enzyme-catalyzed degradation of multicompartment polyelectrolyte multilayer capsules was observed at Fig. 5. [265] It illuminated incorporation of synthetic polyelectrolyte layers in the shell of capsules composed of otherwise biodegradable polymers significantly slows down degradation and release of encapsulated material. On contrary, increasing the concentration of pronase (enzyme), which causes polypeptide degradation, enhances the degradation rate.

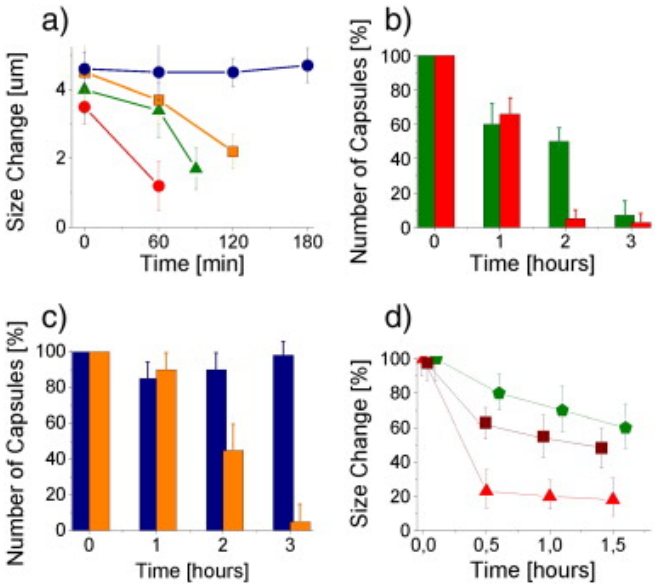


Fig. 5 a) The average size decrease of capsules upon biodegradation. The following notations are used: degradation of $(pArg/pGlu)_4$ is shown in the curve with red circles, $(pArg/pGlu)_8$ with green triangles, $(PAH/PSS)(pArg/pGlu)_3$ with orange squares, while degradation of $(pArg/pGlu)_3(PAH/PSS)$ capsules is represented by the curve with blue circles. Size decrease incurred from sampling kinetics of degradation for: b) $(pArg/pGlu)_4$ (red) $(pArg/pGlu)_8$ (green), c) $(PAH/PSS)(pArg/pGlu)_3$ (orange) and $(pArg/pGlu)_3(PAH/PSS)$ (dark blue). Data in (d) are collected in an in-situ measurement when the same capsules are continuously monitored under CLSM for $(pArg/pGlu)_4$ (red triangles) and $(pArg/pGlu)_8$ (green pentagons) both at 1 mg/mL of Pronase as well as for $(pArg/pGlu)_4$ (dark red squares) at 5 mg/mL Pronase. Statistics was collected for over thirty capsules and three experiments. Reprinted with permission from ref. [265]. Copyright 2021 Elsevier.

3.2.4. Dual- and multiple- stimuli

It is difficult to satisfy requirements in various applications with a single trigger release stimulus. So, novel strategies are needed among which are the so-called dual- and multi-responsive systems. They integrate internal and external stimuli receptors into one system.[266,267] Further, Yi et al modified pH-responsive microcapsules with UV-responsive benzophenone (BP) groups to increase their stability. [268] Liang et al developed a LBL assembled polymer capsules poly(2-diisopropylaminoethyl methacrylate) (PDPA) which responds to variation of pH and redon potential. [269] This dual-responsive microcapsules present reversible size changes with pH and cleavage of the redox-responsive cross-linker in reducing conditions. Gunawan et al. reported a LbL-assembled polymer capsule system combining the pH-responsive behavior and an enzyme-specific degradable cross-linker. [270] This approach represents a highly modular strategy, combining the advantages of an engineered peptide and pH responsiveness to enhance *in vitro* polymeric

carrier degradation. Simple and efficient combination of multiple stimuli which can trigger dual/multiple stimuli-responsive cargo release broadens the application range of such “smart” capsules for therapeutic and diagnostic applications.

4. Applications of microcapsules

In this review, we have identified several important application areas, which are divided based on the extent of development. By far, the largest application area is that dedicated to biomedical applications (section 4.1), which is covered first in this review. Subsequently, cosmetics-, fragrance-, and volatile compound-based encapsulation is presented (section 4.2), followed by food-related applications (section 4.3). These sections follow by the so-called specialty applications (section 4.4), which are seeing the most essential developments and are undergoing further development phases. The largest area, biomedical applications, is sub-divided into a number of sub-areas where some noticeable advancement include pre-clinical studies, Fig. 6.

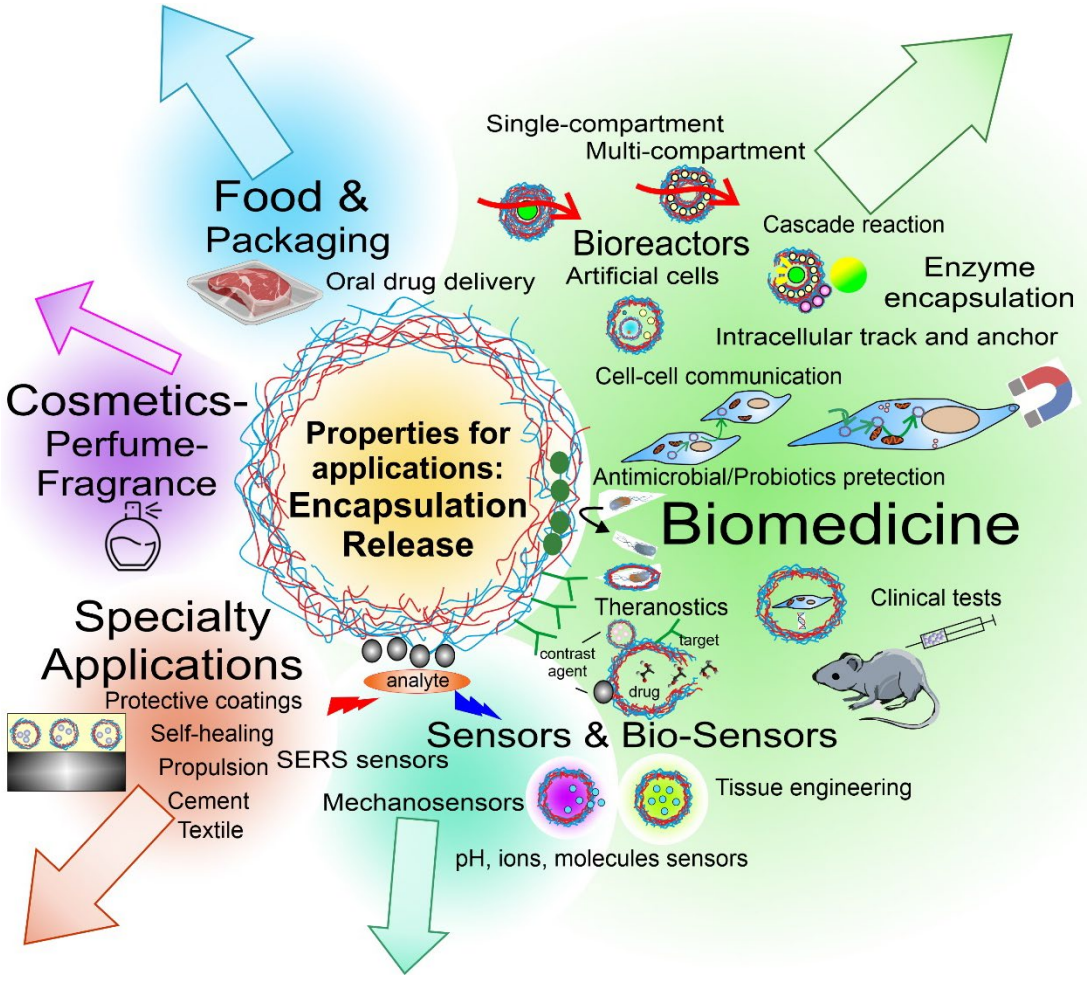


Fig. 6 Schematic showing various application areas of polyelectrolyte multilayer capsules and outlook for future developments denoted by arrows.

4.1. Biomedicine

4.1.1. Cell biology applications and delivery into cells

LBL microcapsules is an attractive platform for cells because of their controlled biochemical composition, topographical features and mechanical properties. [271,272] Cells have been shown to uptake polyelectrolyte multilayer capsules. [273–276] Generally, cell membranes have a net negative charge, although, some positively charged domains also exist. Adhesion of microcapsules to cells has been studied by atomic force microscopy (AFM) upon mounting them on a tipless cantilever.[274] An increasing uptake was reported by Brueckner et al. through increasing microcapsule/cell ratio, which is independent of the properties of microcapsules. [275]

Pavlov et al. demonstrated a strategy to use multilayer capsules loaded with iron oxide magnetic nanoparticles functioning as anchors to remotely control mobility of live cells which internalize these capsules via a magnetic field. [277] This strategy was inspired by cell uptake of responsible capsules. Additionally, the presence of magnetite nanoparticles in LbL microcapsules provides the possibility for MR imaging application. Another interesting application based on the internalization of microcapsules is cell-cell communication. Zhu et al. developed a methodology enable local lysosomal Ca^{2+} release which directly controls intra- and intercellular communication. [278] To achieve this, cells are loaded with PEM capsules with unified plasmonic nanoparticles, Fig. 7, spreading of Ca^{2+} waves to interconnected cells or cells without direct contact was recorded in 2D cells, even 3D tumor spheroid upon laser irradiation.

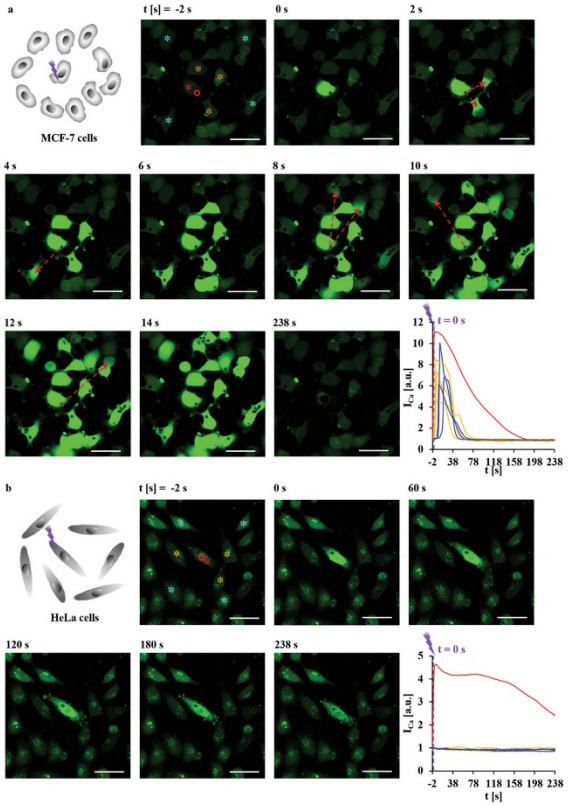


Fig. 7 a) MCF-7 and b) HeLa cells were seeded at densities in which cells were not in direct contact with each other. At time t = 0 s, one endocytosed capsule with embedded star-shaped Au NPs, as indicated by the red circle, was irradiated at 830 nm with an irradiation area of A_{laser} = 12.56 µm2 (20× objective, LSM880) at P_{laser} = 71.25 mW (at the illumination spot) for Δt_{laser} = 0.039 s. The scale bars represent 50 µm.

Images were taken every 2 seconds. The integrated fluorescence intensity of the calcium indicator Fluo-4,I_{Ca}, over the cross-section of the whole cell area was normalized to that before irradiation (t = −2 s), which relates to the $[Ca^{2+}]i$, is plotted versus time t. The colors of the curves indicate the cells in which the Fluo-4 intensities were measured, as given by the color of the stars labeling the respective cells. Red stars indicate irradiated cells. Yellow or blue stars indicate cells close to or far away from the irradiated cell. Red arrows indicate the calcium spread direction from irradiated cells to adjacent cells. Reprinted with permission from ref. [278] with permission from Wiley, copyright 2021.

Another active field of research, cell encapsulation, which build up LBL coating shell on cell template has gained enormous attention. [115,279–284] A wide variety of living cells can be used as templates for encapsulation assembly, ranging from bacterial or filamentous fungi to mammalian cells and multicellular cell clusters. Red blood cells were some of the first cells for LBL self-assembly. [285,286] The choice of a modification shell is determined mostly by properties of the modified biological system and by a possible need for keeping it viable during and after the encapsulation. Immunological or physical protection for cells is one obvious benefit that microcapsule structure introduce. [287,288] Mechanical properties of microcapsules are becoming stronger with an increased number of layers or addition of nanoparticles. [175,289,290] But another way of developing capsules suitable for bio-medical applications is to mimic the properties of red blood cells, [291] because the deformability is important to study for assuring delivery in biomedicine.[292,293] Elasticity, similarly to properties of RBC, is important because that allows for capsules to restore their shape after deformations. [294] Kozlovskaya et al. formed LBL assembly utilizing hydrogen-bonded interactions of a natural polyphenol (tannic acid) with poly(N-vinylpyrrolidone) deposited on the islet cells surface to treat Type 1 diabetes. [295] Intracellular release for different types of cells, for example neuron cells, [296] represents a powerful tool for targeted delivery. Biocompatible microcapsules were metabolized by bio-molecular cell machinery without affecting cell viability. Our previous work demonstrated the release of encapsulated standard molecules, fluorescent AF-488 dextran, from polyelectrolyte-multilayer inside living cells upon illumination by laser beam. [297] Cisplatin, an anti-cancer drug commonly used for treatment of solid malignancies, was efficiently encapsulated and delivered into HeLa and MCF-7 cancer cells. [298] Fig. 8 demonstrates the remote release of tagged proteins can be achieved in worms using a near-infrared laser light as a trigger from polymeric microcapsules and novel hydrogel microcapsules functionalized with silver nanoparticles, respectively, which extends possible future strategy for gene delivery in worms, insects, and other organisms. [299,300]

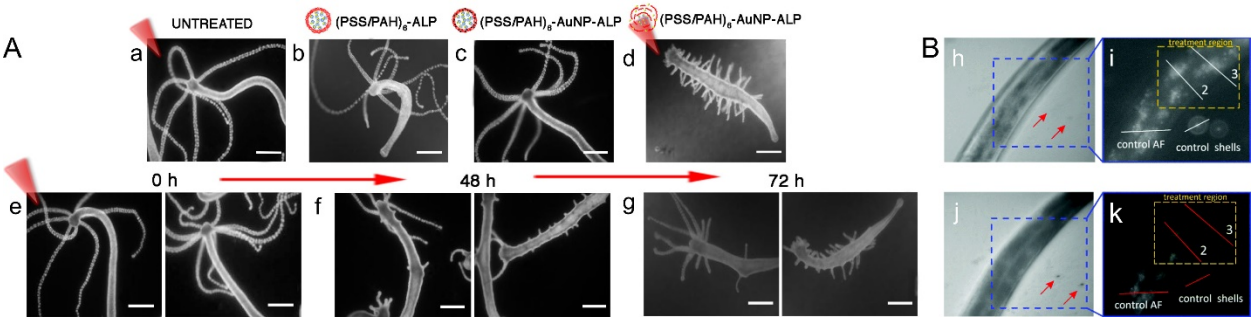


Fig. 8 A) Spherical structures detected by contrast phase imaging are nematocytes, i.e., the stinging cells present on Hydra ectoderm, employed by the animal for prey capture. At 72 h after irradiation, no effects were detectable in (a) untreated animals, irradiated; (b) polyps treated with $(PSS/PAH)_6$-ALP, not irradiated; (c) polyps treated with light responsive $(PSS/PAH)_6$-AuNP-ALP, not irradiated. Typical ALP morphologies were induced in (d) polyps treated with $(PSS/PAH)_6$-AuNP-ALP and irradiated. The dynamic of tentacle emergence is shown at 48 h (f) and 72 h (g) post irradiation. Scale bars: 500 µm in (a–g). B)

Optical and fluorescent images of the same section of *C. elegans* with uptaken silver-alginate shells possessing encapsulated TRITC–BSA immediately prior to (upper row, h and i) and after (lower row, j and k) laser irradiation at 15 mW. Reproduced from ref. [299,300] with permission of 2016 American Chemical Society and 2018 The Royal Society of Chemistry respectively.

PEM capsules which are assembled under native conditions where active molecules are not chemically altered or inactivated have many advantages that lend to their application as cargo delivery vehicles, [301] such as drugs, [302] cells, [303] protein, [304,305] genes [306] et al. Incorporation of bioactive compounds onto polymer fibrous scaffolds with further control of drug release kinetics is essential to improve the functionality of scaffolds for personalized drug delivery. [307] Microcapsule-based drug delivery system have attracted broad interests for cancer treatment in recent years due to their distinct characteristics, including the capability enhancing permeability and retention (EPR) effect with reduced size and the possibility to refine the surface for precisely recognizing the attributes of the healthy cells and cancer cells in the clinical contexts. [308,309] Co-delivery of dual drugs, doxorubicin (DOX) and mitoxantrone (MTX), has been developed based on liposomal nanoparticle capsules which significantly reduce the clearance rate of the two drugs and prolong their circulation time *in vivo*. [310] Microcapsules not only provide cells containment at implantation site but also protect them from adverse environment such as host immunoresponse, degradation and shear stress. In parallel, the semipermeable membrane allows oxygen, nutrients and signaling molecules entering to these microcarriers. Various cells, for example, red blood cells, liver cells, stem cells, fibroblasts cells, and endothelial cells, entrapped in microcapsules can be genetically altered to produce specific bioactive products such as hormones, neurotransmitters, growth factors, enzymes, and antibodies. It is worth noting, so far, only a few cell vehicle applications have reached clinical trials. The main challenges that still interfere progress of these carriers towards clinical application is limited cell survival *in vivo*.

Microcapsules can also enable intracellular delivery of encapsulated bioactive molecules. [311–313] The pathway of cellular internalization (uptake and fate) of PEM capsules has been investigated. [314,315] These either lipid or polymer coated microcapsules appear to have only a minor influence on cellular metabolism. [316] Luciferase enzyme and plasmid DNA were delivered to cells with biodegradable microcapsules containing a layer of magnetite nanoparticles. [11]

The application of PEM capsules in the field of gene delivery has gained increasing interest due to its capability to easily load genetic material, and, moreover, the possibility to load dual, even multiple molecules within an individual carrier, which increases transfection efficiency and enables more functions. [317] PEM capsule-based carriers can be used for delivery of diverse nucleic acids: plasmid DNA (pDNA), small interfering RNA (siRNA), messenger RNA, and genome-editing tools. [318–321] Fig. 9 represents promising microcapsules working as non-viral platforms for efficient and safe gene editing. Co-delivery of drug and siRNA within a single PEM capsule provide a promising method in cancer therapy since the combination of drugs and siRNA can alter multiple disease pathways for tumor treatment. [322,323] pH-sensitive cationic liposome (CL) was developed for co-delivery of sorafenib and siRNA to the tumor tissue. [324]

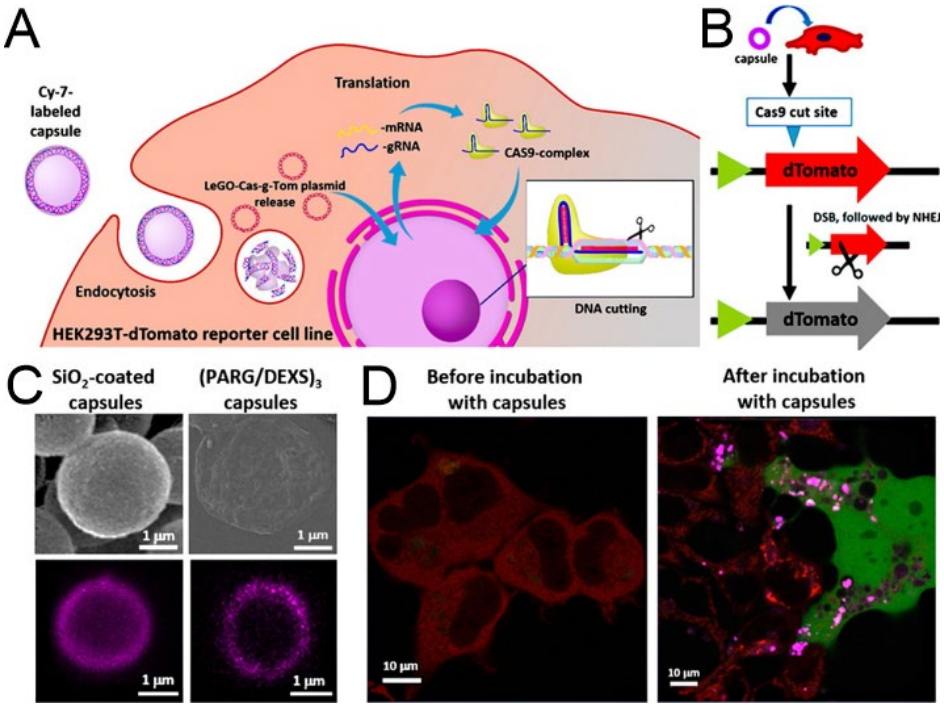


Fig. 9 Principle of dTomato knockout in the HEK293T-based indicator cell line. A) The illustration shows application of microcapsules for intracellular LeGO-Cas-gTom plasmid delivery and gene editing. B) Schematic representation shows that delivery of LeGO-Cas-gTom plasmid introduces double-strand breaks in dTomato gene, which are repaired by non-homologous end-joining (NHEJ) often resulting in insertion/deletion (Indel) mutations corrupting the open-reading frame and thus impairing protein expression in the affected cell. C) SEM and CLSM images of SiO_2-coated capsules and (PARG/DEXS), respectively. D) CLSM images of HEK293T-dTomato cells incubated with (PARG/DEXS)3 capsules containing Cy-7/LeGO-Cas-gTom plasmid, hollow (PARG/DEXS)3 capsules with Cy-7 and without LeGO-Cas-gTom and free LeGO-Cas-gTom plasmid during 144 h of cultivation. Red signal, dTomato protein; green signal, eGFP protein; violet signal, Cy-7. Reprinted with permission from ref. [318]. Copyright 2018 Elsevier.

4.1.2. Sensors and biosensors

PEM capsules function as elements of sensing systems. It was shown that PEM micro/nano structures can significantly enhance sensitivity and selectivity of these sensors and biosensors due to their self-assembly capability with oppositely charged components to obtain a multilayer structure. Control of their structure at the micro/nanoscale level enables an improvement of intrinsic properties in comparison with the traditional bulk materials. [325,326]

Various sensors implemented with PEM microcapsules have been classified in three distinct categories: chemical, physical, and biological. [327] Within the last decade, microcapsule-based sensors possessing such reporters as fluorescent dyes and enzymes are of growing importance. A variety of fluorescent dyes is used to convert chemical into optical signals. [328] These strategies enable investigation of change of surrounding environment in local proximity to a particular surface, for instance, analytic concentration and ion strength. [329] Monitoring the surrounding pH value of a solution is considered as an important application of these chemosensors developed by Parak and co-workers. [330] In that report, a pH-sensitive high molecular weight SNARF-1-dextran, was loaded in microcapsules. The spectral properties of the dye

were maintained after the encapsulation. This method requires a confocal laser scanning microscope equipped with spectral read-out capabilities showing shift of fluorescence signal from green to red channel upon changing pH values from 6 to 9, respectively. In another study, triple dyes (fluorescein, Oregon Green, and rhodamine B) were simultaneously embedded in microcapsules and served as real-time localized pH sensors (in the range of 3.3–6.5). [331] Microcapsule-based biosensors allowed control of cell growth upon pH changes due to variations of the surface charges caused by protonation/deprotonation of carboxylic groups, Fig. 10. [24] Enzyme encapsulation further extends the application range of capsules. [8] In this regard, PEM capsules with a built-in pH-based fluorescent sensor allowed a highly sensitive and high-throughput study of carrier internalization by living cells. [332]

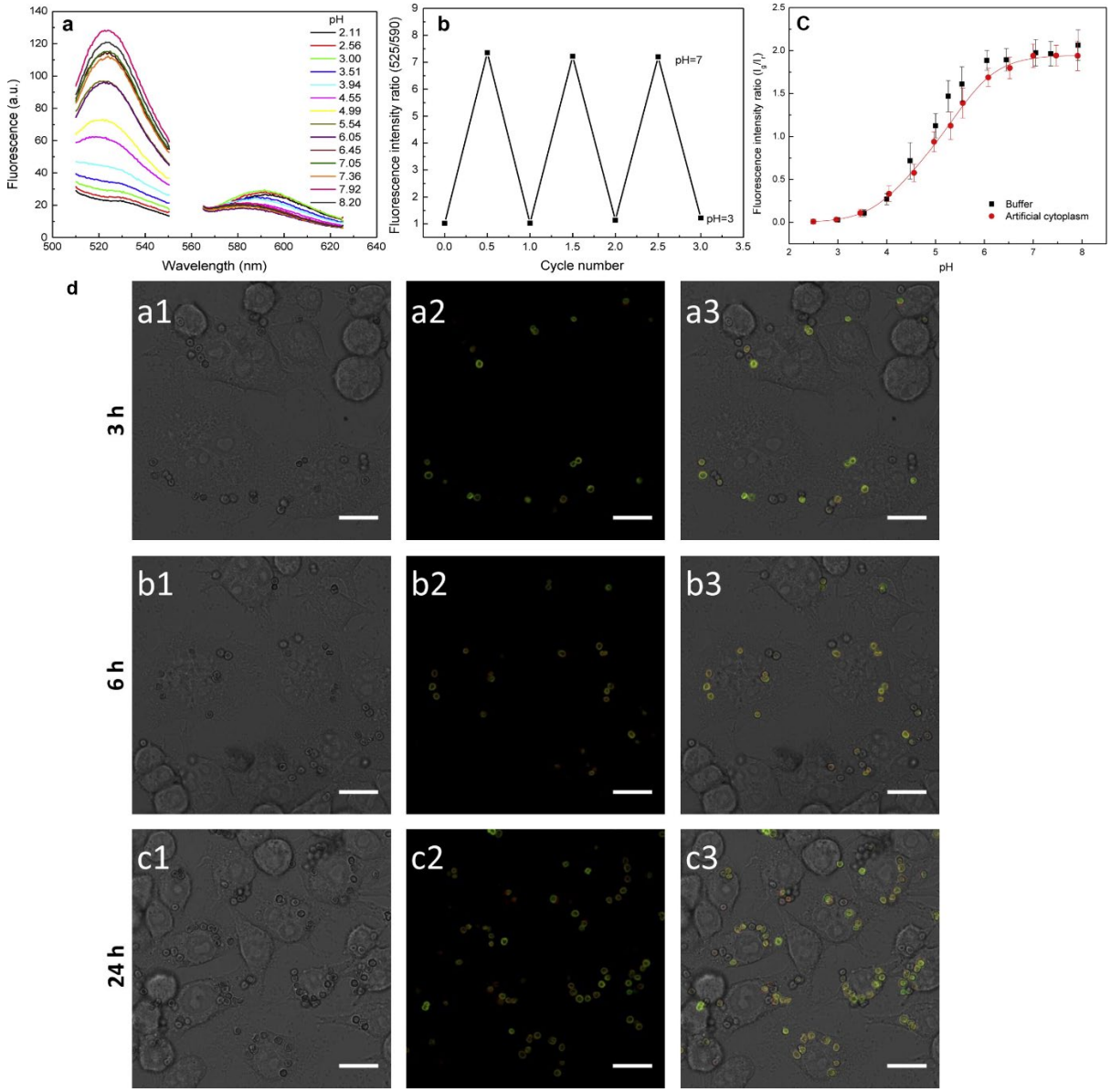
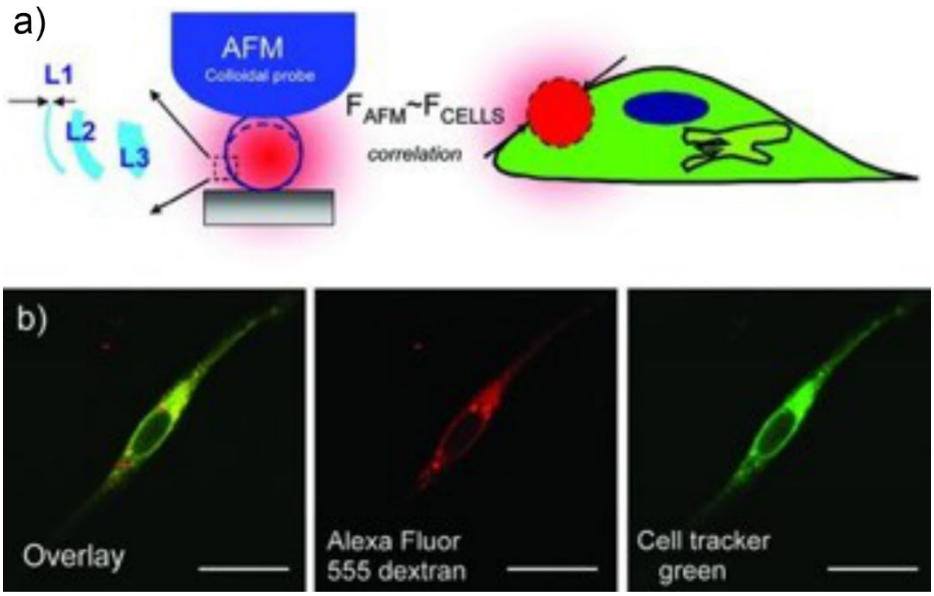


Fig. 10 (a) Fluorescence emission spectra of microcapsules in buffers of various pH values. (b) pH reversibility study of microcapsules between pH 3 and pH 7. (c) *In vitro* calibrations of the capsule sensors. Calibration was carried out in buffers and artificial cytoplasm. Calibration in the artificial cytoplasm was fitted with an equation. [333] (d) CLSM images of RAW 246.7 cells with internalized triple-labeled

662 microcapsules after 3 h (a1-3), 6 h (b1-3), and 24 h (c1-3). Left column: bright filed images; middle column:
663 overlay images of the green and red channels showing the microcapsules; right column: overlay images
664 of the bright filed images and the corresponding fluorescence images. Scale bar is 15 µm. Reproduced
665 from ref. [331] with permission of 2014 Elsevier.

666 ### 4.1.3. Mechanosensors for mechanobiology

667 In addition, capsules under physical stimuli can serve as mechanosensors because of controllability of
668 mechanical properties. [334,335] Development in this area is based on earlier work investigating mechanical
669 properties of microcapsules. Studies [336,337] conducted employing an AFM revealed that forces in the range
670 of hundreds of piconewtons led to buckling of those capsules which were not mechanically enhanced, for
671 example, by a thermally treatment. Mechanical properties (the Young's modulus or stiffness) of thermally
672 shrunk(PSS/PDADMAC)$_4$ capsules increased by four times after heating them for 20 min at 50 °C, and even
673 more remarkably, by more than ten times upon heat treatment at 55 °C. [338] The improvement of the
674 stiffness is attributed to an increase of the wall thickness that accompanies the heat shrinking. Further,
675 Delcea et al. developed three different types of microcapsules which own increasing mechanical strength,
676 and incorporate those capsules into cell line, Fig. 11, a threshold of pressure force of approximately 0.2
677 µN exerted by cells upon incorporation of capsules was noticed. [339] Fernandes et al presented a novel
678 approach, in which AFM was coupled to a fluorescence microscope allowing to investigate the correlation
679 between release of entrapped molecules and mechanical deformation of individual microcapsule. [189] The
680 quantification of release upon mechanical deformation presented in that work is useful for designing
681 microcapsules with optimal mechanical properties. This is particularly relevant for intracellular delivery,
682 pharmaceutical and biomedical applications.



683

684 **Fig. 11** a) Schematics representing the use of capsules made of synthetic polymers as sensors to estimate
685 the force exerted by cells upon intracellular incorporation. This is done by correlating the force applied by
686 the AFM colloidal probe method with successful delivery into cells. b) Fluorescence images of a cell after
687 incorporation of microcapsules shrunk at 55 °C and containing encapsulated Alexa Fluor 555 dextran. The
688 left panel shows the overlay (the left panel) depicting the leakage of Alexa Fluor 555 dextran molecules
689 (the red channel, the middle panel) introduced into intracellular environment (the green channel, the

right panel). The scale bars correspond to 30 µm. Modified with permission from ref. [339]. Published with permission of 2010 Wiley.

4.1.4. Bioreactors: single- and multi-compartment – towards artificial cells

Capsules having the ability to entrap active biomolecules in the large hollow shell have found application in the diverse field as bioreactors, biomimetics and artificial organelles. [68,340–342]

Conventional bioreactions are carried out in plastic tubes or multi-well plates where they take place and involve pre-treatment steps for samples. Miniaturization of bioreaction in PEM capsules brings the possibility to downsize samples and reagents, Fig. 12. [343,344] The shell structure of capsules can also provide a protective barrier to prevent other irrelevant molecules entering and interfering with the bioreaction.

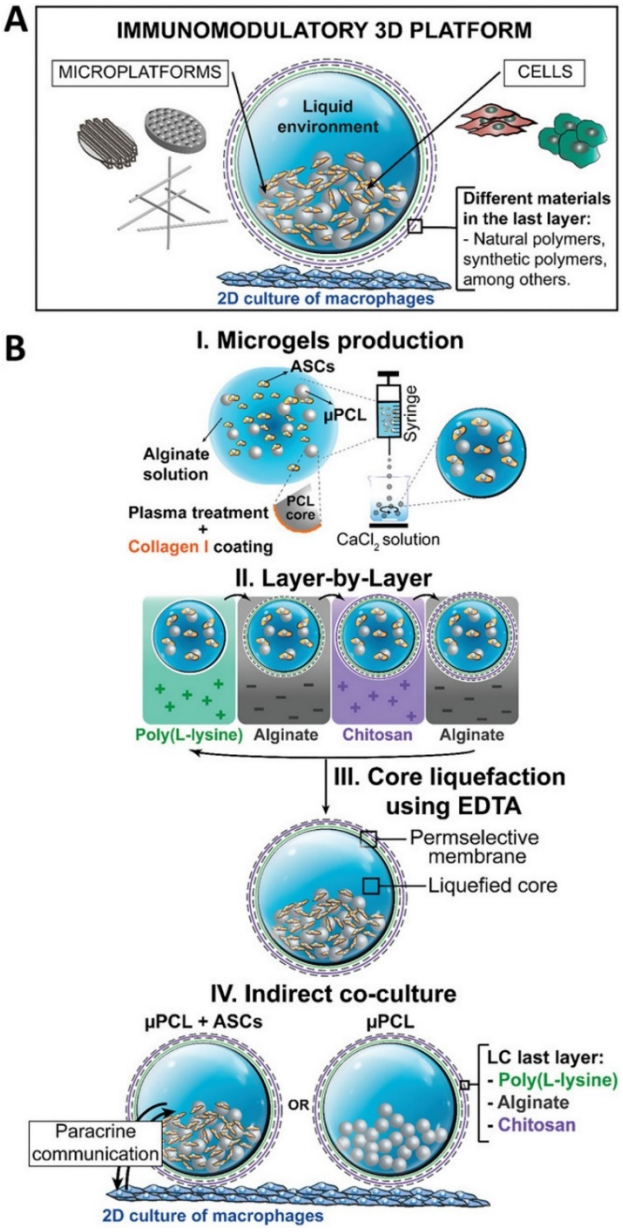


Fig. 12 A) Immunomodulatory miniaturized 3D platform using liquefied capsules for the in vitro high-throughput combinatorial screening of different biomaterials, cells, and bioinstructive microplatforms. B) Production and culture of the liquefied capsules: (I) Microgels are obtained by the ionotropic gelation of alginate containing adipose-derived mesenchymal stem cells (ASCs) and surface functionalized poly(ε-caprolactone) microparticles (μPCL) in calcium chloride ($CaCl_2$) solution. (II) Then, to produce a permselective nano-layered membrane, the layer-by-layer technique is performed using three different polyelectrolytes, namely poly(L-lysine) (PLL), alginate (ALG), and chitosan (CHT). (III) The liquefied core is obtained by chelation with ethylenediaminetetraacetic acid (EDTA). (IV) Three different encapsulation systems were developed, each one ending with a different polyelectrolyte, namely PLL, ALG, or CHT. Ultimately, the different immunomodulatory 3D platforms with or without cells are added on top of 2D culture of macrophages. Reprinted with permission from ref. [344]. Copyright 2021 Wiley.

In addition, the formation of microcapsules to carry out enzyme catalyzed reactions is another emerging application area. [345–347] Often ultrasound triggered destruction of polyelectrolyte capsules could be used for catalyzing reactions. Our previous work demonstrated capsule suspension which shell composite embedded silver nanoparticles after short sonic exposure can catalyze the reduction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP) by sodium borohydride ($NaBH_4$). [348] Tseng et al. designed silver/titania (Ag/TiO_2) composite microcapsules which TiO_2 shell avoided the encapsulated silver nanoparticles from breaking away under moderate loading. Consequently, the mesoporous shell served as a channel allowing embedding of Ag ions, which upon release, can kill bacteria in aqueous solutions. [349]

Fusion of PEM microcapsules has enormous potential towards biomimetics and bioreactors. The fusion study on cell-sized microcapsules also provides perspectives for potential applications in gene transfection and drug transport across multilayers. A fusion of capsules, which has been triggered by salts [350] and pH [351] as well as by laser irradiation [352] can act as a highly effective multifunctional bio/chem reactor, Fig. 13.

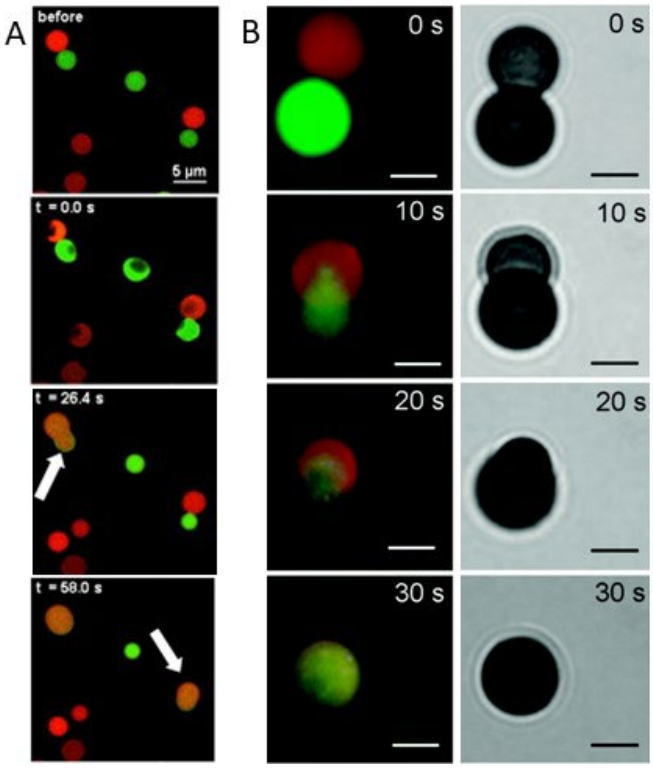


Fig. 13 A) A series of fluorescence snapshots of the salt-induced microcapsule fusion. At t = 0, a solution of 3 M NaCl was added to a mixture of FITC- and TRITC-dextran-filled $(PDADMAC/PSS)_4$ microcapsules. Time lapse images showing the fusion process at 26.4 s, and 58 s after adding NaCl solution. B) Fluorescence (left) and bright field (right) images of a series of snapshots of the laser induced $(PDADMAC/PSS)_5$/AuNP capsule fusion. At t = 0, laser light with a power of 30 mW was directed on a mixture of FITC- and TRITC-dextran filled $(PDADMAC/PSS)_5$/AuNP capsules. Time lapse images showing the fusion process at 10 s, 20 s, and 30 s after laser radiation. Scale bar = 5 µm. Modified with permission from ref. [350,352]. Published with permission of 2010 and 2015 The Royal Society of Chemistry.

An advanced multicompartment microcapsule system is able of comprising of multiple compartments for integrating multiple functions within a single architectural. Multicompartmentalization is one of the most crucial architectural features and universal organizational principles of capsules. Previously, a few different multicompartment structures have been reported with the advent of the development of new microreactor architectures based on LbL capsules, [353,354] and only single enzyme reactions were described. A hierarchical and graded design for the interior space and shell of the microcapsule is common structure for multicompartmental microcapsules. Complex templates, such as satellite nanoparticles and porous microparticles [355], polymersomes [356] or polymer vesicles[357] as a main component, microfluidic method[358] and Pickering emulsion polymerization [145] have been employed to fabricate multicompartment microcapsules. Dual-compartment capsule-in-capsules architecture which can be used for conducting bioreactions and release of cargos in confined spaces were constructed by fabrication of the inner and outer parts of multicompartmental microcapsules. [360–363] Emerging microcapsules with multiple separate sub-compartments and independently triggered release functionality under different stimuli, the so-called multicompartmental “smart” microcapsules, have been also proposed. Additionally, the release of diverse payloads can be programmably triggered by preprogramming the order of the stimuli. [364] Nanocapsule@microcapsules structure, Fig. 14, was fabricated by absorbing negatively charged nanocapsules onto positively charged melamine-formaldehyde-polyethyleneimine microcapsule surface. [365] This pH-responsive assembling and disassembling of nanocapsule@microcapsules was shown at pH 7 and pH 3. Application of microcapsules regarding applications of artificial organelles and cell mimicry was discussed considering light of broader biomedical applications. [366]

With the inspiration of such a talented structure, multicompartmental microcapsules which mimic the compartmentalized architecture of living cells have received considerable attention towards the artificial cells field. [367–369] Various compartments distributing in the capsules can mimic organelles, subcellular structures, that spatially separate cellular processes with an established intercompartment communication network for signal transduction.

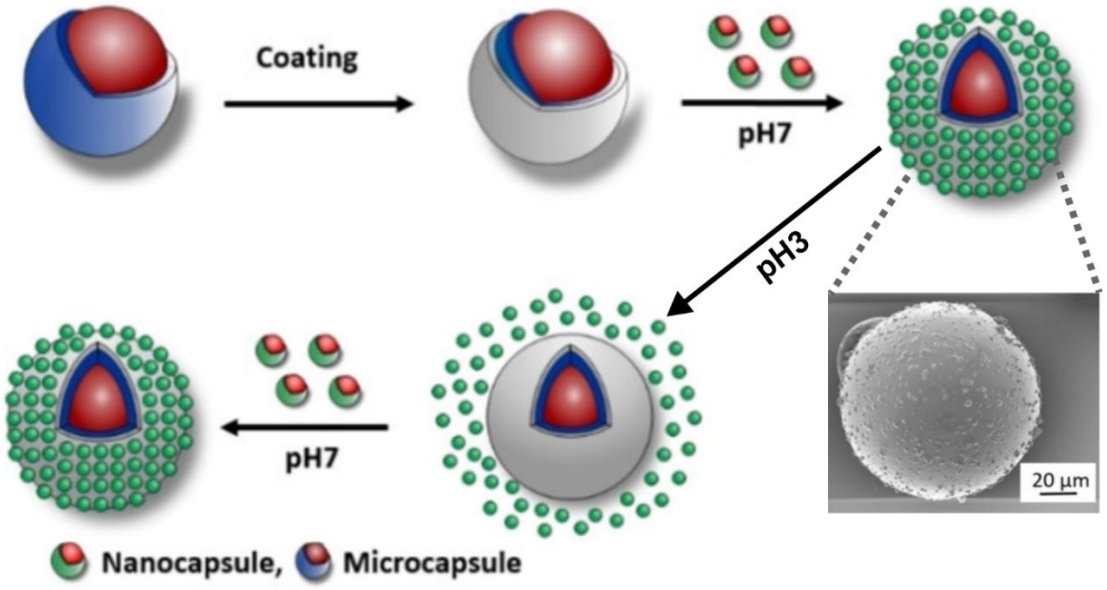


Fig. 14 Flow chart of multicompartment microcapsule synthesis and pH-responsive disassembly. A novel coating for microcapsules was applied to change the surface potential from negative to positive. Nanocapsules with a negative surface charge were added to positively charged multilayered capsule to form a multicompartment microcapsule structure. Insect SEM images of spherical MF-PEI-coated microcapsules with some inhomogeneity at the surface. Reproduced, modified, with permission from ref. [365] Published with permission of 2021 Wiley.

4.1.5. Enzyme encapsulation

A wide variety of enzymatic reactions have been performed in the PEM capsules. Encapsulation of enzymes with multilayer capsules allows to preserve their biological activities in various surrounding conditions, such as exposure to elevated temperature or to proteases, which enable their extensive application *in vivo* [187] and *in vitro*. [370] In our previous work, an optimal temperature window for encapsulation of the enzyme ALP with PDADMAC/PSS shell was found, and it is situated just above the glass transition temperature of polyelectrolyte PDADMAC/PSS pair. [171] This novel procedure for temperature-based encapsulation of enzymes was proven to maintain their catalytic bioactivity. Spider silk protein eADF4(C16) assembled capsules, which are mechanically stable and semi-permeable, was shown capable of entrapping the enzyme β-galactosidase, thus highlighting broad applicability of such containers. [371]

4.1.6. Theranostics

An unique role of microcapsules in theranostics is that they can co-encapsulate different molecules, i.e. those serving as sensors and those having therapeutic functionality. [372] Microcapsules, designed with targeting capability and allowing prolonged release of drugs are of interest. [373,374] Sindeeva et al. investigated the dynamics of blood flow parameters of the mice liver and kidneys after intravenous administration of magnetic microcapsules which would assist in imaging of damaged tissue areas in clinics, Fig. 15 A. [375] LBL capsules have been shown to be a suitable vehicle for delivering therapeutics to different sites, Fig. 15 B. [376,377] Another study investigated not only the capsule's bio- distribution and accumulation in the tumor, but also release of loaded drugs for chemotherapy triggered by irradiation of NIR light. [378] One emerging concept in this field is multicompartment capsules which already promote development of

theranostics. [379] Multicompartment capsules equipped with different sub-compartments can be triggered by various stimuli for detection and therapy in the same delivery vehicle.

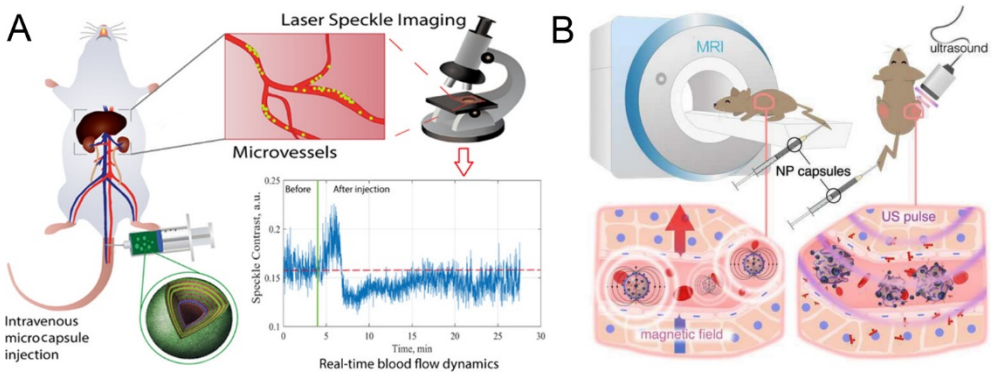


Fig. 15 A) Schematic representation of investigating the real-time blood flow changes in vital organs *in vivo* after intravenous injection of microcapsules using a laser speckle contrast imaging system. B) Schematic representation of *in vivo* administration of DOX-loaded nanoparticle-modified (NP) capsules: DOX-$(TA/PVPON)_6(Fe_2O_3/PVPON)_2$. The capsules are capable of both *in vivo* imaging and US-triggered drug delivery: athymic nude female mice were injected with MDA-MB-231 triple negative breast cancer cells and allowed to grow bilateral flank tumors. The mice were injected with 2×10^8 capsules per milliliter and 30 µL kg^{-1} Definity microbubbles during simultaneous treatment with 1.0 MHz FUS (750 mVp p^{-1} 10 ms bursts; 1 Hz repetition rate [1% duty cycle]; 120 s). Reproduced from ref. [375,376] with permission of 2020 American Chemical Society and 2018 Wiley, respectively.

4.1.7. Antibacterial and antimicrobial

PEM microcapsule composites can be used as effective antimicrobial agents to suppress the growth of various bacterial strains. [380–382] Encapsulation of bacterial cells with microcapsules which can offer protection to rhizobacteria against biotic and abiotic soil stresses has been challenged and used mainly in the agricultural industry. [383] In addition, microcapsules enable microbial inoculant large-scale production to be applied in agricultural industry. For example, the ability to synthesize Ag nanoparticle-based composites under gentle conditions shows the additional promise to produce versatile antimicrobial agents. [384–387] The self-assembly microcapsules of charged biopolymer, diethylaminoethyl-dextran hydrochloride (dex+) and dextran sulfate (dex-), also demonstrated inherent antibacterial capacity. [388] The release of active tea polyphenols (TP) and ε-poly-L-lysine hydrochloride (ε-PL) molecules from the TP/ε-PL composite microcapsules enable improved antibacterial performance than that of single preservatives, Fig. 16. [389] The long-term antibacterial properties of microcapsules, including the composite itself and the release of antimicrobial contents, compared to the free antibacterial agent, have potential value for application in the preservation of food and agriculture. [390]

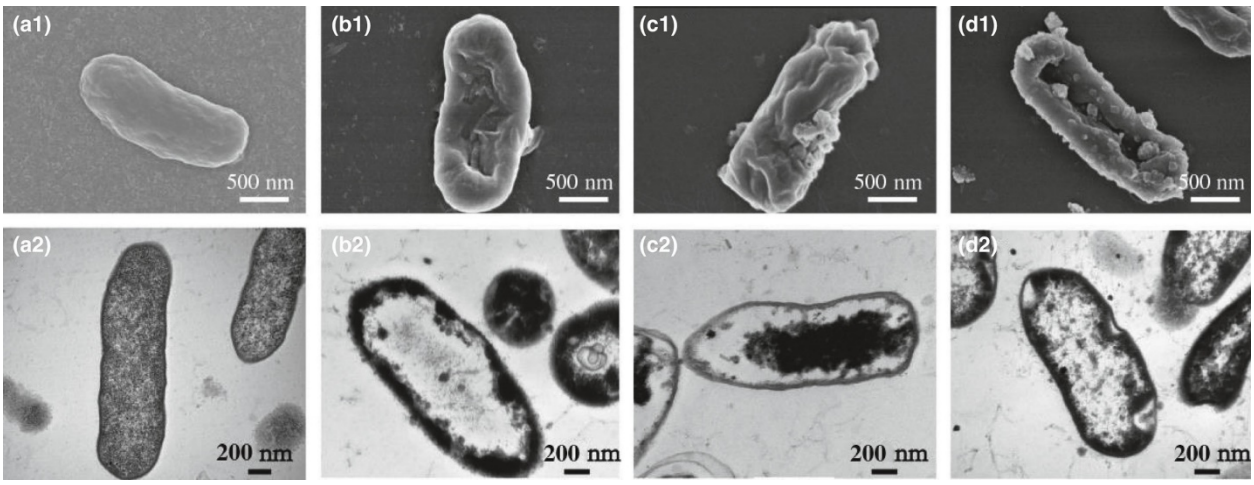


Fig. 16 The SEM (1) and TEM (2) images of the Shewanella putrefaciens before and after treated by different microcapsules: (a) control, (b) TP microcapsules, (c) ε-PL microcapsules, (d) TP/ε-PL microcapsules. Reprinted with permission from ref. [389]. Copyright 2020 Wiley.

4.1.8. Tissue engineering

The key approach in tissue engineering is to employ artificial scaffolds to treat defect or loss of tissues; these constructs should be capable of hosting, protecting and releasing bioactive that guide cellular behavior. Polyelectrolyte multilayer capsules is a straightforward candidate to integrating bioactive into the scaffolds because of their well-defined nano/microstructures, controllable and scalable synthesis, excellent stability, non-cytotoxicity, good tissue compatibility, and versatile modification with functional organic groups. Significant progress has been made for the design of scaffolds for the repair of a variety of tissues using microcapsule-based materials. [391,392] del Mercato et al. [393], functionalized 3D collagen porous scaffolds with biodegradable vaterite-templated PARG/dextran sulphate (DS) bio-capsules. It was reported that the structure, porosity, and other physical features of the microcapsule-based scaffolds were similar to those of pristine scaffolds. Since the scaffolds composed of PEMCs mainly retained the original properties of an ideal scaffold for tissue engineering applications, this finding suggested that the generation of new scaffolds with controlled bioactive delivery and protection has been achieved via capsule integration which indicates that such methodology may be easily and cheaply implemented. Recently, Mano et al. [394] fabricated biomimetic bone niche utilizing liquefied microcapsules which enable successful development of viable microtissues, ensuring the high diffusion of bioactive factors. Furthermore, the incorporation of macrophages within the fabricated microcapsules allows to recreate an appropriate bone microenvironment for developing new bone mineralized microtissues. This method could inspire a broader use of immune cells as a pro-regenerative component of implanted 3D tissue constructs.

4.1.9. *In vivo* and preclinical studies

To meet the need for clinical translation, there is an increased demand for more precisely controlled release technology. [395] As cell microencapsulation and delivery has been successfully applied by microcapsules and demonstrated great success in regenerative cell therapy, microcapsules is a promising approach to conceal cells from the host's immune system in cell-based therapy. [396,397] The approach presented in this work opens perspectives for preclinical studies of tissue and organ repair, accelerate their clinical translation. Muslimov et al. developed biocompatible polymers [tannic acid–human serum albumin (TA/HSA)] microcapsules on Actinium-225 (225Ac) radiolabeled core, which improved the

efficiency of local α-radionuclide therapy in melanoma models. [398] By selecting biocompatible polyelectrolytes such as dextran, dextran sulfate, collagen I and fibrin, the translation into *in vivo* and clinical setting is becoming more probable. [399]

4.2. Food and packaging

Microcapsules allow protecting the functional ingredients used to regulate color, flavor [400] or texture of the final food product. [401–403] As well as protection of functional ingredients, controlled release of bioactive ingredients, such as vitamin, [404,405] essential oils (EOs) and anthocyanins (ANs) [406,407], which have been encapsulated to preserve their stability during food processing and storage can avoid undesired interactions between other ingredients present in the food matrix and improve the effectiveness of food additives, broaden the application range of food ingredients, and ensure optimal dosage. [408] Ingredients generally Recognized as Safe (GRAS) [127] by the U.S. Food and Drug Administration (FDA) can be used. Furthermore, microcapsules can enhance physico-chemical properties of food ingredients to allow an easier packaging and handling.

Nano/microcapsules which function continuously during the processing, storage, and distribution of meat products has been discussed recently. [409] Abbaspourrad and coworkers [406] fabricated chondroitin sulfate (CHS)/chitosan (CS)microcapsules via layer-by-layer assembly (LBL) as carriers for co-pigmented ANs. Co-pigmentation with CHS of moderate concentration increased the encapsulation efficiency of anthocyanin, favored anthocyanin retention in the microcapsule and improved the prolonged release of anthocyanin in a simulated gastrointestinal environment. These results strongly support the combined use of polyelectrolyte microcapsules and co-pigmentation techniques for the development of novel systems targeting the stabilization and controlled release of bioactive ingredients. EOs from virous fruit and plants loaded in polymer-based delivery microcapsule has potential application and developmental value prospects in food industries. [410–412] Jian et al. [413] encapsulated orange EOs with biopolymers, soybean protein isolate and Arabic gum, in the optimum ratio 1:1 and pH 4 to carry out complex coacervation. Flavor components were well retained without loses of limonene in these spherical without holes on the surface microcapsules. Similar work was done by Wang et al. [414] to employ the complex coacervation of ginger EOs using gelatin and sodium alginate as wall material for ginger EOs microencapsulation. Ginger EOs encapsulated into the microcapsules exhibited higher thermal stability than the neat ginger EOs, gelatin, and sodium alginate, which indicated that the release of ginger EOs from microcapsules was much higher in simulated intestinal fluid, compared with that in simulated-gastric fluid.

All of these attributes used to provide protection against degradation, volatilization or undesirable interactions with other compounds, controlled release or mask some unpleasant effects are also fundamental when developing active packaging systems through the incorporation of active compounds in the matrix. [415] Microcapsule-based systems have been developed in recent years for the diverse areas to improve packaging performance mainly focusing on the modification of barrier properties in the food packaging field. Vieira and coworkers found carvacrol microcapsules (CMF) with higher values of thickness (0.41 ± 0.04 mm), moisture content (13 ± 1 g water/100 g film), opacity (20 ± 1%), water vapor permeability (WVP) $(4.4 \pm 0.4) \times 10^{-10}$ $gPa^{-1}s^{-1}m^{-1}$, oxygen permeability (O_2P) $(1.3 \pm 0.3) \times 10^{-12}$ $gPa^{-1}s^{-1}m^{-1}$ and carbon dioxide permeability (CO_2P) $(1.3 \pm 0.3) \times 10^{-12}$ $gPa^{-1}s^{-1}m^{-1}$ as compared to those of the chitosan control film can increases the shelf-life of refrigerated salmon to 4–7 days of storage. [416] Andersson et al. developed a self-healing capsule with a biopolymer shell of ethylcellulose for treating the surface of paperboard. The treated paper presents a reduced tendency for deteriorated barrier properties and local termination of cracks formed upon creasing. [417] Microcapsules are allowing the establishment of new concepts for packages, such as intelligent and active packages but it still limited for packaging applications.

4.3. Perfume, fragrance, and cosmetics

As well as food field, the use of EOs is a very promising topic for perfume, fragrance, and cosmeceutical industries. [418–420] Since most of the fragrances or aroma compounds, [421–423] including esters, terpenes, aldehydes, and alcohols, are volatile compounds, [424] effective preservation and controlled release of fragrance with appropriate substrate material is essential in practical application.[425] Polymeric microcapsules, indeed, resulted in being effective at overcoming the main concerns related to volatile compound preservation, delivery as well as release, and several industrial products contain fragrances in an encapsulated form for the final usage of customers. [426] Controlled Release of fragrance can be also triggered by both pH [427] and thermal [420] change. Microcapsules can improve the shelf life and the delivery of highly volatile fragrances, with a gradual release of the encapsulated functional ingredient. [428]

Sansukcharearnpon et al. [429] encapsulated six fragrances: camphor, citronellal, eucalyptol, limonene, menthol and 4-*tert*-butylcyclohexyl acetate using the solvent displacement method (ethanol displaced by water) and a polymer blends of ethyl cellulose, hydroxypropyl methylcellulose and poly(vinyl alcohol) as polymeric carriers. Limonene showed the fastest release with essentially no retention by the nanoparticles, while eucalyptol and menthol showed the slowest release. Recently, Herrmann et al. [430] developed a model physical fragrance carrier based on either poly(N-(2-hydroxypropyl)methacrylamide) (PHPMA) copolymers as a representative for polymeric profragrances or polyurethane/polyurea-type core–shell microcapsules which modified with phage-display-identified peptides that can bind to human hair under shampooing conditions. Such peptide-functionalized (10 wt%) polyurethane/polyurea-type core–shell microcapsules containing a model perfume resulted in an approximately 20-fold enhancement of deposition onto human hair compared to the fragrance microcapsules without peptide. This work tackled the challenge of the deposition of fragrance delivery systems onto human hair from a shampoo formulation.

Durable fragrances are still one of the main attractions in the cosmetics. Microcapsules can promote cosmetic base products by introducing novel functional properties and bringing in added value, which would open new avenues for the exploitation of novel compounds including phenolic extracts in cosmetic industry applications. [431] Because of the slow and sustained release of fragrances, encapsulation of molecules in microcapsules can represent a revolutionary contribution to some fields such as the future of toiletries, body deodorant products, and in washing and cleaning sectors. [432]

4.4. Specialty applications

4.4.1. Protective coatings, corrosion, and self-healing

Advances in the control over the dimensions and properties of microcapsules enabled to enlarge their use beyond that as microcarriers. By adjusting the crosslinking strategies, the functionalities of the capsules can be further tailored. Hollow polymer microcapsules are not only applicable to a range of fundamental and applied hollow structure “containers” but also to the fabrication of surface coatings consisting of networks of interconnected assemblies of these hollow polymer structures. Fabrication of hollow and semipermeable capsule assemblies on sacrificial substrates permitted triggered delamination and subsequent transfer of these coatings to secondary surfaces such as glass or other colloidal substrates where exceptionally anticorrosive performance is required. Potential applications in catalysis and controlled release could be achieved. [433]

Excellent mechanical strength of the wall of microcapsules ensures possible protection for vulnerable objectives such as probiotic bacteria. Microencapsulation is recognized as one effective way to enhance

probiotic bacteria survival. [434] In order to improve the bioavailability of probiotic bacteria, encapsulation of the micro-organism in matrix has been investigated by many researchers. [435,436] Encapsulation of probiotic microorganisms into polymer matrices reduce cell death during gastric passage. [437] The increasing numbers of polyelectrolyte layers effect on both the survival and controlled release of the probiotic bacteria, after encapsulation in a multilayer shell. [438] LbL microcapsules is an effective method to enhance the efficacy of probiotics by protecting them from the low pH of the stomach via oral administration. [439] And the range of applications of microcapsules in the coatings has only been extending. [440]

In addition to mechanical protection provided by microcapsules, protection against corrosion (Fig. 17 A) is another useful property provided by the microcapsule shell. [441–443] Organic coatings are widely used in the corrosion protection of substrates such as metals and concrete. Microcapsules can effectively enhance anticorrosion performance of the coating. Graphene oxide (GO)-modified double-walled polyurea microcapsules (Fig. 17 b) functioned as an excellent barrier providing anticorrosive properties which have been proven to be useful in different fields where exceptionally anticorrosive performance is required. [444] White and coworkers [445] reported novel capsules incorporating an embedded healing agent that is released upon crack intrusion. Inspired by this seminal work, diverse materials such as bulk polymers, even cement, [446,447] and asphalt [221] have been functionalized with capsules most commonly to impart self-healing properties to them. Generally, reagent was loaded into capsules and subsequently involved in polymerization reactions responsible for the self-healing of materials when microcapsules break. Despite such progress, there are still significant challenges involved in the fabrication of capsules imparted functional bulk materials that go beyond self-healing properties. [448]

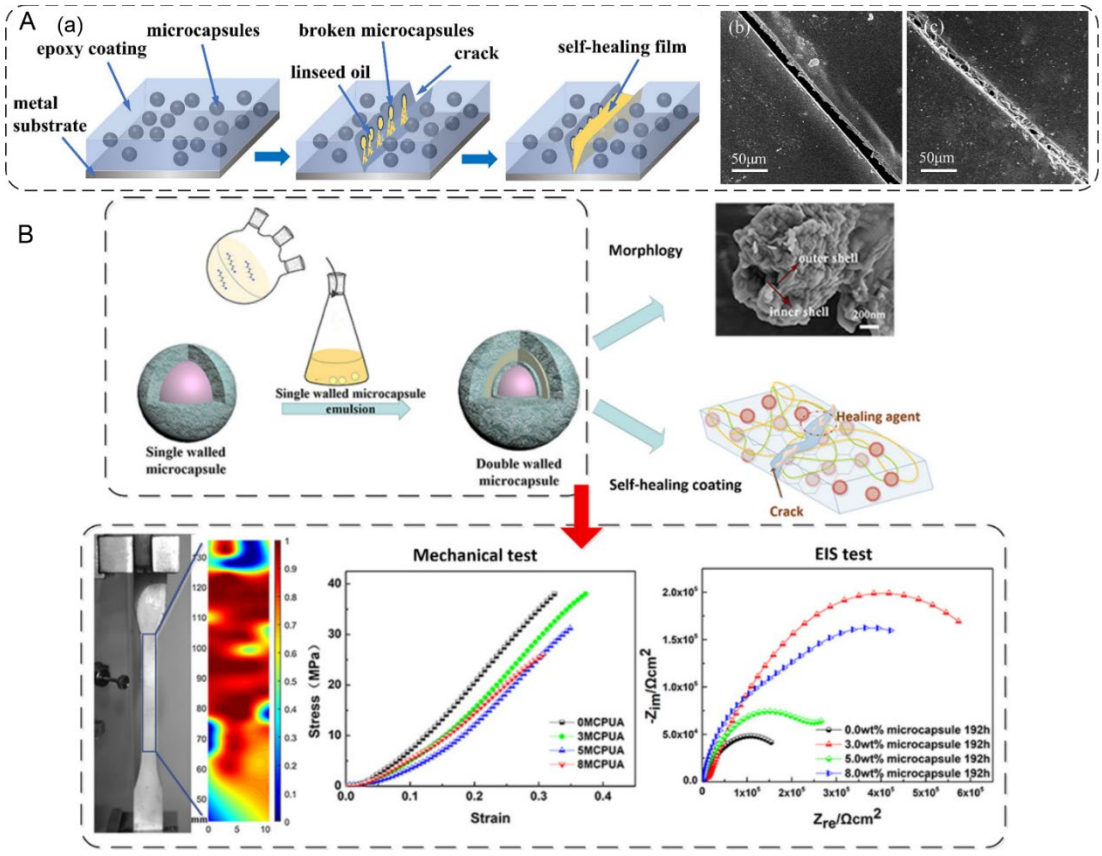


Fig. 17 A: Self-healing and anti-corrosion mechanism of epoxy coating containing microcapsules (a) schematic diagram of self-healing process (b) scratched crack area for pure epoxy coating (c) healed crack area for self-healing epoxy coating containing 10 wt% microcapsules. B: Schematic representation of the preparation process of GO modified double-walled microcapsules and anticorrosive performance of self-healing coating. Reproduced from ref. [442,444] with permission of 2022 and 2020 Elsevier, respectively.

4.4.2. Textile

The application of microcapsules in textiles follows the current interest of industries in functionalization technologies that give different properties to textile products, such as aroma finish, [449] insect repellency, [450] antimicrobial activity, [451] and thermal comfort. [452,453] Very recently, Yang and coworkers [454] craft zein-based hybrid microcapsule coated with TiO_2 in the outer shell by interfacial condensation and anti-solvent precipitation approach. Sustained release of *artemisia argyis* essence (merely 9% in 9 h) and superior self-cleaning performance allowed these microcapsules using in various textile fields, such as leather finishes, textile printing and so on.

4.4.3. Propulsion: anisotropic and Janus capsules

The development of microcapsule-based autonomous artificial micro/ nanomotors has gained considerable attention because of their potential in various application filed. [455–457] These tiny “engines” can be powered by various forms of energy from chemical reaction and physical triggers including, light, heat, electric, ultrasound or magnetic fields. [458,459] He and coworkers [460] fabricated a fuel-free, near-infrared (NIR)-driven Janus microcapsule motor with a maximum speed of 42 $\mu m \cdot s^{-1}$ in water via template-assisted polyelectrolyte layer-by-layer assembly, followed by spraying of a gold layer on one side. Xing et al. [461] constructed hollow mesoporous carbon nanocarrier which has a high loading efficiency (1370 mg/g) of doxorubicin drug can also achieve the enhanced motion powered by introducing the NIR-light irradiation due to the local thermophoresis from the upward temperature of HMCNs as well as introducing H_2O_2 that drives by the asymmetric decomposition. Such NIR-propelled Janus microcapsule motors and other autonomous motors can move efficiently in cell culture medium and have no obvious effects on the cell, broaden considerable applications for future biomedical and energy field.

4.4.4. Arrays with microcapsules

Sukhorukov et al. have used microcapsules but arranged them in arrays, in such an arrangement, one can selectively activate individual cells of arrays initiating various reactions. [462] Other applications and preparation of the microcapsule arrays based on composite capsule was discussed by Sergeeva and co-workers. [463] Further capsule-based array applications have been realized recently. 3D printed stimuli-responsive capsules for programmable release of payload represent a powerful new pattern tool to enable spatiotemporal control over biomolecular gradients. 3D multiplexed arrays of enzyme-loaded capsule shell loaded with plasmonic gold nanorods can realize the precise control over space, time, and selectivity triggered by laser (Fig. 18). [464] Another fully printed capsule-based arrays fabricating odor molecules-containing carried out programmable release of more than 20 spices of geranium. [465]

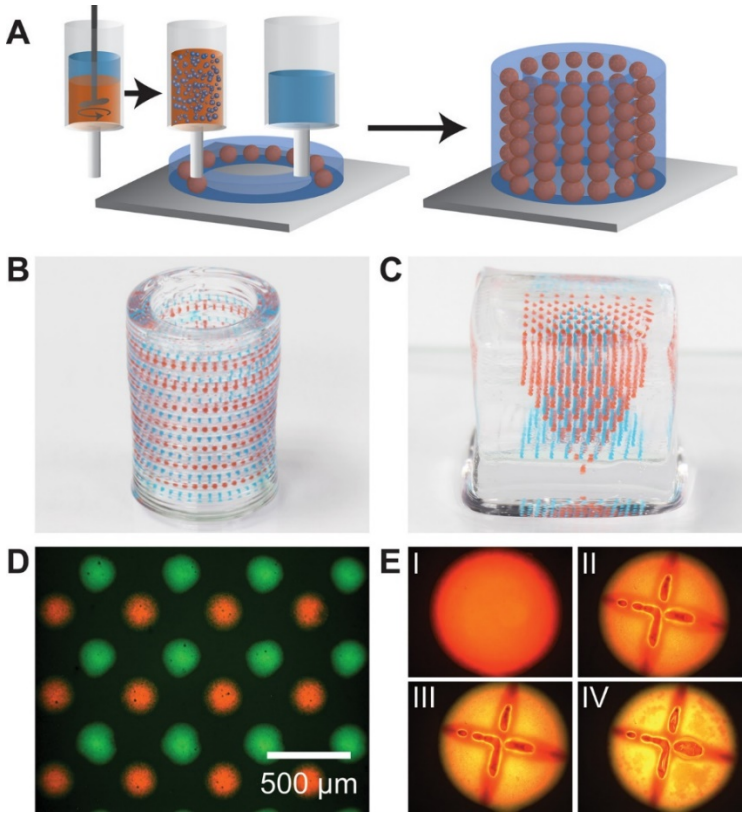


Fig. 18 3D printing of hierarchically multiplexed capsule arrays. (A) Schematic illustrating an emulsion ink-based method to 3D print complex capsule arrays. The emulsion ink is prepared by directly dispersing the aqueous core in the PLGA solution. The hydrogel and emulsion inks are sequentially printed in a layer-by-layer manner to form a 3D structure. (B, C) Optical images of 3D multiplexed capsule arrays directly printed in cylindrical and square hydrogel matrices, respectively (colors of the capsules are from food dyes in the dispersed cores). (D) Fluorescent optical image of a single layer of a multiplexed emulsion-based capsule array. (E) Fluorescent optical images showing rupture and release of fluorescein dye (poly(fluorescein isothiocyanate allylamine hydrochloride)) from an emulsion capsule with Nile red stained PLGA (I: before laser rupture; II, III, IV: 15 min, 1 h, and 2 h after laser rupture; diameter of the capsule: ~300 µm). Reprinted with permission from ref. [464]. Published with permission of 2015 American Chemical Society.

4.4.5. SERS sensors

Adsorption of noble metal (gold, silver, *et al.*) nanoparticles in the interior or on the surface of PEM capsules allow achieving surface-enhanced Raman scattering (SERS) sensing. It should be noted that both the design of assembly of amplifying nanoparticles and surface chemistry control are essential for SERS sensing. [466] SERS-based PEM capsules have been applied in detection of module molecules, pH, bacteria and even miRNA. [467–472]

5. Conclusions and future directions

In conclusion, polyelectrolyte multilayer micro- and nano-capsules are continuing to draw essential interest by the research community. Having undergone from their discovery, through the stage of developing encapsulation and release methods, they are now entering the mainstream of very diverse

applications. Initially, knowledge has been taken from flat-LbL films, but an essential difference of polyelectrolyte multilayer capsules is that polyelectrolytes are not connected to any substrate, because the spherical substrate (template) is removed in the process of preparation of capsules. That enabled to study the mobility of polyelectrolytes, the influence of physico-chemical methods on their fabrication, which resulted in developing and discovering essential applications – for example, fusion of capsules.

Properties of polyelectrolyte multilayer capsules have been extensively studied and the first decade of research on capsules has been dedicated to development of essential encapsulation and release methods.[473] Due to involvement and contributions of researchers from interdisciplinary fields, very diverse and quite complementary methods have been developed for both encapsulation and release: chemical (pH, salts), physical (light, heat, ultrasound, mechanical), and biological (enzymes, targeting). It is therefore not surprising that after basic understanding of their properties and development of essential encapsulation and release methods, the past decade has seen broadening of application areas. And a range of application is continuing to grow, where biomedical applications represent the highest application area. In this area, cells, microorganisms, and other *in vivo* applications have been already developed. These areas are summarized in this review, where the largest is biomedical applications. And in the area of biomedical applications, pre-clinical trials have been recently reported, which ultimately brings the whole field to a state which is relevant for clinics and biomedicine in general. Capsules would be useful for building novel nanoarchitectonics applications. [474] It should be also noted that for applying capsules in research and industry, high-throughput methods of their fabrication are needed, but essential steps have been already proposed. [475–482]

This review, on the one hand, provides summary of properties, particularly encapsulation in and release from capsules, describes their components and composition, which should be useful for both researchers who used and applied capsules in their applications and new incoming groups, which could benefit from knowing such properties and thinking of developing their own research lines. On the other hand, it should allow researchers to extend the existing application range and expand into new application areas. An outlook of future development can be seen in Figure 6, where radial arrows and their thickness show anticipated future trends of developments of these areas. Regarding new application areas, these are expected to be further extended, but it is expected that collaboration with new groups (for example, in biomedicine, food science, *etc*) should be particularly fruitful here. Many of these new applications can be of interest for industrial transfer, and in regard, scale-up production capabilities will be essential.

One can see thus that polyelectrolyte multilayer capsules have become an indispensable part of materials research and biosciences; capsules can be used to solve many problems and develop new and emerging applications of nanomaterials. [483] Following the above-outlined possibilities for applying PEM capsules to diverse fields, several challenges still remain. Further research is needed for: development of biocompatible and biodegradable polymers, particularly those with a positive charge; controlling monodispersity and sizes of templates; preventing aggregation of templates and capsules particularly in the small size-range; automation of the preparation of PEM capsules; and more detailed understanding of the LbL assembly at the nanoscale,[484] where essential efforts have been put by the founder of this area Prof. Helmuth Möhwald. [485]

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