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Complete List of Authors:	Wang, Yifei; Texas A&M University System, Materials Science and Engineering Starvaggi, Nicholas; Texas A&M University System, Chemistry Pentzer, Emily; Texas A&M University System, Chemistry, Materials Science and Engineering

Capsules with Responsive Polymeric Shells for Applications Beyond Drug Delivery

Yifei Wang,[1] Nicholas Starvaggi,[2] Emily Pentzer[1,2,*]

[1]Department of Materials Science and Engineering, Texas A&M University, College Station, TX, 77840, USA
[2]Department of Chemistry, Texas A&M University, College Station, TX, 77843, USA
*Correspondence: emilypentzer@tamu.edu

Abstract. Polymeric capsules with core-shell structures have been widely explored for molecule separations, energy storage, and catalysis, among other applications. To tailor the application-oriented performance of these structures, researchers have imparted stimuli-responsive properties to the shells. In contrast to capsules with “static” shells, stimuli-responsive capsule shells not only protect the core from the external environment, but also aid in handling and impart properties such as on-demand release of cargo and varied shell permeability, as well as provide a platform for the fabrication of advanced structures. The composition and properties of polymer shells can be tuned through incorporation of dynamic covalent bonds into the polymer backbones, or introduction of segments or pendant side chains which can leverage intermolecular (e.g., hydrogen bonding) or electrostatic interactions to give response. Most reports on responsive polymer capsules focus on their application in cargo delivery, a topic that is heavily reviewed elsewhere. In complement, this minireview addresses responsive polymer capsules and their applications beyond drug delivery, focusing on structure-property relationships. We first highlight the most common fabrication techniques for core-shell structures including hard template, soft template, and microfluidic methods, among which we emphasize our utilization of interfacial polymerization and polymer precipitation within a Pickering emulsion template. We then provide a concise review of commonly employed chemistries for responsive polymer shells based on stimuli, including our contribution on the incorporation of dynamic covalent polymer backbones into thermo-responsive capsule shells. Application-oriented performances of the responsive core-shell structures are then highlighted. Finally, we outline opportunities for advancing the performance-related properties of responsive capsules, wherein we propose new directions where responsive polymer-based capsules can have critical impact in the development of new technologies.

1. Introduction

Microcapsules with core-shell structures have garnered significant attention in biomedicine,[1] cosmetics,[2] foodstuffs,[3] and energy management,[4] among other fields,[5, 6] for their remarkable ability to store, transport, and handle active materials. Encapsulation resolves challenges associated with bulk liquid processing (e.g., high viscosity) and simultaneously increases the active surface area, which may assist in the mass transfer of molecules across the interface, e.g., in separations. In contrast to capsules with inorganic shells, polymeric shells provide additional flexibility to tune the shell composition,[7, 8] and offer enhanced versatility to incorporate other functional components.[9] Among the core-shells structures, capsules with stimuli-responsive

polymeric shells are of particular interest,[10, 11] as the incorporation of dynamicity within the polymeric framework yields architectures that can actively participate in cargo release, tailored (de)construction, healing, and anti-corrosion. To date, most of the reports in this area focus on the design and preparation of structures for deployment in biomedicine, with an emphasis on payload release for drug delivery. The research in this subfield has been extensively summarized in a number of informative review articles. For example, De Koker et al. offered a comprehensive overview of recent advances in polymeric multilayer capsules with special emphasis on the capsule engineering to produce well-defined drug carriers.[12] Further, De Geest et al. reviewed layer-by-layer (LbL) assembly as a general approach for capsule fabrication as well as the diverse triggers used to achieve targeted drug release.[13] Lastly, we note that Delcea et al. provided an excellent review of recent developments in the field of stimuli responsive polymeric capsules prepared from LbL for application in nanomedicine with stimuli grouped into physical (light, electric, etc.), chemical (pH, ionic strength, etc.), and biological (enzymes, receptors, etc.) categories.[14]

Recent years have witnessed a rising demand to broaden the scope of responsive polymeric core-shell structures for different applications. Although controlled release remains an active field of research, responsive capsules have applications in a variety of other areas, including as fillers for coating composites with anti-corrosive or self-healing properties and (de)construction of monolithic structures. To provide an account of the state-of-the-art development of responsive polymeric core-shell structures beyond the drug delivery application realm, in this minireview, we summarize commonly employed methods for preparing liquid core/polymer shell capsules, responsivity mechanisms to different stimuli, and application-related performance. Capsule fabrication techniques reviewed include interfacial crosslinking, LbL assembly, and polymer precipitation via hard (e.g., solid inorganic particles) or soft (e.g., emulsion) templates, as well as microfluidic techniques which often require specialized experimental setups. We discuss different responsivity mechanisms under chemical stimuli (e.g., pH, ionic strength, redox) and physical stimuli (e.g., temperature, light irradiation). Finally, application-related performances including triggered release of non-drug active agents, (de)construction of higher ordered hybrid structures, and contributing to healing/anti-corrosion are illustrated. This minireview culminates in discussion of the current gaps in the development of responsive capsules and identification of opportunities for advancements in applications.

2. Fabrication Techniques for Capsules with Polymeric Shells

To prepare core-shell structures, hard templates and soft templates are generally employed,[15, 16] where the hard-templating method indicates capsule shell formation on a sacrificial hard core (e.g., silica particle, polymer spheres, carbon spheres) and soft-templating method indicates that the capsule shell is formed using a biphasic system, such as emulsions. In the hard-templating methods, the solid core templates are usually removed under harsh conditions such as acid etching, carbonization, or calcination; these methods give good control of the size and homogeneity of capsules and eliminate the use of additives such as surfactants. Alternatively, soft-templating methods do not have the burden of removing templates but typically give poor control of capsules size and size distributions; with this said, in soft template methods incorporation of active agents in the

capsule structure, i.e., through functionalization of surfactants or adjusting the two fluid phases used, can be more readily realized. In addition, microfluidic devices, consisting of dispersed phase-injection capillaries and continuous phase-containing capillaries, provide a facile approach for the preparation of soft templates (e.g., emulsion droplets) with well-controlled size distribution and morphology.[17] Selection of the hard template or soft template method is determined by many factors such as desired core and shell materials, and stability of components under different conditions. After hard/soft template construction, polymeric shells can then be fabricated mainly through interfacial crosslinking, precipitation, and LbL assembly, which are specifically illustrated below.

2.1 Soft Template Methods

The most widely employed soft template for preparing core-polymeric shell structures is based on an emulsion system in which one fluid phase is dispersed as surfactant-stabilized droplets in a second fluid phase. To achieve interfacial crosslinking, monomers are required to be dissolved/dispersed in corresponding fluid phases and subsequently diffuse to the fluid-fluid interface, where they react to form a polymer barrier, which is typically cross-linked. Our group has encapsulated a diverse range of so-called active fluids using interfacial polymerization in Pickering emulsions stabilized by 2D particles, most notably graphene oxide (GO) nanosheets and modified derivatives.[4, 18, 19] Taking the systems shown in **Figure 1A** as examples, ionic liquid (IL)-in-water emulsion stabilized by GO nanosheets and IL-in-oil emulsion stabilized by octadecylamine-functionalized GO were prepared; diisocyanate was dissolved in the IL and diamine was dissolved in water for the IL-in-water system and for the IL-in-oil system, diisocyanate was dissolved in octane and diamine in IL. Step-growth polymerization occurred at the fluid-fluid interface, around the nanosheets, to yield capsules with polyurea/nanosheet shells that were isolated by gravity filtration.[18] The emulsion templates can be broadened to different fluid-fluid phases (e.g., oil-in-water, oil-in-oil), monomers, as well as different functional surfactants (e.g., MXene nanosheets), depending on the desired applications needs.[19, 20] Interfacial polymerization provides an efficient way for encapsulation[21] of active core after formation of the emulsion templates and it is easy to tune shell composition by changing the monomer identity and amount. However, the polymerization reaction rate can be limited, and the heat transfer can be a problem as the polymer precipitates at the fluid-fluid interface[22] and thus this method is not suitable for formation of thick shells. Moreover, removal of excess monomers generally requires complicated/time-consuming post-processing.

In addition to interfacial polymerization, LbL assembly of oppositely charged polyelectrolytes on soft templates has been leveraged to prepare microcapsules. For instance, Shchukin et al. stabilized a dodecane-in-water emulsion with the small molecule surfactant didodecyldimethylammonium bromide. Capsules with polyelectrolyte shells were achieved through LbL deposition of the oppositely charged polymers in the aqueous dispersions: negatively charged poly(sodium 4-styrenesulfonate) (PSS) and positively charged poly(diallyldimethylammonium chloride) (PDADMAC) were alternately deposited on the colloidal templates (**Figure 1B**).[23, 24] Similarly, Stöver et al. prepared capsules with PSS/PDADMAC shells from a xylene-in-water Pickering emulsion stabilized by PSS-functionalized silica particles (LUDOX CL).[25] Interestingly, the authors demonstrated that

LbL assembly does not necessarily require two oppositely charged polyelectrolytes but can be achieved through the use of an oppositely charged polyelectrolyte and particles (e.g., PDADMAC and LUDOX HS-30 silica particles). Polyelectrolyte/particle layer composites increase the mechanical strength and compactness of the capsule shells. Notably, LbL assembly provides control of the capsule shell thickness by selection of how many electrostatic bilayers are used. LbL can be performed solely in continuous phase,[26] without the consideration of choosing monomers with different polarity to dissolve in the dispersed and continuous phases, as required for interfacial polymerization. One potential limitation of polyelectrolyte-composed shells is that they are typically not as strong as polymers shells containing covalent cross-linking and may be less stable to relevant conditions.

Precipitation or deposition of polymers onto soft templates is an efficient method to produce capsules with polymeric shells,[27] especially for those that cannot be prepared through interfacial crosslinking or LbL assembly. Moreover, the precipitation/deposition technique provides an effective methodology for maintaining a pristine core, which would otherwise be contaminated with monomer. Our group recently demonstrated this approach for the preparation of capsules with a core of ionic liquid or salt hydrate phase change materials: 1-ethyl-3-methylimidazolium hexafluorophosphate ([EMIM][PF6])-in-toluene or magnesium nitrate hexahydrate ([MNH])-in-toluene emulsion templates stabilized by hexylamine-functionalized GO were prepared, then solutions of polymer in organic solvent were added (polystyrene/toluene, poly(methyl methacrylate)/ dichloromethane, polyethylene/toluene). Change in solubility of the polymer led to its precipitation onto the emulsion droplets, effectively forming a core-shell structure (**Figure 1C**).[28] Notably, the non-aqueous platform was required to form droplets of the water-miscible and hygroscopic ionic liquids and phase change materials (PCM), and the polymer precipitation method was required to maintain the pristine MNH core, desirable since the performance is dictated by composition. In a similar vein, Reddy et al. prepared PCM@pectin capsules by emulsification of a PCM and pectin aqueous solution stabilized with tween-80, where the formed emulsion was added to a barium chloride solution which induced ionic gelation and precipitation of the pectin shells.[29]

In addition to the above-mentioned direct or ion-induced precipitation methods, the emulsion-solvent evaporation method can also be used to prepare polymeric capsule shell through precipitation. Briefly, polymer is first dissolved in a mixture of good solvent and poor solvent which serves as the dispersed phase, then emulsification is used to form an oil/water emulsion. The poor solvent is then partially removed from the dispersed phase, which induces phase separation and leads to the formation of solid polymer inside the droplets. The polymer then diffuses to the interface and precipitates as all the solvents continues to evaporate.[30, 31] The precipitation/deposition-based techniques take advantages of pre-prepared and purified polymers and thus support core purity, as no monomers or catalyst is needed.[30, 31] However, special attention must be given to securing an appropriate solution condition, as well as concentration, for the polymer to precipitate.

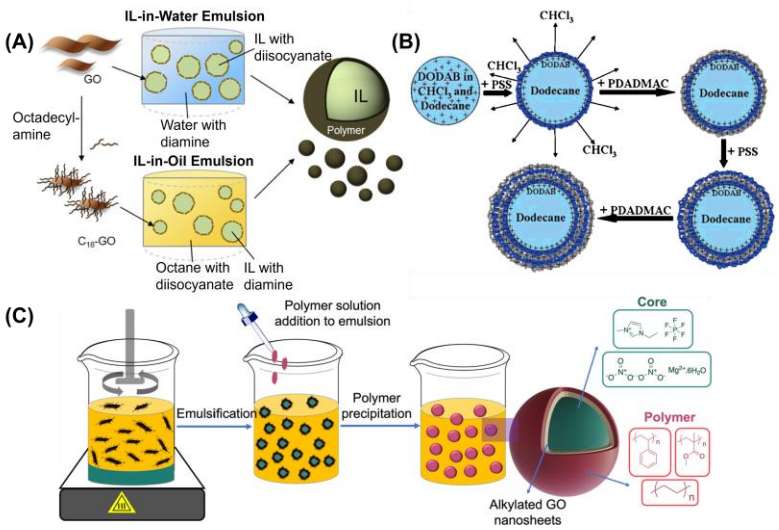

Figure 1. Soft template approaches for core-shell capsule formation. (A) Fabrication of IL-containing capsules with polyurea shells through interfacial polymerization based on IL-in-water and IL-in-oil templates. Reproduced from ref (18) with permission from American Chemical Society (2019). (B) Formation of capsules with dodecane core and PSS/PDADMAC shells through LbL assembly on dodecane-in-water emulsion. Reproduced from ref (23) with permission from American Chemical Society (2008). (C) Preparation of polymer capsules with IL or PCM core through polymer precipitation in non-aqueous emulsion templates. Reproduced from ref (28) with permission from Elsevier Inc. (2022).

2.2 Hard Template Methods

As with the soft template method, LbL assembly or interfacial crosslinking are also frequently used in hard templates for preparing microcapsules, with the difference that a sacrificial hard core is employed in the hard template method, and the reactions occur on the surface of the template which is subsequently removed. Active liquid core is thus loaded into the hollow shell, after the hard core is removed. For example, Gao et al. prepared core-shell structures through the LbL deposition of poly(allylamine hydrochloride)-g-β-cyclodextrin (PAH-g-β-CD) and PAH-g-ferrocene onto $CaCO_3$ particles, where host-guest interactions between β-CD and ferrocene led to capsule shell formation. The $CaCO_3$ template was then removed by immersion in a solution of disodium ethylene diamine tetraacetate dihydrate (EDTA) (**Figure 2A**) to yield hollow capsules.[32] Alternatively, Kitayama and Harada prepared spherical polymer particles by dissolving poly(2-cinnamoyl methacrylate-2-dimethylaminoethyl methacrylate) (P(DEAEMA-CEMA)) into chloroform, then homogenized the system with an aqueous solution of polyvinyl alcohol to form spherical polymer particle templates; upon irradiation with 254 nm light, the pendent cinnamoyl groups of P(DEAEMA-CEMA) on the surface underwent dimerization to form the crosslinked capsule shell. Non-crosslinked polymer chains in the core of the particles were removed with tetrahydrofuran to obtain hollow capsules for subsequent liquid core loading (**Figure 2B**).[33] Different from interfacial polymerization at the fluid-fluid interface of emulsion templates, interfacial crosslinking based on hard templates happens at the surface of spherical particles and thus requires the hard templates to possess functional groups. The hard template methods eliminate the use of more than one monomer and reduce the impact of excess monomers trapped in the dispersed phase, as for interfacial polymerization in the soft template method.

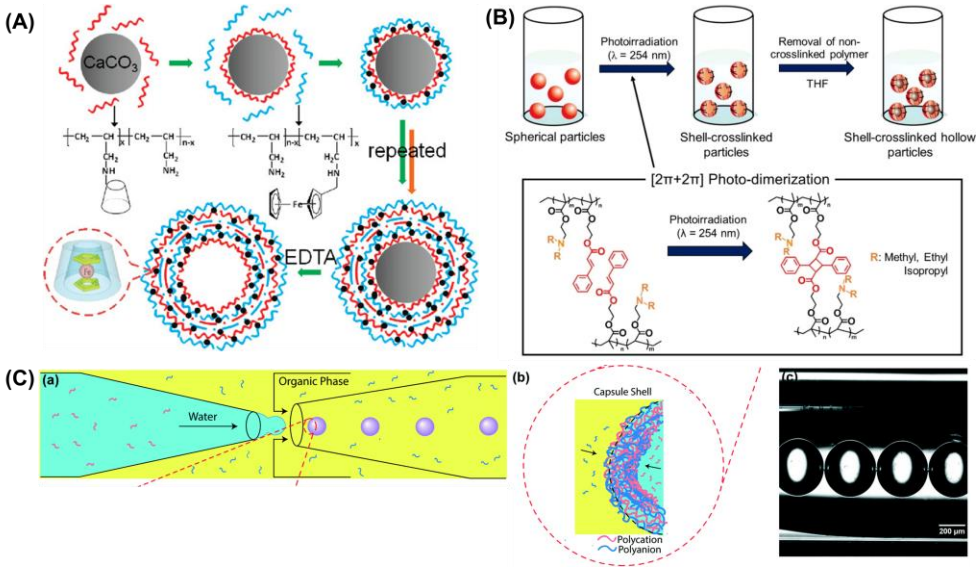

Figure 2. Hard template and microfluidic approaches for core-shell capsule formation. (A) Preparation of capsules with β-CD/ferrocene shells through LbL assembly of PAH-g-β-CD and PAH-g-ferrocene on $CaCO_3$ hard templates. Reproduced from ref (32) with permission from American Chemical Society (2008). (B) Fabrication of P(DEAEMA-CEMA) capsules through dimerization of cinnamoyl groups on the surface of the polymer particles. Reproduced from ref (33) with permission from American Chemical Society (2021). (C) Schematic illustration of microfluidic device for producing core-shell structures (a); the polycation (chitosan with amine groups protonated) and polyanion (s-SEBS with sulfonate groups charged) were dispersed in the aqueous and organic phase, respectively, and LbL assembly formed the capsule shell (b); and optical microscope image of obtained capsules (c). Reproduced from ref (34) with permission from Royal Society of Chemistry (2014).

2.3 Microfluidic Methods

Although less prevalent for the fabrication of responsive polymeric microcapsules, the microfluidic technique has also been leveraged to produce core-shell structures.[34-36] Consisting of dispersed phase-injection capillaries and continuous phase-containing capillaries, microfluidic devices form emulsion droplets by flowing the dispersed phase through the continuous phase with shell components (e.g., polyelectrolytes, monomers, crosslinkers) dissolved in the corresponding phases. As illustrated in **Figure 2C**, capsules with chitosan and polystyrene-*b*-poly(ethylene-*r*-butylene)-*b*-polystyrene (s-SEBS) complexed shells and aqueous core were successfully achieved through the capillary system. An aqueous solution of chitosan was passed through the toluene solution of s-SEBS to form emulsion droplets, followed by the electrostatic interaction between the positively charged protonated amines of the chitosan and the negatively charged sulfonate of s-SEBS, as reported by the Osuji lab.[34]

Microfluidic methods offer an efficient way to control the size distribution and morphology of the capsules and can eliminate the use of surfactants to stabilize the droplets, since capsule formation happens immediately upon formation of emulsion droplets. However, this method requires careful design/setup of complex capillary systems and fluids of high viscosity tend to be difficult to integrate. Moreover, the integration of, e.g., solid particles,

as well as liquid combinations other than oil/water have yet to be fully realized. As with the soft template method, limitations may also include sensitivity of desired active components to reagents required for shell formation.

3. Responsive Mechanisms at Different Stimuli

The primary advantage of polymeric capsules is their potential for stimuli responsivity, which can be imparted to the shell during fabrication. Recent advances in this field have been devoted to designing “smart” micro- and nanosized containers which respond to a wide range of external stimuli. Herein, we describe common mechanisms for responsivity and highlight corresponding examples reported in the literature. Stimuli are grouped into two main categories: chemical (pH, ionic strength, redox) and physical (temperature, light). Additionally, we investigate a special class of responsive capsules in which the stimuli responsivity is enhanced by the integration of guest particles into the polymeric framework. Other examples of stimuli used for polymeric capsules responsivity include carbon dioxide (CO_2)[37] and enzymes,[38, 39] which will not be discussed specifically in this review as these are seldomly reported or focused more on drug delivery.

3.1 Chemical Stimuli

3.1.1 pH

One of the most popular mechanisms for pH-responsive polymer shells involves the protonation and deprotonation of amine groups on the polymer, which induces changes in electrostatic interactions between polymer chains and thus leads to shrinkage or swelling of the capsules.[40, 41] For example, in 2021, Kitayama and Harada prepared capsules with (P(DEAEMA-CEMA)) shells and rhodamine (RhB)/dimethylsulfoxide (DMSO) core where the tertiary amine groups on the DEAMEMA segments impart the capsules with the pH-responsivity.[40] As shown in **Figure 3A (a)**, protonation of the tertiary amine leads the capsules from shrunken state to swollen state in which the encapsulated Rhodamine B dyes can be released. To further confirm the shell permeability change is based on protonation, capsules shells of poly(butyl methacrylate-*co*-2-cinnamoylethyl methacrylate) (P(BMA-CEMA)), which do not possess protonatable amines, were also prepared. As shown in **Figure 3A (b) and (c),** the absorbance intensity of the dye released from the P(DEAEMA-CEMA) capsules is dramatically increased when exposed to an acidic environment, but no obvious changes are observed for P(BMA-CEMA) capsules. Similarly, Pan and colleagues successfully prepared capsules with PDEAEMA shells crosslinked by 1,6-hexanediol diacrylate (HDAA) and fluoroalkylsilane as core material; the amino groups from DEAEMA segments can undergo protonation in acidic environment which results in the swelling of the capsule shells. Average diameter of the capsules change from 712.1 nm to 901.8 nm upon pH varies from 7 to 3, as determined by dynamic light scattering (DLS) (**Figure 3B**).[41]

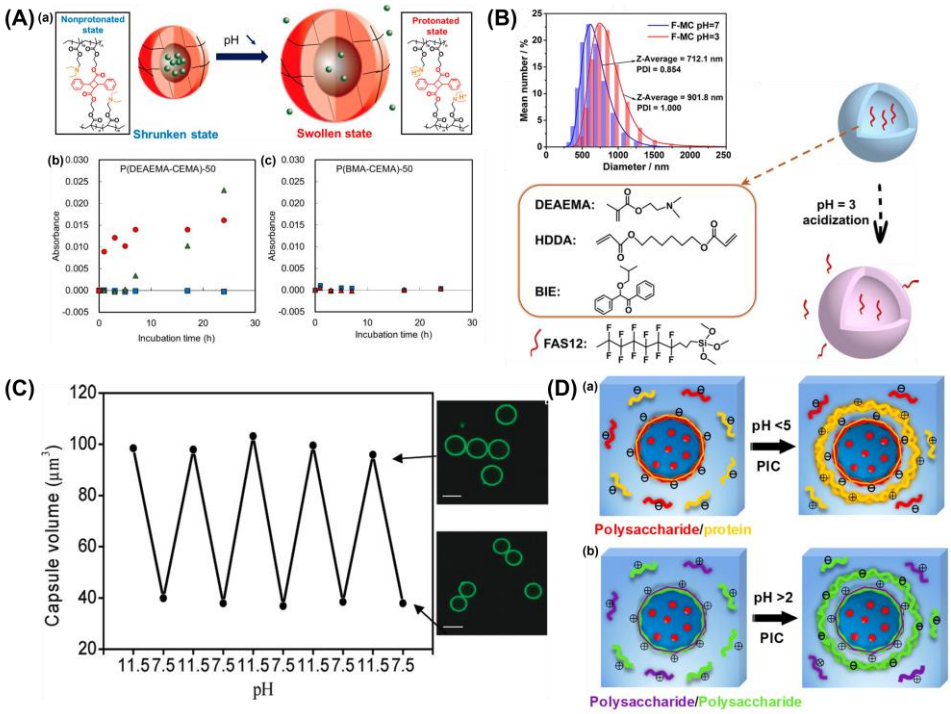

Figure 3. (A) Capsules experience shell swollen as environmental pH decreases due to the protonation of the amine groups of the polymer side chains (a); and release profile of Rhodamine B from P(DEAEMA-CEMA) (b) and P(BMA-CEMA) (c) capsules (red dots: pH=3.5; green triangles: pH=5.5; blue squares: pH=7.4). Reproduced from ref (40) with permission from American Chemical Society (2021). (B) Capsules with P(DEAEMA-HDDA) shells show volume expansion when exposed to acidic conditions. Reproduced from ref (41) with permission from American Chemical Society (2020). (C) Reversible change of PEI-(SF-PG/SF-PL)$_9$ capsule volume as environmental pH changes between 11.5 and 7.5. Reproduced from ref (42) with permission from American Chemical Society (2011). (D) Formation of polyelectrolytic interfacial complexation (PIC) shells for capsules with polysaccharide/protein (a) or polysaccharide/polysaccharide (b) shells by varying pH to achieve ionization of suspended protein or polysaccharide. Reproduced from ref (43) with permission from American Chemical Society (2019).

Integration of multiple pH responsive functional groups that can be protonated or deprotonated into the capsule shells can enhance the stability and versatility of the system. In 2011, Ye et al. demonstrated that incorporating both silk-poly(glutamic) acid (SF-PG) and silk-poly(lysine) (SF-PL) into capsule shells can give robust responsivity at pH below 2.5 or above 11, but shell stability at intermediate pH values. At acidic conditions (i.e., pH < 2.5) the carboxyl group on SF-PG are protonated, but at very basic condition (i.e., pH > 11) the amino group on SF-PL will be deprotonated, and both can lead to the capsule swelling. Repeatedly alternating the pH between 7.5 and 11.5 gives capsule swelling and shrinking with good reversibility, as highlighted in **Figure 3C**.[42]

In addition to achieving capsules' swollen and shrunken states, researchers have addressed tuning capsule shell charges for complexation with external molecules suspended in dispersion environments. Thus, pH changes can enhance capsule shell thickness and thus provide better protection of the core. **Figure 3D (a)** shows that bovine serum albumin (BSA) proteins deposit onto the as-prepared negatively charged capsule

shells when the pH reaches BSA's isoelectric point; the ionized BSA complexes with the negatively charged polysaccharide/protein capsule shells. Alternatively, **Figure 3D (b)** depicts the deposition of negatively charged polysaccharide onto the positively charged capsule shells, where additional shells were successfully coated onto the as-prepared positively charged capsules, reported by the Abbaspourrad lab.[43]

3.1.2 Ionic Strength

Ionic strength (e.g., salt concentration) has also been used as a stimulus for polymeric responsive capsules and generally employs free ions (e.g., ions from NaCl) to induce molecular level rearrangements of the shells (e.g., hydrogen bonding rearrangements) or to tune the electrostatic interactions between the capsule shell components.[44-46] Of note, ionic strength-responsive polymeric capsules are mostly prepared from multilayer-deposited polyelectrolytes (e.g., prepared by LbL) due to the relatively weak interactions between the multilayers. As shown in **Figure 4A**, Ibarz and coworkers prepared hollow capsules with PSS /PAH alternative layer shells where the capsule shell permeability can be changed by dispersing them in aqueous solutions of NaCl. The capsules can be used to load macromolecules by changing to "open" state (permeable) and can be sealed to store the molecules inside by removing the salt and returning to "closed" state, where reopening the capsules can release the payload. It is noteworthy that when loading molecules into the hollow capsules, increasing the salt concentration can increase the percentage of capsules that were filled (from 4.6% at 0.0001 mol/L salt concentration to 100% at 0.01 mol/L salt concentration), proving that the capsule shell permeability relies on the ionic strength.[45] Although the mechanism for the reversible shell "open" and "closed" process is not delineated, it is hypothesized that free ions disrupt the polyanion/polycation interactions of the shells and thus allow the macromolecules to easily enter and leave the capsules.

Alternatively, Dolatkhah and colleagues constructed saline-responsive capsules possessing polyaniline (PANI) shells with anti-corrosion agents (e.g., benzotriazole) encapsulated.[46] Intramolecular hydrogen bonding between the PANI backbones and intermolecular hydrogen bonding between PANI and the encapsulated nitrogenous molecules drives the saline-responsivity. Upon addition of salt solution (e.g., NaCl), the PANI backbone experiences cation-doping, which induces the emeraldine base form changing to emeraldine salt form. This breaks the intramolecular hydrogen bonding and thus increases the shell permeability (**Figure 4B**).

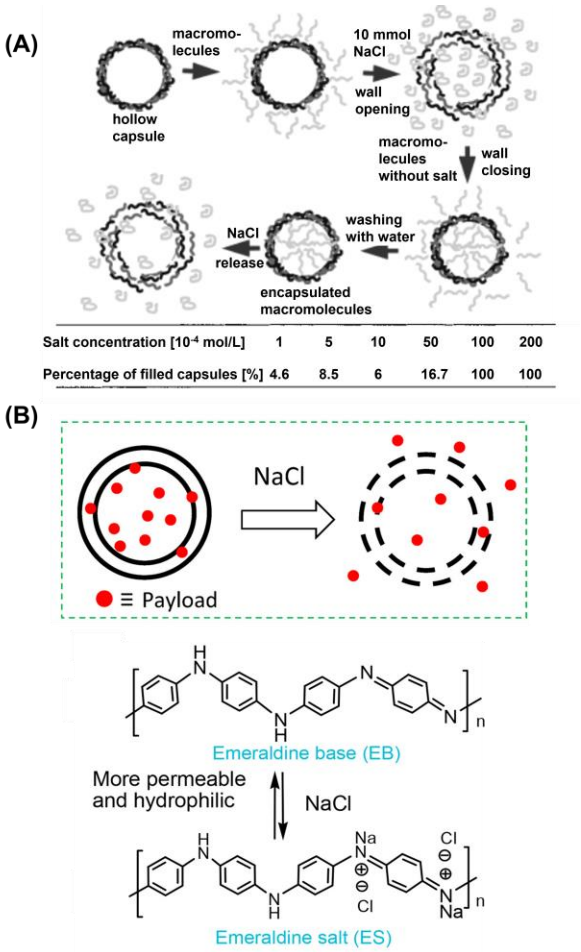

Figure 4. (A) Schematic illustration of PSS/PAH capsule shells "open" and "closed" upon addition and removal of NaCl, respectively; increasing salt concentration can increase the percentage of filled capsules when loading macromolecules. Reproduced from ref (45) with permission from WILEY‐VCH Verlag GmbH, Weinheim, Fed. Rep. of Germany (2001). (B) Addition of NaCl induces the transformation of PANI shells from the emeraldine base state to the emeraldine salt state, altering shell permeability. Reproduced from ref (46) with permission from American Chemical Society (2020).

3.1.3 Redox

Redox-responsive capsule shells require the presence of chemical bonds that can be cleaved or undergo molecular-level conformational change when exposed to reducing or oxidizing agents.[47-50] In the past few decades, researchers have been engaged in integrating di-/tetra-sulfide bonds, polyaniline, host-guest molecule interactions, etc. into polymeric capsule shells to achieve this responsivity. For instance, Jiang et al. prepared capsules with poly-bis(2-methacryloyl)oxyethyl disulfide (PDSDMA) shells and 2-mercaptobenzothiazole (MBT, a corrosion inhibitor) core where the disulfide bonds in the capsule shells can be cleaved by the reducing agent tris(2-carboxyethyl)phosphine hydrochloride (TCEP·HCl) (**Figure 5A**); 25% more of the encapsulated MBT can then be released from the capsules in the presence of the reducing agent than without.[47] Likewise, Takeuchi et al. prepared capsules with poly(N-cinnamoyl-N′-methyacryloylcystamine-*co*-methyl methacrylate) (P(MCC-MMA)) shells where Rhodamine B/DMSO solution is

utilized as core material to evaluate the release profile of the capsules. **Figure 5B** illustrates the comparison of non-redox-responsive capsules with poly(2-cinnamoylethyl methacrylate-co-methyl methacrylate) (P(CEMA-MMA)) shells (**Figure 5B (a)**) and redox-responsive capsules with P(MCC-MMA) shells (**Figure 5B (b)**) when exposed to TCEP-containing aqueous/DMSO media. The dispersion of P(CEMA-MMA) capsules was still turbid after exposure, but the dispersion of P(MMC-MMA) capsules became clear, indicating that the reducing agent destroyed only the disulfide-containing shells. Estimation of the transmittance of the dispersion at 500 nm wavelength as a function of time was consistent with that observed by the naked eyes, with the opacity of the dispersion decreased over time for P(MMC-MMA) capsules, but not for P(CEMA-MMA) capsules.[48]

In addition to the above-mentioned examples, employment of conductive polymers such as polyaniline as capsule shells is a popular route for producing redox-responsive capsules, since these polymer backbones can not only be reduced, but also oxidized to give the capsules switchable releasing performance. For example, reduction of the PANI backbone results in conversion of the emeraldine base to emeraldine salt, the latter of which is less conjugated and has weaker interchain hydrogen bonds, which leads to more permeable capsule shells. These changes can also alter the shell affinity to hydrophobic and hydrophilic molecules and thus make the capsules promising for different kinds of cargo loading and release. In contrast, oxidation of PANI strengthens intermolecular hydrogen bonding interactions and effectively seals the capsule shell, and thus can prevent the active core from releasing, as reported by Crespy et al. in 2013.[49]

Another redox-active chemistry for preparing capsule shells that cannot be ignored is poly(vinylferrocene) (PVF),[31, 51, 52] as PVF can be easily transformed to poly(vinylferrocenium) by oxidation with, e.g., hydrogen peroxide or potassium permanganate which causes the polymer to swell with water. As reported by Staff and colleagues, capsules with poly(vinylferrocene)-block-poly(methyl methacrylate) (PVFc-b-PMMA) shells and core of hydrophobe (e.g., hexadecane) can be fabricated through homogenization of aqueous solution of sodium dodecyl sulfate and PVFc-b-PMMA/dichloromethane followed by removal of dichloromethane. The resulting 236 nm diameter capsules experience hydrodynamic diameter increase to 310 nm and 282 nm after oxidization by hydrogen peroxide and potassium permanganate, respectively.[51]

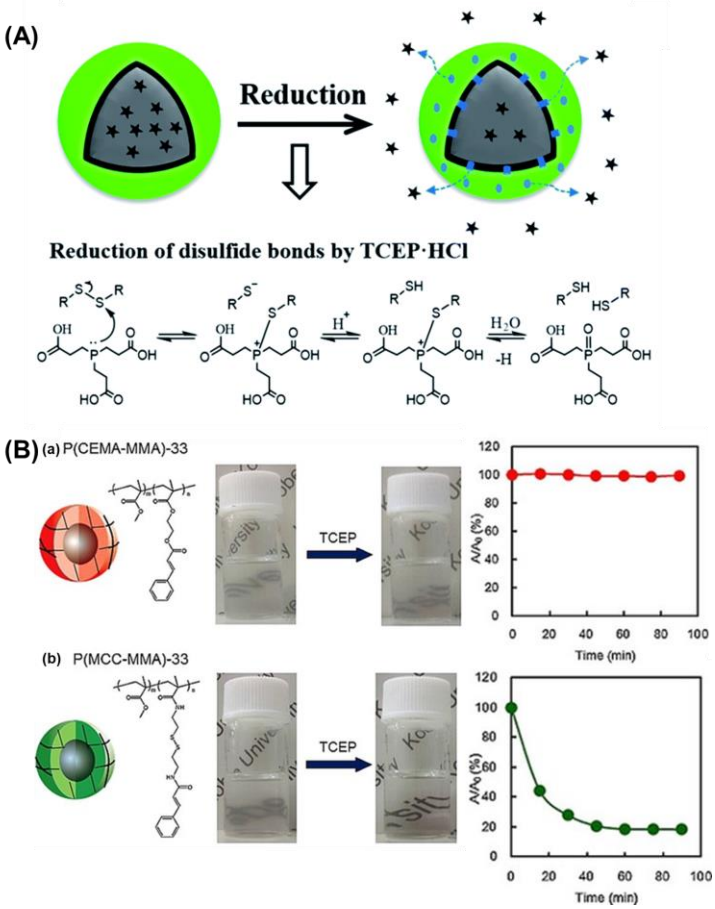

Figure 5. (A) Addition of the reducing agent (TCEP·HCl) leads to the reduction of the disulfide bonds in the PDSDMA capsule shells and changes the shell permeability. Reproduced from ref (47) with permission from Royal Society of Chemistry (2016). (B) Comparison of capsule degradation extent between non-redox-responsive shells of P(CEMA-MMA) (a) and redox-responsive shells of P(MCC-MMA) (b) in the presence of TCEP. Reproduced from ref (48) with permission from Wiley‐VCH Verlag GmbH & Co. KGaA, Weinheim (2017).

3.2 Physical Stimuli

3.2.1 Temperature

Development of capsules with shells responsive to heat have gained increased attention, not only stimulated at high temperatures, but also at mild heating to broaden the potential applications in common environments. Generally, most temperature-responsive polymeric shells depend on the polymers having desired melting temperature or incorporation of temperature-responsive microgels into the shells.[53-55] In 2019, Goertz and colleagues fabricated capsules using wax as shells where the melting temperature was tuned from 38 °C to over 60 °C, dictated by the type of wax employed. Bio-detective agents (e.g., hydrogen peroxide), hazardous chemicals, or fluorescent dyes were successfully encapsulated hermetically inside the capsules (**Figure 6A (a)**), and triggered burst release was observed at corresponding temperatures (**Figure 6A (b)**).[53] Furthermore, poly(N-isopropylacrylamide) (PNIPAm), a thermo-responsive polymer in aqueous media shows excellent hydrophilicity at room temperature. Above the lower critical solution temperature (LCST, between 30 °C to 40 °C depending on chemical

environment), the polymer becomes more hydrophobic and shrinks due to interruption of the hydrogen bonding between the polymer backbone and the water molecules, making it a popular component for temperature-responsive shells. For instance, the Dinsmore lab fabricated capsules with PNIPAm-*co*-acrylic acid microgel particle shells where the capsules reversibly shrink when heated above the LCST.[54] Similarly, the Zhang lab constructed capsules with PNIPAm/silica hybrid shells and observed similar capsule shrinking performance upon heating.[55]

Unlike the previous reports about employing meltable polymer shells or thermo-responsive microgel as shell components, our group has contributed to this area by utilizing thermo-responsive dynamic covalent chemistry incorporated into the polymer shell, specifically hindered polyureas.[56] Differentiated from traditional urea bonds, hindered ureas are formed upon reaction of a secondary diamine and diisocyanate. The bulky group on the nitrogen atom of the diamine disrupts the planarity of the urea bonds and thus gives a thermally accessible reverse reaction (**Figure 6B (a)**). Isolated, dry capsules with shells that contained the hindered urea bonds were stable at ambient temperature but were transformed to a monolithic structure under compaction and heating or underwent shell destruction upon addition of a primary amine and solvent under heating (**Figure 6B (b)**).

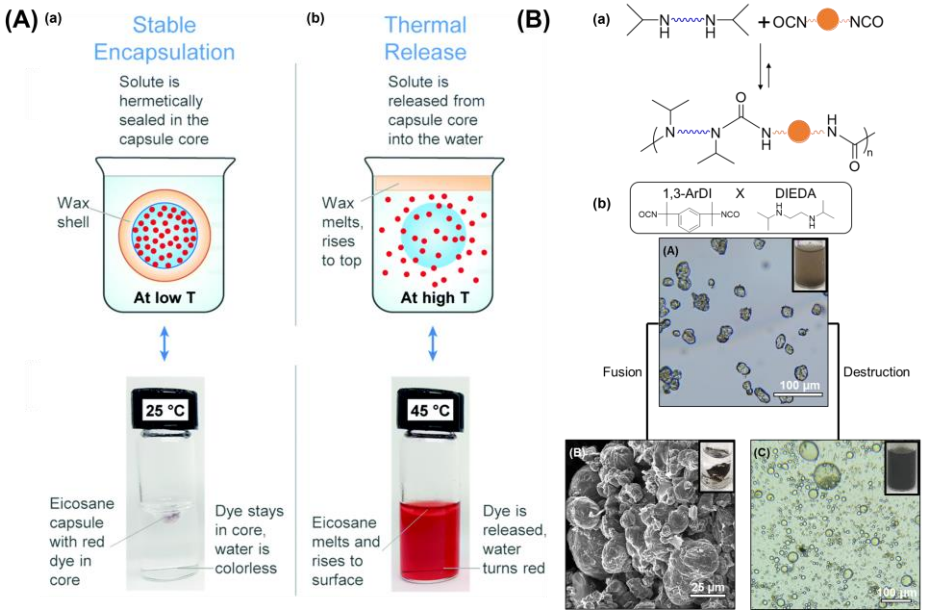

Figure 6. (A) Capsules with wax shells can be stable at room temperature (a) and experience shell melting at elevated temperature (b) to release encapsulated dye. Reproduced from ref (53) with permission from Royal Society of Chemistry (2019). (B) Hindered polyurea chemistry (a) and dynamic capsules with hindered polyurea shells can experience inter-capsule shell bonding and capsule shell destruction under heating (b). Reproduced from ref (56) with permission from Royal Society of Chemistry (2021).

3.2.2 Light

Light irradiation is one of the most efficient stimuli which doesn't require direct physical contact with the stimuli sources. Generally, light-responsive polymers or segments are

integrated into the capsule shells;[57-61] UV-responsive ones such as azobenzene and coumarin are the mostly commonly utilized since UV is the most frequently employed light source in today's world and coumarin is significant for bio-mimic compound. **Figure 7A** reveals the capsule shells prepared from poly(1-(4-(3-carboxy-4-hydroxyphenylazo)benzenesulfonamido)-1,2-ethanediyl, sodium salt) (PAZO) and PDADMAC, with the light-responsive azobenzene segments in PAZO. Upon irradiation by UV (366 nm), capsules experienced shell disruption and even destruction which was attributed to the UV-triggered J (tail-to-tail) aggregation of the azobenzene-containing segments. These microscopic conformational changes exert stress on the capsule shell from a macroscopic perspective.[57] Similar chemistry was used in the work of Marturano and colleagues where capsule shells were fabricated from polymerization of 1,8-diaminooctane, 4,4′-bis(chlorocarbonyl)-2,2′-dimethoxy azobenzene and 1,3,5-benzenetricarbonyl trichloride, with natural active agents (e.g., thyme oil, an antimicrobial compound) encapsulated. The azobenzene ring on the capsule shell is selectively responsive to green and white light irradiation, which makes the capsules switchable carriers (**Figure 7B**).[58] In this case, controlled release of the core was attributed to the isomerization of the azobenzene segments. This is in line with work from the same group demonstrating a coumarin-6 dye core can be released upon irradiation (**Figure 7C**).[59]

Takeuchi et al. employed poly(7-(2-methacryloyloxy ethoxy)coumarin-*co*-methyl methacrylate) (P(COMA-MMA)) as capsule shells where dimerized coumarin groups of the COMA side chains can undergo bond breakage when irradiated at 254 nm, as shown in **Figure 7D (a)**. Capsules were dispersed in DMSO to perform the photodegradation test. Turbidity as a function of photoirradiation time illustrated that the turbid capsule dispersion became clearer with increased irradiation time (**Figure 7D (b)**), which indicates degradation of capsule shells and which was consistent with visual observation of the dispersion in vials (**Figure 7D (c) and 7D (d)**).[60]

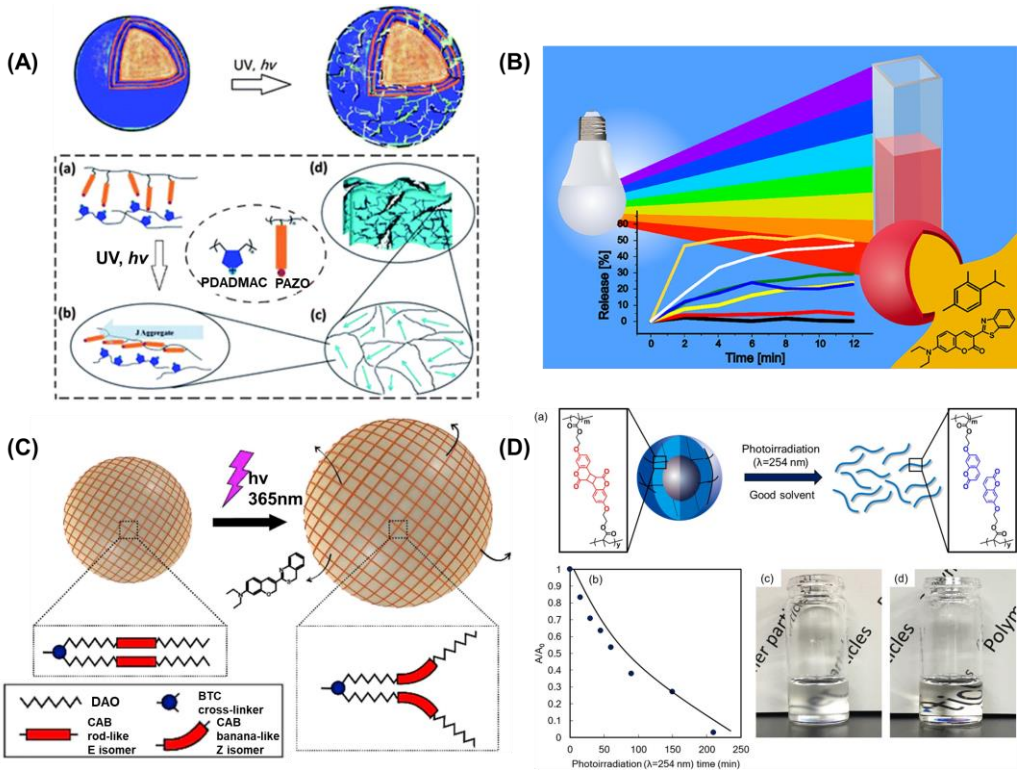

Figure 7. (A) UV irradiation-induced J aggregates of PDADMAC/PAZO capsule shell leads to capsule shell destruction (λ = 320-500 nm). Reproduced from ref (57) with permission from Royal Society of Chemistry (2014). (B) Release of natural active agents from capsules with polyamide shells bearing azobenzene groups under selective light wavelengths (λ = 400-700 nm). Reproduced from ref (58) with permission from American Chemical Society (2019). (C) UV irradiation-induced capsule shell swelling due to the E to Z isomerization of azobenzene groups in the capsule shell (λ = 360 nm). Reproduced from ref (59) with permission from Elsevier Ltd (2015). (D) Photodegradation of P(COMA-MMA) particles due to breakage of dimerized coumarin groups (a); and turbidity as a function of photoirradiation time (λ = 600 nm) (b); and optical images of capsule dispersion before (c) and after (d) the irradiation (λ = 254 nm). Reproduced from ref (60) with permission from American Chemical Society (2020).

3.3 Post-Processing of Capsule Shell to Strengthen Stimuli

In this section, we illustrate a special class of responsive polymeric shells in which responsivity is assisted/enhanced by guest metal nanoparticles integrated into the polymers. Such composite shells are typically needed when the polymers themselves cannot give noticeable responsivity to mild external stimuli, with the guest particles sensitizing the shell to the stimuli to induce responsivity. A typical example is the integration of gold nanoparticles into polymer shells. The gold nanoparticles act as heat locators upon irradiation, which can be used to initiate capsule shell destruction, as reported by Yi et al.[62] Capsules with oppositely charged diazo-resin multilayers as shells and encapsulation of Rhodamine B (RhB) were successfully constructed, and gold particles were integrated into the shells through deposition such that 840 nm near-infrared laser irradiation could be employed to stimulate the rapid heating of capsule shells. It was confirmed that rapid localized heating caused destruction of the capsule shells and subsequent release of RhB. Similar phenomenon can be found in the work of Skirtach et al., where capsules with PAH/PSS/gold particles hybrid shells and RhB-labeled PSS core

underwent shell deformation upon irradiation, releasing the encapsulated polymers.[63] Composite shells provide a route to prepare responsive capsules when it is impossible to directly leverage dynamic covalent bonds or intra-/inter-molecular interactions, for example with protons or redox reagents. However, one-step procedures are needed for incorporating the active particles during the capsule fabrication process, as incorporation of the active particles in a post-processing step is cumbersome and time consuming.

4. Applications

4.1 Active Agents Delivery

Employing responsive polymeric capsules as payload carriers for targeted delivery has been explored for decades.[64] Stimuli-responsive delivery provides the flexibility of release at desired environments and time periods. Beyond drug delivery, triggered release can be used for delivery of active agents such as perfume and antimicrobial agents, which is significant for cosmetic industry, agriculture, as well as adhesive development. Notably, selective and switchable release is of great importance since this guarantees the release of desired reagents at specific time slots. For example, Marturano and collaborators fabricated capsules with polyamide shells and coumarin-6 or thyme oil encapsulated. As shown in **Figure 8A**, the capsules show the release of the core liquid upon irradiation with green light, contrasting with trace release under darkness, where that controlled release could be observed when pulsed light and multiple “on” and “off” cycles, which is critical for antimicrobial protection in crop industry.[58] **Figure 8B** highlights the release profile of capsules with PANI shells and poly(dimethylsiloxane) diglycidyl ether terminated (PDMS-DE) core where the shells were at different states. When the capsule shells were reduced (black curve), capsules show rapid release within 10 mins compared to the control sample (blue curve). Instead, oxidation (red curve) effectively sealed the shells and slowed the release; upon subsequent reduction of the shells, rapid release can be triggered again (pink curve).[49]

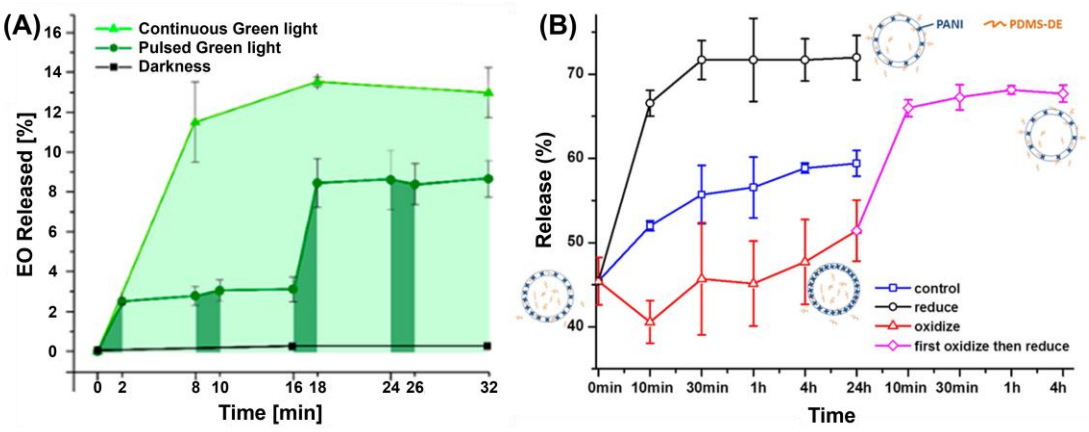

Figure 8. (A) Release profile of thyme oil under continuous and pulsed irradiation of capsules with polyamide shells under green light. Reproduced from ref (58) with permission from American Chemical Society (2019). (B) Controlled release of PDMS-DE from PANI capsules under varied conditions. Reproduced from ref (49) with permission from American Chemical Society (2013).

4.2 Transport and Transformation

In addition to the most prevalently utilized targeted delivery function, responsive capsules can be used for transport of active material followed by transformation for other architectures. Our group has produced temperature-responsive capsules with shells composed of hindered poly(urea-urethane) and core of oil or ionic liquid/oil mixture. Inter-capsule bond exchange in compacted capsules yields monolithic structures with fluid channels, thus providing a template for producing fluid-containing or porous structures possessing potential applications in molecule separation, energy storage, etc. Alternatively, upon addition of a primary amine small molecule, in suspension the capsule shells can be destructed to form an emulsion (**Figure 9A**), which is significant when direct release of (or access to) the core materials is important, such as in pesticide delivery and the coating industry. Of note, the responsive temperature can be tuned through controlling the hindrance of the diamine (tert-butyl, iso-propyl, ethyl) used to form the polymeric shells (**Figure 9B**), with bulkier diamines giving lower responsive temperature. Moreover, the identity and polarity of encapsulated liquids impact the bond exchange temperature and morphology of the monolithic structures produced: a core of the IL 1-hexyl-3-methylimidazolium bis(trifluormethylsulfonyl)imide dramatically lowers the temperature required for bond exchange and produces monoliths with much smoother morphology, as compared to capsules with cores of *N*,*N*-dimethylformamide (DMF).[65]

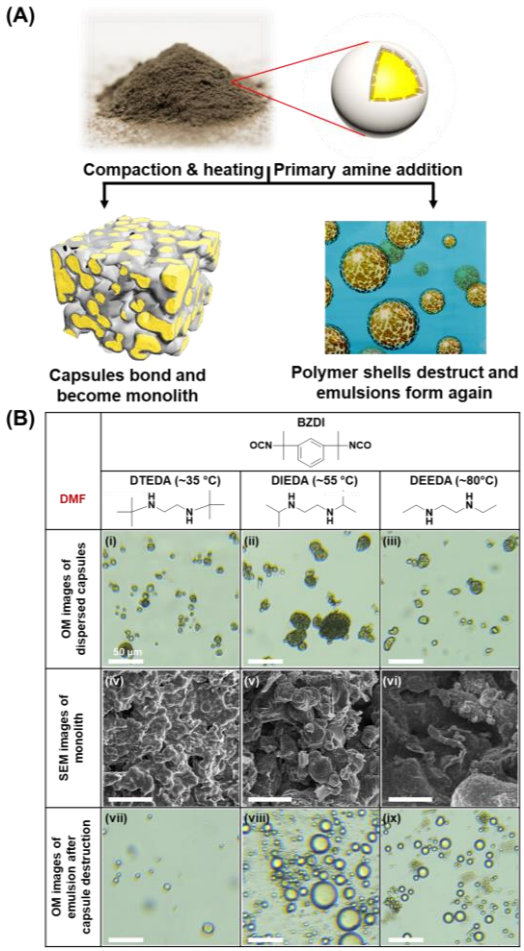

Figure 9. (A) Schematic illustration of capsules with dynamic shells which can undergo inter-capsule bonding to become a monolithic structure containing fluid channels or shell destruction

to produce an emulsion. (B) Optical microscope images of as-prepared individual capsules (i-iii) and newly formed emulsion droplets (vii-ix) after capsule shell destruction and SEM images of monolithic structures after inter-capsule bonding (iv-vi), for capsule shells formed from different diamines. Reproduced from ref (65) with permission from American Chemical Society (2022).

4.3 Anti-Corrosion and Healing

Anti-corrosion of metal-based materials in efficient and cost-effective ways has been a hotspot in the past decades for the significance in protecting infrastructure and transportation, as well as aerospace devices. Developing responsive capsules as fillers of coating materials is a promising tool because this reduces the use of large amounts of anti-corrosion coating and can stop/repair corroded areas when necessary.[66-69] Zhu and colleagues constructed capsules with shells of poly(butyl acrylate-*co*-1,6-hexanediol diacrylate) and core of 1,3-bis(glycidoxypropyl)tetramethyldisiloxane (epoxy) and triarylsulfonium hexafluorphosphate salt solution (cationic photoinitiator) in propylene carbonate as the anti-corrosion/healing agents. Integration of the capsules into silicon resin produced a composite coating for glass substrate (**Figure 10A (a)**). Scratching the coating mechanically broke the capsules and led to leakage of some of the encapsulated healing agents , which helped to repair the crack (**Figure 10A (b)**). More importantly, upon UV irradiation, the capsule shells can degrade and thus release additional healing agents to repair the damage, overcoming the need for deformation (**Figure 10A (c) and 10A (d)**). This can be confirmed by the SEM imaging (**Figure 10B (a)**) of the sample before and after UV-accelerated weather treatment tests, where the sample didn't show significant change in morphology; further the FTIR spectra was consistent after different treatment time length (**Figure 10B (b)**).[66] In complement, Vimalanandan et al. prepared redox-responsive capsules with PANI shells and 3-nitrosalicylic acid (3-NisA) core. The capsules were mixed with poly(vinyl butyral- *co*-vinyl alcohol-co-vinyl acetate) (PVB) to produce a coating for a zinc surface. In an aqueous solution of KCl, corrosion-prevention ability was evaluated through corrosion potential measurements, as shown in **Figure 10C**. **Figure 10D** illustrates that only samples covered by coatings composed of 3-NisA wrapped capsules/PVB show an elevation of potential, which proves the hinderance of continuous zinc corrosion (purple curve). Samples coated with pure PVB (black curve) or capsule without 3-NisA/PVB (red curve) showed similar corrosion profiles.[67]

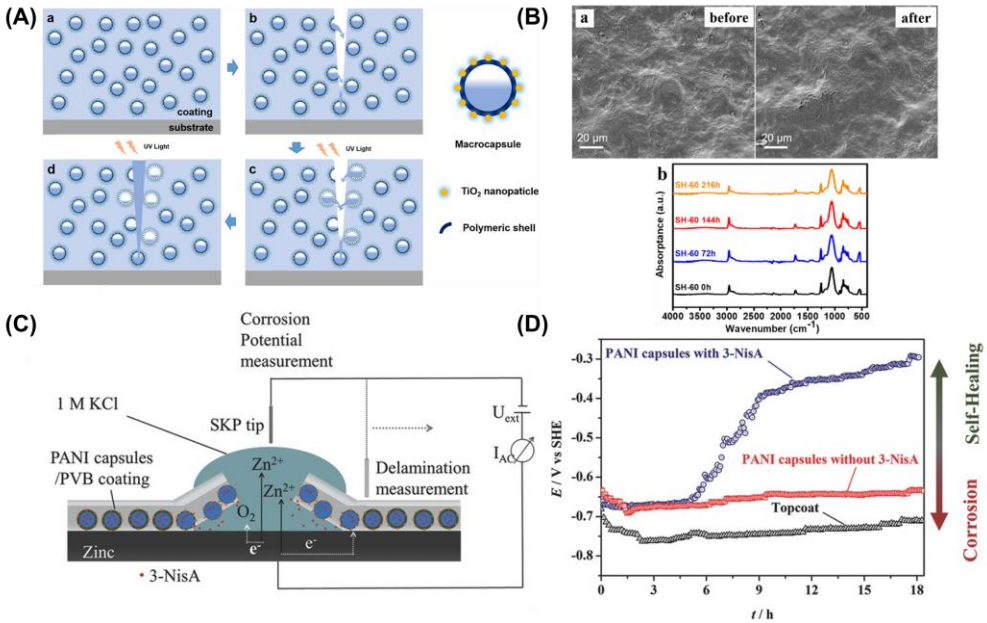

Figure 10. (A) Schematic illustration of employing UV-responsive microcapsules as coating fillers (a) and release of healing agent through mechanically cleavage and UV light-induced shell degradation (b,c), for repairing the cracks on the substrate (d). Reproduced from ref (66) with permission from American Chemical Society (2019). (B) SEM images of SH-60 (60 wt% of capsules contained in the coating) sample before and after experiencing UV accelerated weathering test for 216 h (a); and FTIR spectra of the sample at different testing time length (b). Reproduced from ref (66) with permission from American Chemical Society (2019). (C) Schematic illustration of utilizing 3-NisA encapsulated PANI capsules as coating fillers for protecting zinc substrate in high salinity environments and evaluation of corrosion-prevention ability through corrosion potential measurement. Reproduced from ref (67) with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim (2013). (D) Corrosion potential as a function of time in defect area covered by coatings bearing PANI capsules with (purple curve) and without (red curve) 3-NisA encapsulated, and control experiment of PVB topcoat (black curve). Reproduced from ref (67) with permission from WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim (2013).

5. Summary and Outlook

As described herein, responsive capsules can be produced through a variety of methods, including via the hard template method (e.g., sacrificial core) or soft template method (e.g., emulsion), together with interfacial crosslinking, LbL assembly, and polymer precipitation. In most reported cases, inter- and/or intra-molecular van der Waals interactions, electrostatic interactions, or dynamic covalent chemistries are required. Further integration of sensitizer particles within the polymer network can further tune the external stimuli that can be used to induce responsivity of capsule shells. Concerning popular application-based performance, triggered cargo release of non-drug payload (e.g., perfume, tracking agents, etc.) remains the most prevalently reported use of stimuli-responsive core-shell structures, with further applications on material self-healing/protection/anticorrosion being extensively explored. Alternatively, responsive capsules can also be utilized as precursors for advanced architectures such as hollow structures or fluid-containing monoliths.

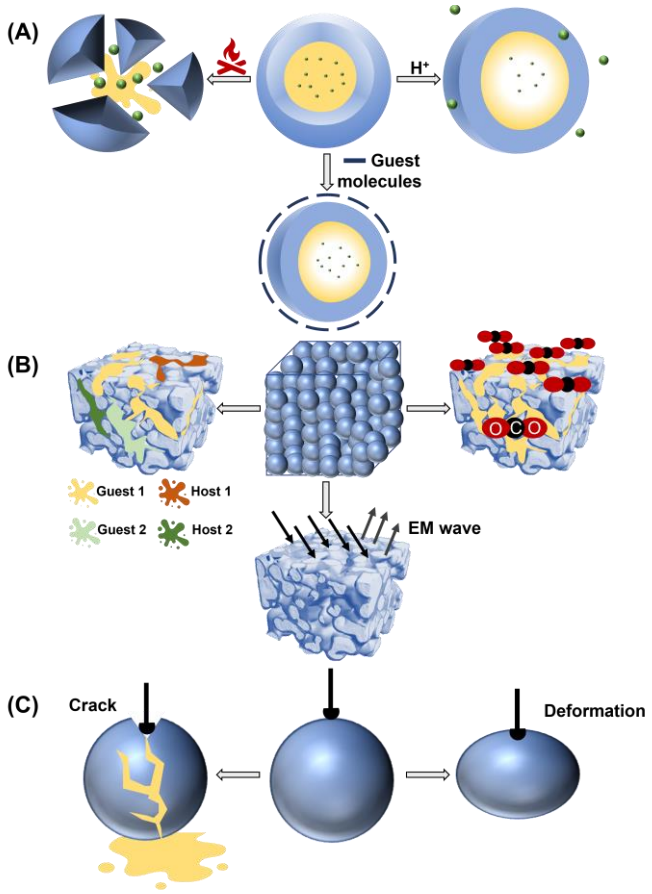

Figure 11. Potential directions for the exploration of responsive capsule shells. (A) Capsules can be responsive to multiple orthogonal or synergistic stimuli. (B) Employing capsules to transport active agents and then form monolithic structures containing fluid channels for gas uptake, orthogonal reactions, or irradiation shielding (e.g., EMI shielding). (C) Mechanical property of capsule shells needs to be illustrated.

Despite noteworthy progress over the past several decades, responsive polymeric capsules have vast potential that has yet to be tapped, especially beyond delivery of therapeutics, and their use in advanced technologies will be expedited by fundamental studies of their properties (**Figure 11**). For instance, capsules with shells that are responsive to multiple stimuli[52] (e.g., triple-responsive, tetra-responsive, etc.) can enhance adaptability and broad applicability. For example, a capsule shell may be responsive to only combined heat and light, but not each stimulus individually. While many studies have addressed single or dual-responsive capsules, only a few are triple-responsive capsules. We stress the importance of exploration of multi-responsive capsules which can show response to three or more stimuli because this could help to better define what conditions a desired response is realized, thereby giving better spatial and temporal control (**Figure 11A**). Further, responsive capsules can provide dual transport and transformation roles, where liquid-filled capsules are prepared and stable to storage until they need to be used as a feedstock to produce, e.g., a different architecture. Such capsules would be especially attractive for additive manufacturing[70] to produce freestanding structures tailored to specific applications. For example,

transformation of capsules to a fluid channel-containing monolithic structures could provide suitable composition and surface area required, e.g., for gas uptake, separations, or irradiation shielding (e.g., electromagnetic interference (EMI) shielding). Such transformations could also find widespread use in coatings and adhesives, where the capsules provide a feedstock of phase separated materials that could otherwise not be integrated into a single film, based on reactivity or orthogonal processing requirements (**Figure 11B**). In addition, functionalized metal particles may be directly integrated as surfactants when preparing capsules so that the need for post-incorporation of metal particles as stimuli-strengthener is eliminated. Moreover, employing multiple emulsions (e.g., double emulsion) to prepare capsules with multiple layers of shells with different responsivity and multiple core materials can also improve the mechanical flexibility and open the compositions of capsules under different working conditions.

In addition to tailoring composition and responsivity of capsules, better and more standardized characterization of the capsules and their performance-related properties are needed. For example, our group recently reported that capsules with polyurea shells and core of IL can be used to remove a dye from water; the capsules were put into an aqueous solution of a small molecule dye and UV-vis spectroscopy of the aqueous phase was used to evaluate the rate and extent of dye movement from the liquid to the core, comparing to capsules with a solid wax core to account for uptake by the shell. We discovered that both the pH of the water and the identity of the polyurea impact the rate of dye uptake.[71] If a common small molecule and characterization technique are used to evaluate movement of materials into/out of capsules, comparison between systems reported in the literature will be possible. Further, understanding the deformation of capsule shells is important to establishing conditions they are stable to. To date, only a handful of the studies address the mechanical strength of responsive capsules (**Figure 11C**), yet mechanical properties not only impact the use of capsules under pressure or deformation, but also influence homogenization of capsules into polymer matrix when composite materials are produced (e.g., do the capsules rupture). Micromanipulation techniques, and use of the “pillar method” can be used to establish the impact of core, shell, and capsule diameter on, e.g., modulus of the capsule. Whereas micromanipulation experiments will be performed on individual capsules, rheological experiments can be used to evaluate the bulk or ensemble properties. In many capsule samples, especially those produced by the soft template method, size distribution is relevant.

Core-shell capsule structures have attracted widespread interest for their impressive ability to protect, store, and transport liquids as core materials. Polymeric shells offer significant advantages over other materials; chiefly, versatility in tuning composition, easy integration of functionalities (including particles), and targeted application-oriented performance. Specifically, capsules fabricated with stimuli-responsive polymeric shells are of growing interest in across soft matter community due to their promising application in targeted cargo release. The polymer shell enables tuning of responsivity to eternal stimuli such as pH, temperature, light, guest-host intermolecular reactions, etc. While this feature has been widely explored by researchers in the delivery of small molecules under physiological conditions, these capsules have significant potential beyond this narrow scope, including in transformation of architectures, payload release under varied

conditions, in self-healing coatings and adhesives, energy management, and additive manufacturing.

Author Information

Corresponding Author

Emily Pentzer − Department of Materials Science & Engineering, Department of Chemistry, Texas A&M University, College Station, Texas, 77840, USA.; ORCID: 0000-0001-6187-6135; Email: emilypentzer@tamu.edu

Authors

Yifei Wang − Department of Materials Science & Engineering, Texas A&M University, College Station, Texas, 77840, USA.; ORCID: 0000-0003-0110-8147

Nicholas Starvaggi − Department of Chemistry, Texas A&M University, College Station, Texas, 77840, USA.; ORCID: 0000-0002-0085-7886

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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