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PERSPECTIVE

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Triggered Release from Polymer Capsules

Aaron P. Esser-Kahn,[†,‡,⊥] Susan A. Odom,[†,‡,⊥] Nancy R. Sottos,[†,§] Scott R. White,[†,∥] and Jeffrey S. Moore*[,†,‡]

[†]Beckman Institute for Advanced Science and Technology, [‡]Department of Chemistry, [§]Department of Materials Science and Engineering, and [∥]Department of Aerospace Engineering, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801, United States

ABSTRACT: Stimuli-responsive capsules are of interest in drug delivery, fragrance release, food preservation, and self-healing materials. Many methods are used to trigger the release of encapsulated contents. Here we highlight mechanisms for the controlled release of encapsulated cargo that utilize chemical reactions occurring in solid polymeric shell walls. Triggering mechanisms responsible for covalent bond cleavage that result in the release of capsule contents include chemical, biological, light, thermal, magnetic, and electrical stimuli. We present methods for encapsulation and release, triggering methods, and mechanisms and conclude with our opinions on interesting obstacles for chemically induced activation with relevance for controlled release.

I. INTRODUCTION

The controlled release of contents from polymeric capsules is of considerable interest in applications such as self-healing materials, nutrient preservation, fragrance release, and drug delivery. The utility of capsules as vehicles for cargo storage stems from their ability to deliver beneficial agents (e.g., fertilizer) "just in time" to affect the outcome of larger systems (e.g., crop growth). Triggering is a stimuli-dependent phenomenon, and the development of appropriate initiators plays a key role in the release of capsule contents to provide the desired outcome. A variety of chemical and physical methods have been developed to release capsule contents. Capsule systems are particularly appealing for delivery of small molecules and particles. Using capsules, a drug, nutrient, or healing agent is delivered without requiring modification. In contrast, the use of triggerable small molecules requires chemical modification, potentially leading to more time-intensive preparations and greater use of triggering groups.

Many mechanisms can initiate changes in a capsule shell wall that results in the release of capsule contents (Figure 1). In drug delivery, light-activated mechanisms are relevant for targeted release in biological tissues (Figure 1, photo). Tissues show negligible absorption in the 800−1200 nm region,[1] providing a window for laser irradiation of near-IR-sensitive capsules. UV- and visible light-sensitive capsules are also used in the cosmetic[2] and agricultural industries[3] where solar irradiation triggers release. Biological triggers are used for drug therapy and vitamin delivery (Figure 1, biological).[4] Slight changes in pH[5] or the presence of certain chemicals (e.g., insulin)[6] cause appropriately designed capsules to release their contents in a patient, requiring only *in vivo* stimuli (Figure 1, chemical). Thermally induced release is useful in applications where subtle changes in temperature occur (Figure 1, thermal). For example, in agricultural applications, an increase in soil temperature can initiate delivery of nutrients.[3,7] Deodorant and antiperspirant materials can be released upon reaching targeted temperatures, allowing for delivery only where a person perspires.[8,9] Magnetically induced release is useful for drug delivery, activating capsules only in tissues subjected to oscillating magnetic fields (Figure 1, magnetic).[10] Electric field release is useful in delivering anticorrosive materials only when a metallic surface is compromised (Figure 1, electrical)[11] and may be useful in battery materials that experience a higher voltage than standard operating potentials.

In this Perspective, we focus our discussion on the use of chemical changes within capsule shell walls as a triggering method. First, we present a background on capsule fabrication methods (section II) in order to familiarize the reader with the chemical constraints each technique places on trigger incorporation and release (section III). In section IV, we discuss triggers responsible for activating chemical reactions including chemical, biological, light, thermal, magnetic, and electrical stimuli. As this is still a nascent field of research, some of the stimuli we discuss have not been fully demonstrated for triggered release via chemical changes in the shell wall. For completeness, we also discuss physical phenomena responsible for capsule release. Finally, in section V we conclude by highlighting persistent technical challenges. We suggest possible solutions and discuss areas where new triggering strategies are desperately needed.

A number of reviews have focused on encapulating and releasing deliverable materials, both on the nano- and microscale.[11−20] As this Perspective focuses on triggering approaches, we provide reference to these reviews for those who are interested in the research area of microencapsulation as a whole.

II. METHODS FOR PREPARING MICROCAPSULES

Microcapsules are prepared by several methods including pan coating, spray drying, centrifugal extrusion, and emulsion-based methods. Several review articles have focused on capsule preparation;[21] here we present methods that utilize emulsions.

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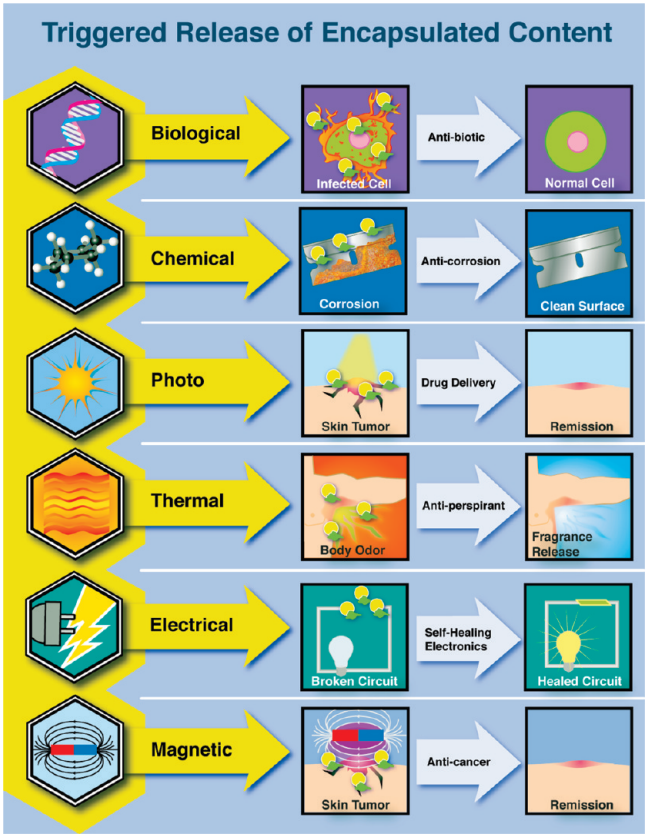


Figure 1. Triggering mechanisms for microcapsule release include biological, chemical, photo, thermal, electrical, and magnetic stimuli.

Each method has advantages for specific applications, which depend on a variety of capsule characteristics. These include shell wall thickness and permeability, chemical composition of the shell wall, mechanical integrity of the shell wall, and capsule size. Of equal importance in choosing a preparation method is the ability to incorporate specific materials within the capsule, whether the core is aqueous, organic, or inorganic. The core material and method for preparation also affects whether capsules are spherical or ellipsoidal.[22] A capsule's ultimate shape results from the shape of its liquid droplet precursor in the emulsion, which depends on the viscosity and surface tension of the core liquid, the direction of flow in the emulsion, and the choice of the surfactants used for droplet stabilization.

Emulsification polymerizations are all forms of self-assembly.[23,24] Whether covalent bonds form, electrostatic interactions dominate, or polymers precipitate from solution, in all cases, the shell wall materials are guided to the organic/aqueous interface, which enables the formation of capsule shell walls. Table 1 highlights the major pros and cons of the methods we present here: emulsification polymerization, layer-by-layer assembly of polyelectrolytes, coacervation, and internal phase separation. We note here that the pros and cons listed in Table 1 and throughout our discussion are generalizations for these capsule types, and improvements in capsule preparation have overcome some of the disadvantages listed. Where relevant, exceptions to these general characteristics will be described in the text. An overview of these techniques is shown in Figures 2 and 3, and specific polymers that we reference in this paper, including their names, abbreviations, and structures, are shown in Chart 1.

II.1. Emulsification Polymerization. Many capsules are prepared through the polymerization of monomer units at the aqueous/organic interface of droplets in an emulsion.[25−27] Emulsions of oil in water or water in oil are typically produced by vigorous agitation or sonication of a biphasic liquid. Stirring or sonication creates droplets, and it is these droplets that become the core material of the capsules. The formation of a polymer at the aqueous/organic interface creates the capsule shell wall that encases the droplet. Polymers may form from condensation reactions[26] (Figure 2A) such as the reaction of amines with aldehydes, acid chlorides, or isocyanates or *in situ* polymerization reactions of monomers such as styrene derivatives.[28−30] While these capsules are not typically thought of as "reloadable", it is possible if the capsule shell wall is permeable enough for core release and refilling.[31]

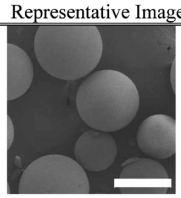
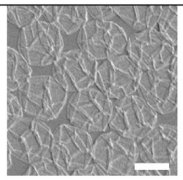
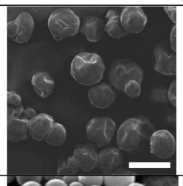
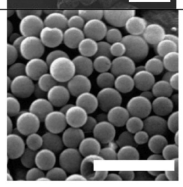
The stability of emulsions depends largely on the miscibility of the organic and aqueous materials and the surface tension of the core liquid. When stability is problematic in emulsification polymerizations, Pickering emulsions are often helpful in capsule preparation. Pickering emulsions are particle-stabilized emulsions[32] that are often more stable and create less foam than surfactant-stabilized emulsions, making them attractive for templating microcapsule formation.[33] Pickering emulsions have been used to synthesize organic/inorganic hybrid capsules in which the nanoparticles are incorporated into the polymer shell wall.[33−35]

II.2. Layer-by-Layer Assembly. Layer-by-layer (LBL) assembly is used to prepare a variety of capsule materials.[33−40] Initially metal oxide particles are suspended in an aqueous solution. In a stepwise fashion, negatively and positvely charged polyelectrolytes are deposited onto these particles, forming layers of polymers held together by electrostatic interaction. After the multilayering is complete, an acid is usually employed to remove the metal oxide core, leaving behind hollow, semipermeable capsules (Figure 2B). More recently, De Geest and others have reported less harsh conditions for core dissolution, such as the removal of $CaCO_3$ cores with ethylenediaminetetraacetate (EDTA).[41] Pastoriza-Santos et al. have reported the use of polystyrene particles as a core in LbL assembly that can be removed by exposing capsules to tetrahydrofuran.[42] Another method for avoiding strong acids involves the use of small organic molecules as cores including toluene[43] and dodecane.[44] Khapli et al. reported the use of frozen cyclohexane as the core material, which was removed after LbL deposition when the capsules were brought to room temperature.[45]

Because of the high permeability of the shell walls, capsule cores can be readily exchanged with external media, allowing for a variety of core materials to be introduced after capsule preparation. Upon isolation in the solid state, the capsules often resemble deflated balloons owing to the weak structural integrity of their shell walls. Recent reports on incorporating cross-links between layers, such as azides, have improved the integrity of the shell walls, including resistance to changes in size and shape in response to changing solvents or the pH of an aqueous solution.[42,46] Preparing air-stable capsules (capsules that do not deflate when dried) is a challenge recently overcome by the incorporation of inorganic nanoparticles as fillers to reinforce the otherwise soft LbL capsule shell walls. Shchukin et al. reported the electroless nickel deposition from a plating solution of nickel acetate, creating capsules that remained intact when isolated in the solid state.[47]

II.3. Coacervation. Self-assembly can be extended to capsule systems using coacervation. Preparing microcapsules and microspheres (solid particles) using coacervation is a common method

Table 1. Advantages and Disadvantages of Emulsion-Based Methods for Preparing Microcapsules[a]

Methods	Representative Image	Advantages	Disadvantages
a: Emulsification Polymerization		high strength capsule shell walls large scale synthesis thick shell wall narrow size distribution	difficult to encapsulate aqueous cores can only be loaded once surfactant and polymerization specific often large size distributions
b: Layer-by-Layer Assembly		compatible with aqueous or organic cores easy trigger incorporation post-fabrication core loading narrow size distributions if sacrificial core particles are uniform in size	laborious fabrication often poor structural integrity dry isolation difficult some cores require strong acid in preparation
c: Coacervation		ease of use in time-release or thermal-release applications simple fabrication	hydrophobic cores are required low strength shell walls slow shell wall formation can only be loaded once often large size distributions
d: Internal Phase Separation		high strength shell walls carbon rich polymers can be used ideally suited for thermal triggers	limited triggering capabilities hydrophobic cores are required limited core/shell polymer combinations can only be loaded once often large size distributions

[a] SEM images of (a) core−shell microcapsules with poly(urea−formaldehyde) wall and dicyclopentadiene core (scale bar = 100 μm),[162] (b) hollow PSS/PAH capsules (scale bar = 1 μm),[37] (c) microcapsule formed from gum arabic/gelatin coacervation (scale bar = 500 μm),[163] and (d) microcapsules formed from the internal phase separation of PMMA (scale bar = 10 μm).[52]

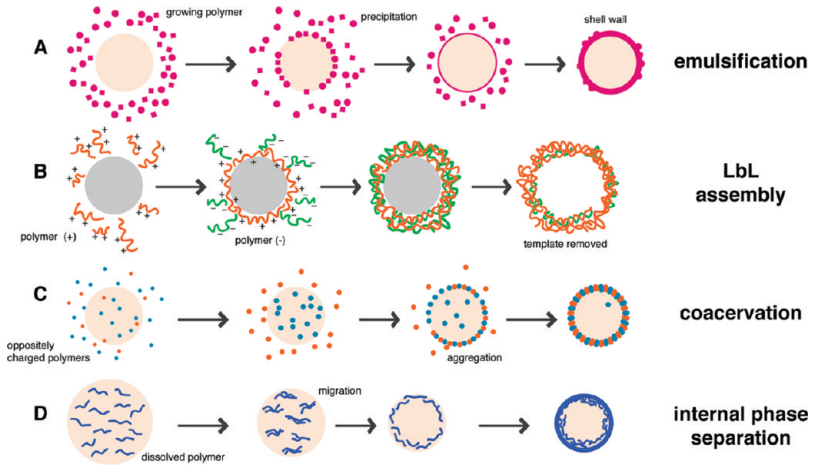


Figure 2. Methods for the dynamic self-assembly of nano- and microcapsules containing deliverable cargo: (a) an emulsification polymerization where a polymer is deposited at an aqueous/organic interface, yielding a polymer shell wall around a stabilized droplet, that becomes the core solution; (b) layer-by-layer (LbL) assembly of polyelectrolytes onto a metal oxide particle, that is removed using acid to create a permeable hollow capsule; (c) coacervation of two oppositely charged polymers that aggregate, forming coacervates, at the oil/water interface; (d) interphase separation in which a polymer is dissolved in a core material with a volatile solvent and precipitates, migrating to the aqueous/organic interface, thus creating the polymer shell wall.

in materials for food and fragrance applications where time release or temperature-induced delivery is a goal. Complex coacervation involves the neutralization of two oppositely charged polymers in aqueous solution, forming an entangled neutralized polymer shell wall.[48,49] The oil phase contains one polymer, and the aqueous phase contains a polymer of the opposite charge. The

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attraction of one polymer to another results in the formation of coacervates, which migrate to the aqueous/organic inferface, thus forming the shell wall (Figure 2C). Gelatin and gum arabic are common complementary components that have been used for capsule preparation.[50]

II.4. Internal Phase Separation. Another method of preparing microcapsules is the controlled phase separation of a polymer within the droplets of an emulsion.[51−53] In this method, a polymer is dissolved in a solvent mixture containing volatile and nonvolatile solvents. Droplets of the resultant solution are suspended in an aqueous layer, which is stabilized by continual agitation and the use of surfactants. As the volatile solvent evaporates, the polymer begins to precipitate and migrate toward the organic/aqueous interface. When the solvent has completely evaporated, the polymers coalesce to form a shell wall (Figure 2D). While this method is convenient for microcapsule preparation and has been demonstrated with PS,[51] PMMA,[52] and PTHF[53] shell walls, it is not feasible if the desired polymer is soluble in its intended core or if the polymer is insoluble in the volatile solvent.

II.5. Flow Focusing Devices. More recently, flow focusing devices have been employed to prepare core−shell microcapsules and polymerosomes. The Weitz group used a microcapillary device to generate double emulsions containing a single internal droplet encased in a middle fluid, which was then dispersed in an outer fluid (Figure 3).[54,55] The middle fluid becomes the shell wall, generating core−shell microcapsules with a high degree of control over capsule size and shell diameter. Shell walls can be formed by cross-linking reactions,[54] by solvent evaporation from a solution of dissolved polymer,[56] and from

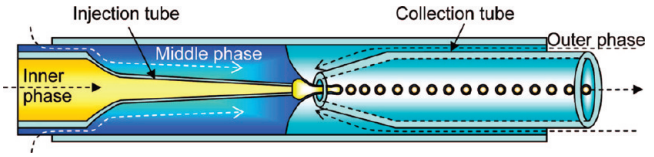
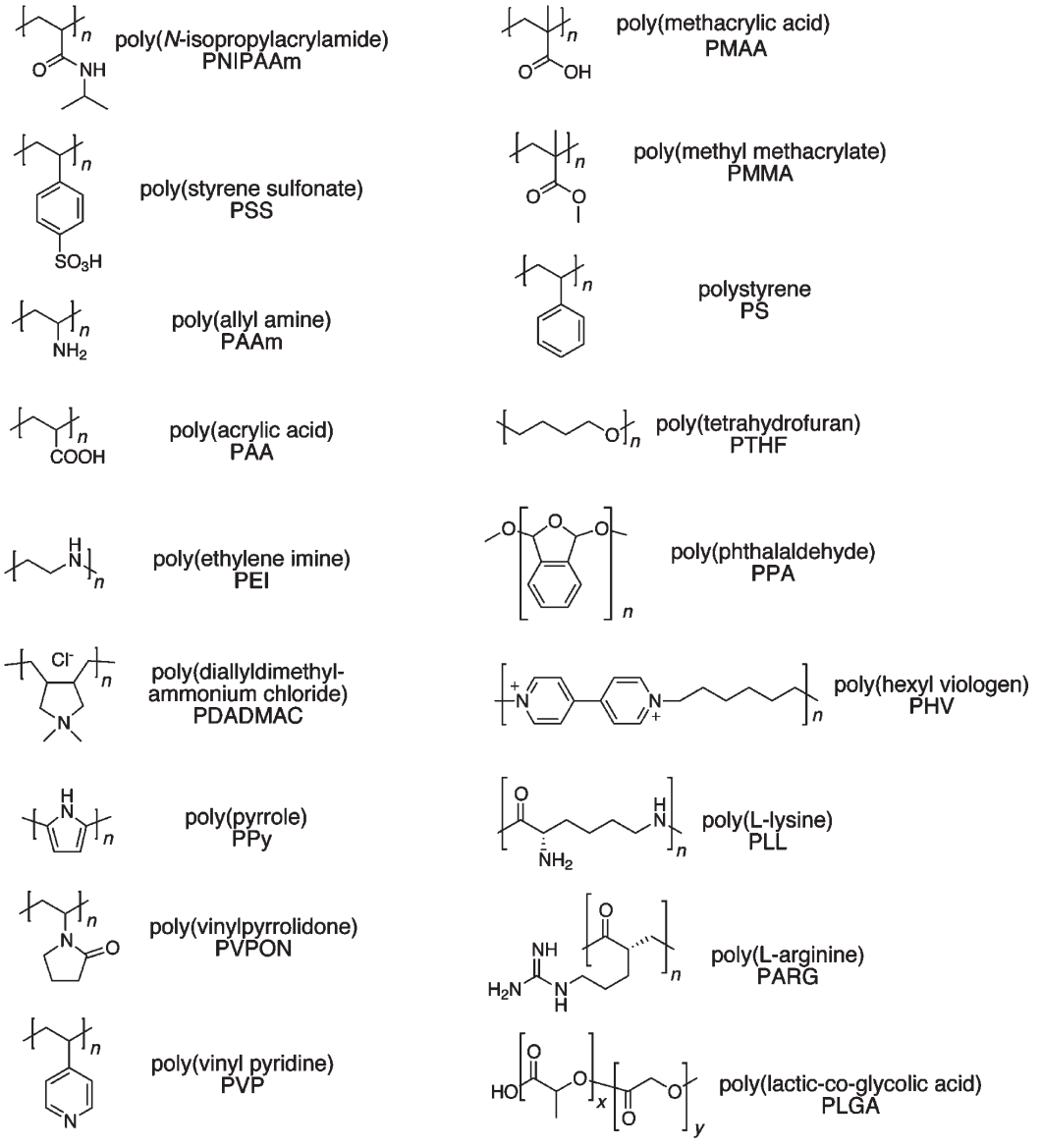


Figure 3. Schematic of a microcapillary device used for generating double emulsions.[55]

Chart 1. Structures, Names, and Abbreviations for the Polymers Mentioned in This Paper



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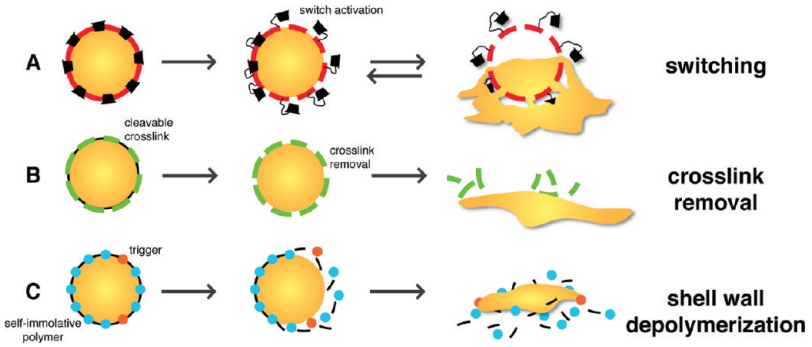


Figure 4. Methods for the chemical disassembly of microcapsule shell walls: (A) opening of pores in the shell wall by a switching mechanism, (B) chemical cleavage of incorporated cross-links resulting in decomposition of the shell wall, and (C) a self-immolative process in which triggers initiate depolymerization of the shell wall.

solidification of a molten polymer.[57] Capsules can be formed with hollow[58,59] or liquid[54,55] cores. Additionally, because the innermost fluid and outermost fluid never come in contact, it is possible for them to be miscible with one another as long as neither is miscible with the middle fluid of the double emulsion. This allows for a variety of liquids to be encapsulated that were incompatible with other emulsification techniques. Finally, multiple emulsions containing droplets with different contents on the same internal level can be used for the synergistic delivery of otherwise incompatible chemicals.[60]

III. APPROACHES FOR SHELL WALL DISASSEMBLY/RELEASE

A variety of external stimuli can be used to trigger the release of capsule materials. These changes are grouped into chemical changes, defined as a trigger that causes chemical reactions with a shell wall material, and physical changes, in which phase transitions and/or mechanical disintegration mechanisms dominate. Physical rupture of capsules embedded in solid materials induced by cracking of the material is used in odorants,[61] self-healing materials,[62,63] scratch and sniff stickers, and carbonless copy paper.[64] Before focusing on specific triggering mechanisms, we wish to highlight these two categories of capsule release.

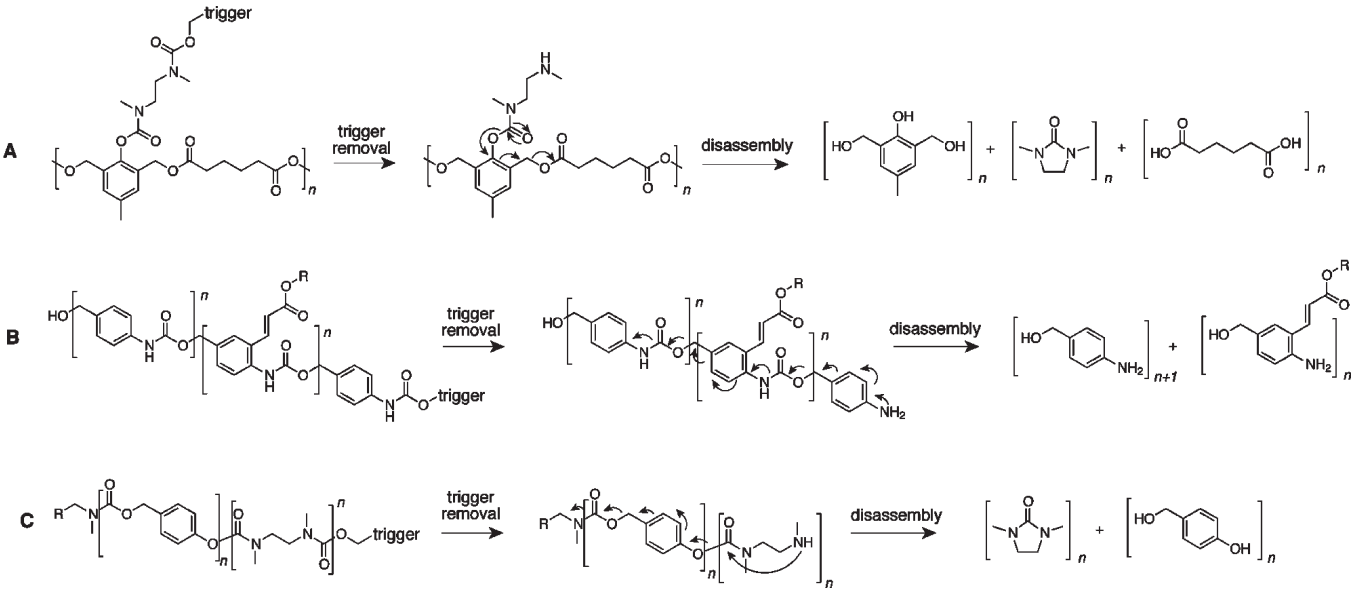
III.1. Chemical Changes. Chemical control over shell wall triggering offers many advantages for designing drug-delivery and self-healing systems. As such, several approaches utilize controlled release of capsule contents via chemical reactions in the shell wall. We have separated these approaches into three categories based on the mechanism of shell wall control: shell wall switching reactions, disintegration of the shell wall via chemical cleavage of cross-links, and triggered depolymerization of the shell wall (Figure 4). Each approach can be beneficial for certain applications based on the desired synthetic and applied parameters. In this section, we detail the concepts behind each approach, give our opinion on the advantages and disadvantages, and list a few illustrative examples.

Switching. We have loosely defined switching reactions as instances in which the porosity of a microcapsule shell wall is controlled by structural changes rather than chemical reactions involving covalent bond formation and cleavage (Figure 4A). Addition of energy through an applied stimulant causes this change in conformation. Electricity,[65] light,[66] and chemicals[67] have all been used as stimulants to modify porosity of a shell wall. The advantages of this technique include the ease of trigger incorporation into the shell wall and the capsule's ability to undergo multiple release cycles, acting as shutters that open and close on command. For example, azo dyes[66,68,69] and viologen derivatives[70] can be used to control permeability when light and electrical potentials, respectively, are applied. However, few chemical species undergo controllable conformational changes, which means the number of demonstrated switches remains limited. Reusability of the capsules also means that release of encapsulated content is slow compared to a burst-release mechanism.

Cross-Link Removal. Cross-link removal reactions disintegrate the shell wall by chemically cleaving shell wall cross-links (Figure 4B). Owing to its synthetic ease, a large number of groups can be incorporated as cross-links. Generally, the cross-links are evenly distributed throughout the shell wall. Many different chemical triggers have been applied, including the reduction of disulfide bonds,[71,72] the cleavage of acetals by acid,[73] the hydrolysis of carbonate esters by base,[41] the cleavage of cinnamates by light,[74] and the cleavage of peptides by enzymes.[75] Advantages of this technique include the ability to control trigger loading and release times. More broken cross-links create faster release, resulting in the capacity for near instantaneous content delivery.[73] This approach is mostly used for targeted payload drug delivery. A disadvantage of this technique is that rapid release requires a large number of cross-links, resulting in more complex microcapsule synthesis and higher loading of triggering units in the shell wall.

Shell Wall Depolymerization. This technique utilizes the triggered depolymerization of a shell wall polymer upon removal of a protecting headgroup (Figure 4C). These head groups are often carbonate esters or carbamates (Scheme 1).[76,77] Noncapsule examples have been shown with PPA as well.[78] Few examples of this new approach exist, providing a large opportunity for expansion. However, much progress has been made since their first publication in 2010. Self-immolative capsules have already been shown to release their contents when stimulated by light, acid, base, and enzymes.[79] Self-immolative reactions are irreversible, and although applications are similar to capsules using cleavage of cross-links, self-immolation offers three distinct advantages. First, given that hundreds of carbonate esters or carbamates have been reported, a diverse set of triggers can be included.[80] Second, signal amplification is built into the mechanism of self-immolative polymers, allowing for the activation of capsules by lower amounts of stimulant. Third, the synthetic route is independent of the trigger, allowing for the rapid formation of many capsule systems. Owing to its many advantages, this approach may be useful in self-healing and

Scheme 1. Self-Immolative Polymers[a]



[a] (A) Self-immolative polymer disassembly used for photo-based deprotection. Liberation of the photosensitive trigger induces cyclization of the diamine spacers, which in turn unmasks an unstable quinone−methide moiety. This iterative disassembly leads to fracture of the shell wall and release of core contents. (B) Azaquinone−methide self-immolative cascade reaction in which the chemical removal of the carbamate trigger unmasks an unstable azaquinone−methide moiety, which leads to disassembly of the polymer and release of core contents. (C) Linear quinone−methide self-immolative polymer. The reactions from (A) are rearranged into a linear sequence similar to (B). This method allows for signal amplification from each trigger for shell wall rupture.

drug-delivery systems. However, the initial systems have required more extensive syntheses than their cross-link cleavage counterparts, making this technique difficult for those lacking synthetic expertise. This is an area in which this approach stands to make major improvements.

III.2. Bulk Changes. Changes on a macroscopic scale can also be used to release encapsulated materials. Macroscopic changes can be as direct as capsule rupture through mechanical cracking of a shell wall from physical damage to a capsule. We have divided this section into four subsections, including pressure-induced rupture, shell wall melting, change in porosity, and thermomechanical degradation of the shell wall. These phenomena are highlighted in Figure 5.

Physical force is an effective trigger for capsule rupture in self-healing materials. Many commercial and research materials rely on force-induced rupture as a mechanism for capsule opening. Mechanical testing of capsules[81,82] and capsule rupture mechanisms[63] for self-healing materials have been covered in previous reviews and are not included here.

Pressure-Induced Rupture. Pressure-induced rupture is a method of releasing core materials in which the internal pressure from within a microcapsule shell wall causes it to burst (Figure 5A). Two main approaches are used to increase pressure on the interior of a microcapsule shell wall. The first is to cause a core liquid to vaporize by heating the capsules. A second approach is to cause the shell wall material to contract. This change is generally thermally initiated (examples include NIPAAm shell walls), and the contracting shell wall can lead to rupture when the internal pressure reaches a critical value.

Shell Wall Melting. Shell wall melting is another method for releasing core materials upon temperature increase (Figure 5B). For shell wall melting to occur instead of pressure-induced rupture, the melting point of a polymer shell wall must be low

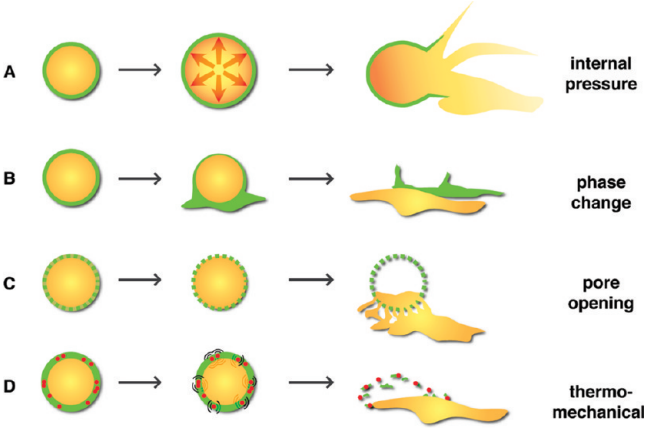


Figure 5. Physical methods of capsule release: (A) shell wall rupture by an increase in internal pressure, (B) melting of the polymer shell wall, (C) change in porosity of the shell wall resulting from a phase transition of a shell wall polymer, and (D) disintegration of the shell wall utilizing nanoparticles that oscillate in response to an external trigger.

enough that melting occurs before core liquid vaporization. Advances in polymer chemistry have allowed for the modification of branched polymers to obtain well-defined melting points that can be finely tuned for specific applications.[83]

Changes in Porosity. Core materials can be released from capsules while keeping the overall structure of the shell wall intact. In this method, the shell wall is comprised of a diblock copolymer or a mixture of two polymers. One of the polymers shrinks when the capsule is heated, and the other polymer remains physically intact, allowing for the creation of pores in the shell wall that release core contents (Figure 5C).[84,85]

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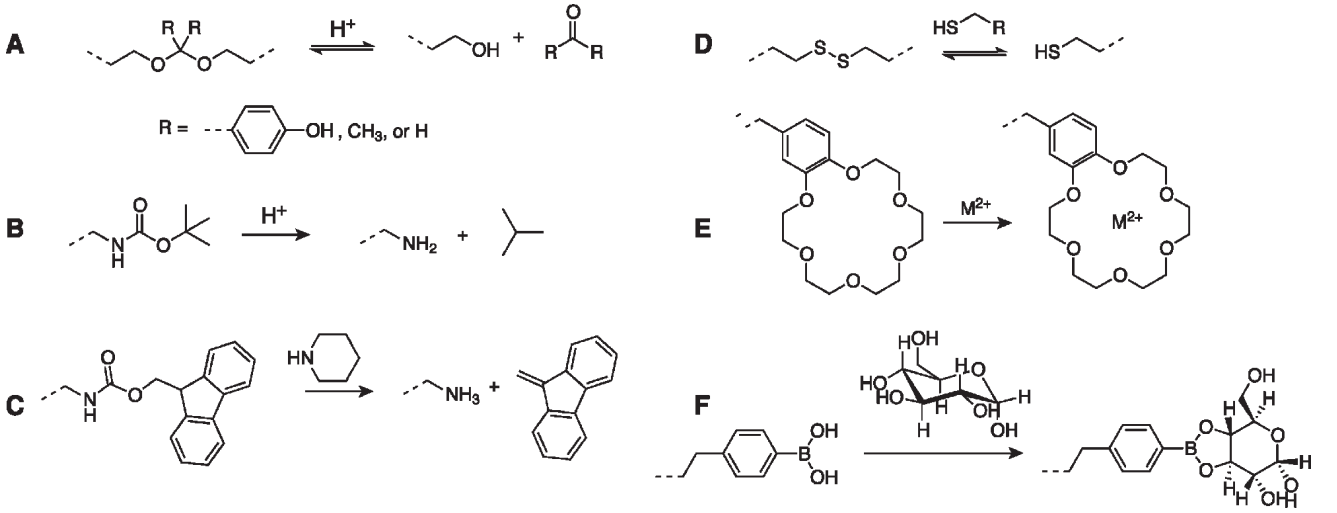
Scheme 2. Chemical Triggers[a]



[a] (A) The cleavage of an acetal group by aqueous acid, (B) the removal of a *tert*-butyl carbamate (tBoc) trigger by acid, (C) the removal of a 9-fluorenylmethyl carbamate (Fmoc) by piperidine, (D) the cleavage/reduction of disulfides by a free thiol (e.g. glutathione), (E) the insertion of a metal cation into a crown ether, and (F) the reaction of boronic acid with glucose.

NIPAAm is commonly used as the thermoresponsive polymer component because it undergoes a reversible lower critical solution temperature (LCST) phase transition, contracting upon heating.

Thermomechanical Degradation of the Shell Wall. Mechanical degradation of the shell wall can result from external impact or cracking, although here we are specifically interested in triggers that cause mechanical degradation and require no direct mechanical input. Mechanical triggering can be caused by exposure to magnetic and electric fields.[10,86] When nanoparticles are incorporated into shell walls, these triggers cause the nanoparticles to oscillate repeatedly. These oscillations eventually cause significant heating and tearing of the capsule shell walls, leading to core release (Figure 5D).

IV. PHYSICAL AND CHEMICAL TRIGGERING PHENOMENA OVERVIEW

IV.1. Chemical Triggers. Currently, chemical reactions have the largest number of citations in which shell wall disassembly is used for triggered release of encapsulated contents. From our perspective, these approaches generally fall along two lines: changes in pH (Scheme 2A−C) and reduction of disulfide bonds (Scheme 2D). Only a few examples have branched out from these stimuli. Both lowering of pH and cleavage of disulfide bonds are used as drug delivery triggers focused on the intracellular environment, either in the cytoplasm, which is reducing due to high levels of glutathione (5 mM), or via endocytotic bodies, which have a lower pH (∼4−6) than the surrounding extracellular environment (pH ∼7). We highlight the prominent work in both pH and disulfide reduction and discuss the possibilities for chemical reactions as a broadly useful class of triggers for capsule release.

Many chemical reactions are activated by acidic conditions, making a lower pH an attractive target for chemical triggering. Both the Fréchet and Caruso groups have made significant contributions in this field, designing many chemically sensitive capsule systems. We highlight a few examples of each. The Fréchet group has used ketals, also known as acetal chemistry, as acid-degradable chemical cross-linkers. At pH < 5, each ketal is converted to a ketone and two alcohols (Scheme 2A), providing the chemical disassembly needed for triggered release. Burst-release capsules were created using this concept, with 50% of the capsules releasing their contents in under an hour.[73] Polyurethanes and polyureas were cross-linked with ketals to create acid-sensitive microparticles.[5] Ketal-containing microgels can deliver proteins to antigen presenting cells (APCs).[87] These results are a testimony to how simple, powerful chemistry can be used to address a variety of different delivery problems. The ketal moiety has also been used in conjunction with a beta-amino-ester linkage to create a dual-pH response that functions like a logic gate, undergoing rapid disassembly and charge repulsion of the disassembled products, creating triggered capsules that burst at the seams.[88] The ketal moiety has also been used in conjunction with metathesis chemistry. In this instance, the ketal was attached to an anthracene fluorophore to give a secondary signaling mechanism.[89] Acetals can switch the hydrophobicity of polymer micelles, resulting in a unique release strategy.[90] A phenolic acetal was used to cross-link polymer micelles created via RAFT polymerization, and its degradation led to release of encapsulated content.[91]

The second approach to acid-triggered release relies on charge switching inside the capsule shell walls mediated by the addition of protons to disrupt ionic or hydrogen-bonding interactions. Caruso and co-workers have contributed significantly in this area. Using LbL assembly, they prepared capsules of various polyelectrolytes including PAA, PAAm, and PSS and showed that these capsules are pH-responsive, opening nanopores based on the charge of the polymer associated with a given pH.[92] Hydrophobic units in polyelectrolyte LbL-assembled capsules can be used to tune responsiveness.[93] Polyelectrolyte approaches were used to create pH-sensitive PSS capsules for control of an enzymatic reaction.[94] De Geest et al. developed a unique polyelectrolyte approach that places charge distribution change in the core of the capsules by using a charged, gel-based core. The core is then expanded and contracted with changing pH, creating "self-exploding" microcapsules.[95,96]

A third approach relies on hydrogen bonding as the mechnanism for pH-based release. Tannic acid was used to create hydrogen-bonded shell walls via LbL assembly of several

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polymers with stability ranging over pH 2−10.[97] Outside this pH window, the capsules release their contents as hydrogen bonding is disrupted. Hydrogen bonding of PVP triggered the release of capsule contents at pH < 5.[98] Polypeptides can also be used as hydrogen-bonded pH-sensitive shell wall components.[99]

Disulfide bond cleavage is another broad area of research in triggered capsules. The reduction of disulfide bonds (Scheme 2D) provides an easy point of control and has been extensively used by Caruso and co-workers. Using LbL deposition with both PMAA as well as PVPON, capsules were formed using cysteamine as the disulfide linkage.[71] The capsules contained one of the following: water-insoluble drugs like doxorubicin,[100] DNA (both double and single stranded),[75] or polymer hydrogels.[101] Control over release of core contents was achieved by tuning the thickness of the polymer films.[101] Recently, these capsules were shown to deliver contents to human colon cancer cells[100] and have been targeted to cell lines via the addition of antibodies to the outside of the capsule.[102] Disulfide bond cleavage has also been exploited for release of contents from polyglycerol nanogels.[103]

The interactions of crown ethers with metal ions such as Ca^{2+} and Ba^{2+} were utilized to open pores in microcapsules formed from NIPAAm (Scheme 2E).[104] This host−guest interaction where the "gate-keeper"—an 18-crown-6-ether—opens the pores was demonstrated for Pb^{2+} ions as a form of metal remediation.[67] Sugars can be used as a triggering stimuli. They rely on the interaction of boronic acid with diols (Scheme 2F) to release insulin when fructose and/or glucose levels spike in the blood, acting as artificial islets of Langerhans.[105,106] A few examples emerged that use chemical triggers for applications in anticorrosion and self-healing coatings.[107] However, the LbL technique commonly applied for triggered capsules proved ineffective as the capsules were not structurally self-supporting in the coating matrix.

IV.2. Biologically Induced Reactions. Biological properties and molecules can be used to trigger release of microcapsule core contents. From the literature, two general strategies emerge. The first utilizes the disassembly of the shell wall based on a specific biological property such as a strongly reducing intracellular environment or an increase in acidity when a capsule is endocytosed. We have included release mechanisms that are primarily a chemical triggering process in section IV.1, but many examples are designed to release their contents in a biological environment. The second approach utilizes triggering via interaction with biomolecules, broadly defined here as molecules used in living systems such as enzymes, sugars, or sequences of oligonucleotides.

For the first approach, we have included a cross section of work being done in this field. An excellent review on this area was published by van Hest et al.[108] and should be consulted for completion. Caruso and others have used LbL deposition to create an impressive number of triggerable capsules using disruption of hydrogen bonds, disulfide cleavage, and pH changes as well as enzymatic degradation to promote disassembly of capsules for drug delivery purposes.[75,100,109,110] A great example of design architecture is found in work reported by DeWit and Gillies, who created head-loaded cascade polymers that formed micelles to trigger the release of drugs in biological conditions.[79] LbL capsules of DNA and PLL shell walls were triggered by increasing salt concentration. These capsules are capable of simultaneous release of DNA from the shell walls and drugs from the core.[111] A further exploration of this polyelectrolyte triggering strategy was demonstrated by placing triggered capsules in 2- and 3-dimensional cell cultures.[112] The pH triggering strategies of Fréchet and co-workers deserve mention here, though they were discussed in full detail in the chemical section.

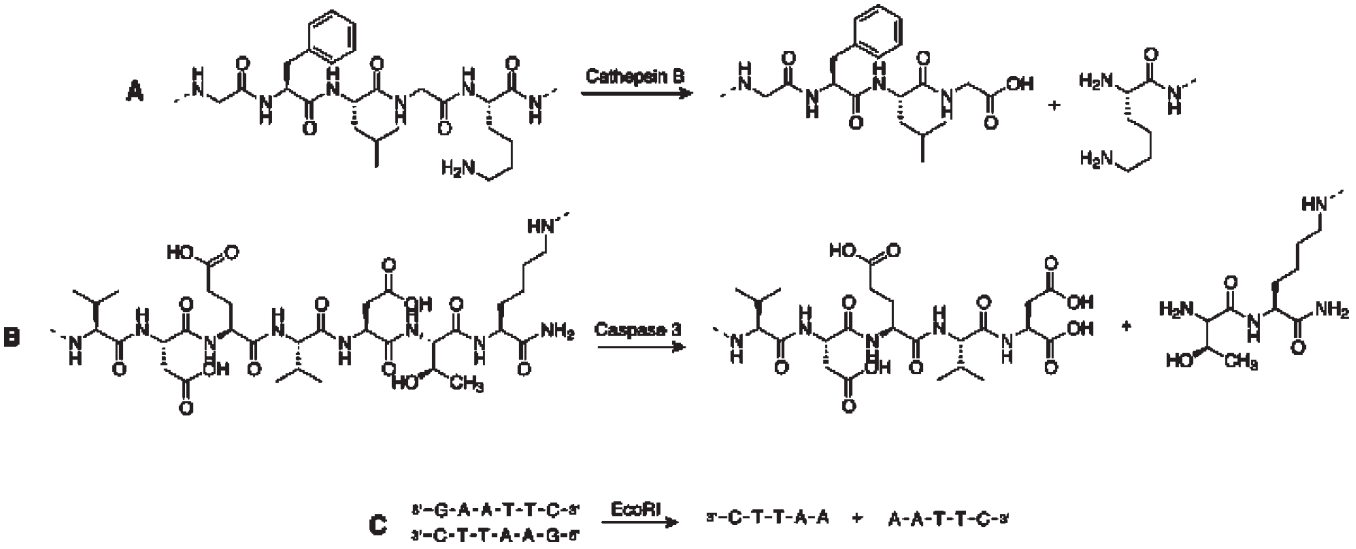
Focusing on the second approach, the disassembly triggered by biomolecules, we highlight several examples. Some of these exceed the definition of "micro"-capsules but are included as creative triggering approaches. Enzymes represent a class of biomolecules that provide a large quantity of potential triggers while maintaining high selectivity of the specific trigger. Glangchai et al. utilized Cathepsin B, a tumor associated protease, to disassemble GFLGK peptide cross-links (Scheme 3A) in order to trigger the release of DNA from nanoparticles.[113] A more sophisticated approach has been demonstrated by the Tang and Wang laboratories where a single protein—in this case caspase 3—is wrapped in a polymeric nanocapsule whose release is triggered by degradation of the peptidic cross-links by a different protease (Scheme 3B). By including a light-sensitive protecting group on the peptide, the researchers created a second trigger to provide spatiotemporal control of triggering. This result stands as one of few examples where triggers were combined to yield highly controlled delivery.[114] Nonspecific enzymatic degradation has been used to disassemble shell walls composed of PARG.[115] A stellar example of enzymatic degradation was demonstrated by Johnston et al., who disassembled capsules using restriction enzymes to cut specific sequences of DNA embedded in the shell wall (Scheme 3C).[116,117] An intriguing approach utilized the enzymatic environment provided by the microflora of the colon to break down capsules comprised of sodium cellulose sulfate and chitosan for colon-specific drug release.[118] This approach utilizes both enzymes and the local, specific environment of the colon to target the release of the capsules. Chitosan was first used as a release mechanism in conjunction with PLL to deliver DNA via hydrolytic enzymes.[119] Esterases, enzymes that cleave esters, have also been used to disassemble dendrimer-based nanocontainers by changing the lipophilicity of the container.[120]

In our collection of references, a triggered release strategy stood out that has not yet been utilized to release the contents of a capsule. This strategy relies on the bonding of specific RNA sequences to a peptide nucleic acid (PNA) that acts as a prodrug.[121] If this strategy could be modified to trigger release of capsule contents, either through disassembly of covalent bonds or through simple disruption of hydrogen bonding in polymer shell walls, it could prove extremely powerful for capsules that could be targeted to a specific nucleotide sequence.

IV.3. Light-Induced Release. Triggered release of capsule contents using light is appealing for a number of applications. Nanoparticles and chromophores absorb light over a range of wavelengths, and their absorption cross sections can be tuned both for one- and multiphoton absorption. For applications in cosmetics and agriculture, UV- and visible-sensitive capsules are used because of the abundance of UV light. Near-IR-absorbing capsules are of greater interest in biological systems because of decreased light scattering in tissues at those wavelengths.[122] For example, light absorption without efficient light emission means an increase in vibrational energy (heat) of a substrate. Therefore, light can be used to activate thermal release mechanisms involving phase transitions and changes in polymer morphology.

Several photoswitches have been incorporated into LbL assembled capsules, and a few switches have been used for nanoparticle assembly and in self-immolative polymer shell walls. In this

Scheme 3. Biological Triggers[a]



[a] (A) The cleavage of the GFLGK peptide by the enzyme cathepsin B, (B) the cleavage of the VDEVGSK peptide by the enzyme caspase 3, and (C) the cleavage of the palindromic EcoRI restriction site by the enzyme EcoRI.

section we present both approaches, although we are particularly interested in changes at the chemical bond level. Where nanoparticles are utilized, we will include only references in which nanoparticles are incorporated into the shell wall itself, although it is worth mentioning the interesting examples of light-induced release of capsule contents through increased temperature of nanoparticle-based cores.[123] A recent review by Sukhorukov et al. highlights many of the examples not covered in this section.[124]

Nanoparticles and nanorods comprised of a variety of metals and metal oxides have been used for microcapsule triggering. Caruso and co-workers have demonstrated the laser-induced release from polyelectrolyte capsules containing gold nanoparticles in the shell walls.[37,125] The authors proposed that laser-induced release involves (1) heating of the capsule shell to high temperatures above the spinodal point of water upon nanoparticle light absorption, (2) the development of thermal stresses within the capsule shell because of the variations in thermal expansion coefficients of shell wall materials, and (3) capsule rupture. A similar study reported by Skirtach et al. demonstrated that gold sulfide−gold core−shell nanoparticles could be used to rupture microcapsules with light.[126] West et al. reported the use of gold nanoparticles in a NIPAAm capsule shell wall to trigger increased microcapsule permeability upon temperature increase.[127] Parak et al. demonstrated the ability to mechanically disintegrate nanoparticle-containing capsules in living breast cancer cells without causing significant cell death.[128]

Metal oxide coatings can be used as capsule triggers. Katagiri et al. showed that the UV irradiation of polyelectrolyte capsules coated with SiO_2/TiO_2 resulted in capsule obliteration due to the UV absorption of TiO_2.[129] In addition to their triggering capabilities, these capsules are unique compared to other polyelectrolyte capsules because of their improved mechanical integrity resulting from the metal oxide coating, which may allow them to better withstand the mechanical loadings of solid-state applications.

Photochemical switches incorporated into the shell walls of polyelectrolyte capsules have been used to demonstrate light-controllable permeability. Azobenzene groups undergo a reversible cis-to-trans isomerization upon absorption of UV or visible light. Möhwald showed that an azo-based dye, when incorporated into the shell walls, altered permeability of capsules exposed to visible light.[68] Bédard and co-workers similarly demonstrated that when the azo dye was directly incorporated into the polyelectrolyte backbone, the permeability of polyelectrolyte capsules could be altered upon light absorption by azobenzene moieties (Scheme 4A).[66] The relative amount of azo dye in a polymer backbone can be used to control the rate of release from capsule cores.[69]

Additional photosensitive groups have been incorporated into the shell wall polymers of polyelectrolyte complex microcapsules. Kono et al. reported the incorporation of triphenylmethane leucohydroxide residues, which dissociate under UV irradiation to give the triphenylmethyl cation (Scheme 4B), into PAA.[130] The release rate from microcapsules incorporating triphenylmethane leucohydroxide residues into the polymer backbone increased under UV irradiation.

Self-immolative polymers containing photosensitive functional groups can be used to trigger release of core contents from polymeric microcapsules. Almutairi et al. reported a light-sensitive self-immolative polymer containing a quinone−methide backbone and photocleavable nitrobenzyl alcohol groups (Scheme 4C) as the triggers.[77] The authors observed that irradiation with 350 nm light resulted in release of encapsulated dye whereas minimal release was observed without irradiation. Also, no release of dye from PLGA nanoparticles was observed when irradiated with UV light, which supports the hypothesis that the release of the dye is due to the self-immolation of the quinone−methide polymer backbone upon photoinduced cleavage of nitrobenzyl groups.

Schärt et al. demonstrated one of the most creative approaches to light-induced capsule release. They functionalized polyorganosiloxane nanoparticles with nitrocinnamate photochemical switches in order to build and disassemble the microcapsule shell walls using light.[76] After assembly, the nanoparticles were cross-linked with UV light in a water/oil/water emulsion to create the microcapsule shell wall through the reaction of cinnamate groups in a reversible 2 + 2 cycloaddition (Scheme 4D). The capsule contents were released upon

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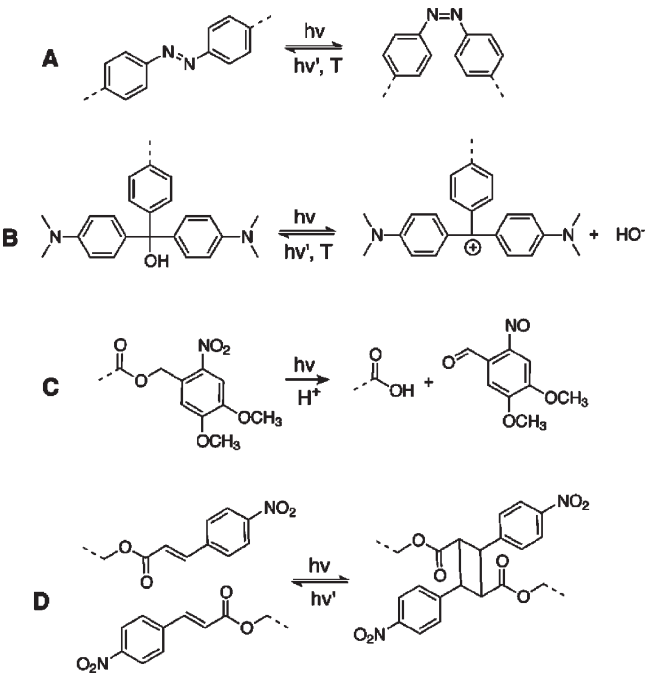
Scheme 4. Photo Triggers[a]



[a] (A) switching of *trans*- to *cis*-azobenzene, (B) dissociation of a triphenylmethane leucohydroxide residue to give a triphenylmethyl cation, (C) cleavage of a nitrobenzyl protecting group, and (D) 2 + 2 cycloaddition of cinnamates.

exposure to UV light, and SEM images of the capsules showed significant cracking of the capsule wall.

IV.4. Thermally Induced Release. Changes in temperature can trigger microcapsule release. Temperature changes can cause the melting of a microcapsule or microsphere polymer or can result in a phase change transition, transforming a swollen, hydrated state to a shrunken, dehydrated state. Increases in temperature can also result in purposeful disassembly of polymers or—depending on one's perspective—polymer decomposition. In addition to directly heating a material, magnetic, light, chemical, and electrical stimuli can result in temperature changes that ultimately lead to capsule triggering. Here we highlight examples where external temperature changes (not other stimuli) result in capsule triggering. Also, while several publications address microcapsule rupture through chemical disassembly of encapsulated blowing agents[131] and solvent boiling,[123] we limited this section to changes in the shell wall itself.

Phase transitions can create pores in the shell wall, resulting in core release. Several food additives and fragrances have been shown to release more quickly upon shell wall melting. As mentioned in section II.2, numerous publications report the use of NIPAAm as a polymer shell wall and rely on its contraction upon heating to initiate thermal release.[88,118] The LCST of NIPAAm can result in pore formation when biphasic capsule walls are heated, leading to increased permeability. Also, NIPAAm microcapsules can burst from increased internal pressure upon contraction of the capsule shell wall due to temperature increase.

Finally, it is possible that chemical disassembly of the shell wall can be triggered with increased temperature. While we did not find specific examples of intentional shell wall disassembly using temperature elevation, numerous TGA traces of shell wall materials indicate the temperatures at which polymers disassemble, allowing for release of core materials. Often, however, a goal of producing core−shell microcapsules is to *raise* the temperature at which shell wall disassembly occurs, allowing microcapsule materials to be incorporated into epoxies and other polymers that undergo high temperature (some over 200 °C) curing conditions in industrial applications. It would be interesting to see future examples of thermally initiated controlled chemical disassembly.

IV.5. Magnetically Initiated Release. Magnetic nanoparticles have been incorporated into microcapsule shell walls[85,86,132−138] and cores[139−144] for both the triggered rupture of microcapsules and to guide microcapsules—without necessarily rupturing them—to a targeted location. Microcapsule release resulting from high-frequency magnetic fields is particularly relevant to drug delivery and biomedical applications. Here we will focus on the examples in which nanoparticles incorporated into microcapsule shells are used to trigger release of contents.[86,133]

Only a few studies have addressed changes in permeability of microcapsule shell walls under oscillating magnetic fields when magnetic nanoparticles are incorporated in the microcapsule shell walls. Kumar and Lvov embedded ferromagnetic gold-coated cobalt nanoparticles into PAA−PSS polyelectrolyte capsule shell walls[86] and demonstrated that the permeability of the capsule shells increased in the presence of an oscillating magnetic field. Similarly, Liu and Chen reported the use of Fe_3O_4 magnetic nanoparticles in PAA−PSS capsule walls and found that the release of core materials increased under oscillating magnetic fields and at higher temperatures.[10] In this case, both microscopy and the release profiles indicate slow release followed by a bursting release event. The authors proposed that the presence of magnetic nanoparticles in the shell structure allowed for a microstructural evolution of the shell wall, potentially due to both the increase in heat caused by magnetic energy dissipation (frictional heating) and stress development within the shell due to mechanical vibrations.

IV.6. Electrical Triggering. Microcapsules that respond to electric fields are of interest for a variety of applications including electronic-ink displays,[145] corrosion resistance,[65,146] self-healing electronics,[147,148] and drug delivery.[65] A variety of electrically sensitive materials have been incorporated into microcapsule shells and cores. Depending on the material, the responses included in this section range from alignment in electric fields, electrical conductivity, and redox reactions.

The incorporation of molecules into shell walls that preferentially align in electric fields can be used to modify release rates of core materials. Kim et al. reported capsules with increased release rates in the presence of an electric field.[149] Utilizing composite microcapsules with shell walls that were comprised of PVA, PAAc, and multiwalled carbon nanotubes, they demonstrated the structural degradation of the shell wall when subjecting the capsules to electrical fields. The release of microcapsule core materials increased under higher applied voltages and with more efficient dispersion of carbon nanotubes throughout the capsule shell walls. Yoshida et al. reported a microcapsule system in which ferroelectric liquid crystalline segments in PS−nylon shell walls allowed for control of permeability using an intermittent external electric field.[150] They proposed that the spontaneously organized liquid crystal texture in the capsule membrane forms a favored substrate channel under electrical stimulus, accelerating the release of encapsulated materials.

Chemical and electrical redox reactions can modify the permeability of microcapsule shell walls. Vansco et al. reported the redox-controllable permeability of polyelectrolyte microcapsules.[65] In this publication, polyelectrolyte capsules were prepared in which both the positively and negatively charged polymers contained ferrocene

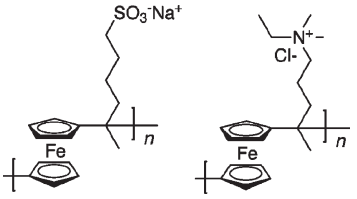


Figure 6. Ferrocene-containing polymers used for electrochemical triggering.[65]

repeat units (PFS− and PFS+, Figure 6). Once the capsules were assembled, the ferrocene units were chemically oxidized, which triggered capsule swelling, thus increasing shell wall permeability. This result is consistent with the electrostatic repulsion within the polyelectrolyte shell due to the excess positive charge on the chains, which would increase the distance between segments.

Shchukin et al. reported the encapsulation and release of redox-sensitive polymers in LbL capsules.[70] In this study, PDADMAC/PSS capsules were loaded with FITC-labeled dextran and PHV. The microcapsules, which were deposited onto an electrode with PPy, could be reversibly loaded and unloaded as long as the rate of change in electrical potential is minimized. A worthwhile control experiment that was not included in the paper, however, is performing the same release and resorption experiments while excluding PHV from the microcapsule core to see the effect in capsule permeability.

An early result relating to permeability of polyelectrolyte capsules containing viologen derivatives in the shell walls actually highlights the importance of performing control experiments without viologen.[151] Shell wall permeability was monitored as the capsules were repeatedly chemically oxidized and reduced. The authors found that the permeability changed with the oxidation state of viologen and, not only that, but the changes in permeability also followed the same trends when no viologen was in the shell wall. An interesting comparison would have been to see what effect a redox-insensitive grafting unit would have on the changes in permeability.

V. LOOKING FORWARD: TOWARD THE IDEAL SYSTEM(S)

An ideal triggerable microcapsule system is easy to prepare from readily available components, exhibits good stimuli selectivity, is compatible with many triggers, and disassembles into products that are inert and gaseous. An ideal capsule would interact with its environment rather than merely be reactive, thereby unlocking new applications for triggered release. Obtaining an ideal system requires improvements in capsule materials and synthetic methods along with goals for future applications and design paradigms. In this section, we briefly discuss what we want to see emerge in each of these areas with a focus toward creating capsules with unique self-healing and drug delivery capabilities, suggesting possible areas of future research.

New Materials. Control of disassembly is the key issue for improving triggered release of capsules. New polymers and disassembly reactions must be explored for this area to blossom. Excellent work has been done by McGrath,[152,153] Phillips,[78] Ito,[154] and Shabat,[155] but a vast amount of chemical space remains unexplored. Some triggers with potential use in industrial applications have been reviewed.[156] The ideal depolymerization reaction would be compatible with a large number of chemical triggers, result in a chemical disassembly mechanism that generated inert byproducts—at least one being a gas—and proceed rapidly. A gaseous byproduct will ensure irreversibility and provide a thermodynamic driving force for the immolative reaction. These conditions actually bear an astonishing resemblance to the exact reverse of the "click" reaction as popularized by Sharpless and co-workers.[157] These types of reactions will be a significant advance to triggered capsules but would likely find general use in materials chemistry.

New Construction Techniques. Ease of synthesis and control of rigidity are fundamental to improving construction techniques. For LbL assembly, shell walls are easily prepared but in some cases are hindered by their reliance on a sacrificial template and the use of strong acids, including HF, for removal of the metal oxide interior. As mentioned in section II.2, new approaches have enabled methods for core removal that do not require strong acids.[41,42,45] An ideal LbL-assembled capsule might instead work directly with a liquid emulsion, allowing deposition on a desired core without the need for etching to remove sacrificial cores. In addition to the improvements made through covalent cross-linking and nanoparticle formation, more general methods to greatly improve shell wall rigidity must also be developed. Control over rigidity will allow chemists to tailor the stiffness of their capsules to the application at hand. The field may benefit from a study exploring the ability to systematically vary shell wall rigidity.

Self-immolative methods are sorely in need of improved construction techniques. Current condensation reactions are practical; however, reagents such as isocyanates and acid chlorides are too labile, reacting prior to shell wall formation. The application of click chemistry approaches may prove useful in the preparation of self-immolative capsules, much as it has benefited LbL assembly.[42,158−160] Thiol−ene chemistry would allow for the construction of emulsion capsules using light as the activating agent. These reactions proceed under aqueous conditions, which are beneficial for emulsion polymerizations.

New Applications. New triggers and new capsule functionality are coupled. Tremendous opportunities exist for triggered capsules to make a significant impact in both the biomedical field and self-healing materials. There are significant advances to be made toward new applications of triggered microcapsules. We discuss a few example areas of potential research and intriguing design motifs that may provide unique functionality.

Drug-delivery applications may benefit from a combination of triggers. For example, combining acid-labile and reduction-sensitive triggers would create the ability to customize capsule delivery. Future capsules may be capable of becoming active only upon entrance into a reducing environment, and then secondary activation could lead to content release. This concept has already been demonstrated with light, but many more combinations seem possible. Another intriguing idea is offered by the sugar/boronic acid example. Will it be possible to create a capsule that releases its contents in the *absence* of a given signal? Such combination of triggering events would provide the complementary negative feedback loop to a typical capsule rupturing method, acting as reporters of disruption in a homeostatic process. Treatable disease states are often marked by the *absence* of a particular biomolecule as much as they are marked by the presence of a biomolecule, diabetes being the canonical example.

Self-healing materials using triggered capsules provide the opportunity to heal a variety of chemical systems as well as to create chemically responsive materials. Batteries present a unique chemical system that undergoes both physical and chemical deterioration during repeated charge and discharge cycles. Triggers incorporated into microcapsules that respond to chemical damage in cycling batteries could lead to self-healing batteries with longer lifetimes. Lubricants, coatings, coolants, and corroded surfaces are all areas that would benefit from self-healing approaches that require chemical triggering to initiate self-healing cycles. Biofilm formation is another

area in which homeostatic regulation of a surface could be tied directly to a chemical signal.[161] The combination of triggers and capsule systems could also play a role in creating self-healing systems with unique response signatures allowing for combinatorial abilities in self-healing systems. Solid-state applications such as self-healing systems require robust shell walls. Our own contribution in this area has focused on a general strategy for the incorporation of triggering groups into robust capsules assembled via emulsification polymerization, relying on self-immolative polymers as the capsule cross-linking agent.[76]

AUTHOR INFORMATION

Corresponding Author

*E-mail jsmoore@illinois.edu, Ph (217) 244-1646, Fax (217) 244-8024.

Author Contributions

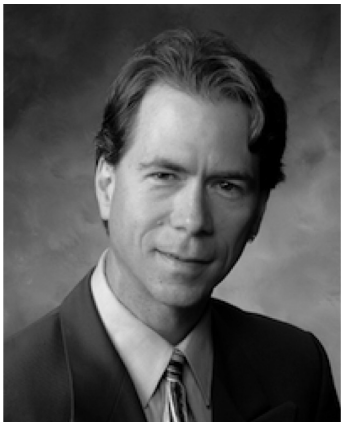
⊥These authors contributed equally to this work.

BIOGRAPHIES

Aaron P. Esser-Kahn received his B.S. degree in Chemistry in 2004 from the California Institute of Technology and his Ph.D. in Chemistry from the University of California, Berkeley, in 2009. He is currently a postdoctoral researcher with Prof. Jeffrey Moore at the University of Illinois at Urbana−Champaign, where his research interests include stimuli-responsive microcapsules and microvascular systems. This year he will start a position as an assistant professor at the University of California, Irvine.

Susan A. Odom received her B.S. degree in Chemistry in 2003 from University of Kentucky (Lexington, KY), after which she obtained a Ph.D. in 2008 from Georgia Institute of Technology (Atlanta, GA). She is currently a postdoctoral researcher with Prof. Jeffrey S. Moore at the University of Illinois at Urbana−Champaign, where her research interests include self-healing electronic materials and additives for life extension of lithium ion batteries. This year she will start a position as an assistant professor at the University of Kentucky.

Nancy R. Sottos received her B.S. degree in Mechanical Engineering (1986) and her Ph.D. (1991) in Mechanical Engineering from the University of Delaware. She is currently the Willett Professor of Engineering in the Department of Materials Science and Engineering at the University of Illinois at Urbana−Champaign. She is also the cochair of the Molecular and Electronic Nanostructures Research Theme at the Beckman Institute for Advanced Science and Technology. Her research group studies the mechanics of complex, heterogeneous materials, such as self-healing polymers, advanced composites, thin film devices, and microelectronic packaging.



Scott R. White received his B.S. degree in Mechanical Engineering (1985) from the University of Missouri—Rolla, an M.S. in Mechanical Engineering (1987) from Washington University (St. Louis, MO), and a Ph.D. in Engineering Science and Mechanics (1990) from Pennsylvania State University. He is currently the Willett Professor of Engineering in the Department of Aerospace Engineering at the University of Illinois at Urbana−Champaign and is the Group Leader for the Autonomous Materials Systems Group at the Beckman Institute for Advanced Science and Technology. His research

focuses on self-healing materials and microvascular materials systems.

Jeffrey S. Moore received his B.S. degree in Chemistry in 1984 and his Ph.D. in Materials Science in 1989, both from the University of Illinois at Urbana−Champaign. After postdoctoral studies at the California Institute of Technology, he began his independent career at the University of Michigan. In 1993, he returned to the University of Illinois where he is currently appointed as the Murchison-Mallory Chair in Chemistry. His research focuses on molecular self-assembly, macromolecular architecture, and self-healing polymers.

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