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# Trigger Chemistries for Better Industrial Formulations

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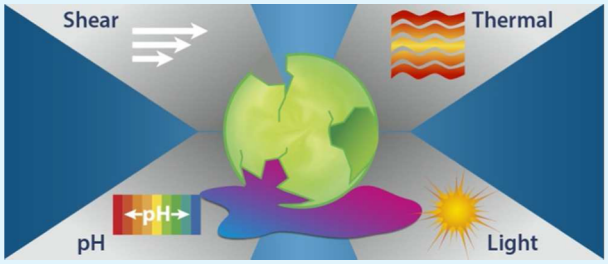
**ABSTRACT:** In recent years, innovations and consumer demands have led to increasingly complex liquid formulations. These growing complexities have provided industrial players and their customers access to new markets through product differentiation, improved performance, and compatibility/stability with other products. One strategy for enabling more complex formulations is the use of active encapsulation. When encapsulation is employed, strategies are required to effect the release of the active at the desired location and time of action. One particular route that has received significant academic research effort is the employment of triggers to induce active release upon a specific stimulus, though little has translated for industrial use to date. To address emerging industrial formulation needs, in this review, we discuss areas of trigger release chemistries and their applications specifically as relevant to industrial use. We focus the discussion on the use of heat, light, shear, and pH triggers as applied in several model polymeric systems for inducing active release. The goal is that through this review trends will emerge for how technologies can be better developed to maximize their value through industrial adaptation.




**KEYWORDS:** *triggered release, capsule, polymersome, self-assembly, UV-induced, depolymerization*

## 1. INTRODUCTION

In recent years, innovations and consumer demands have led to increasingly complex liquid formulations. Formulated liquid products are typically comprised of complex combinations of solvents, surfactants, buffers, defoamers, fragrances, and a host of other additives in order to improve formulation behavior and performance during use.[1] These growing complexities have provided industrial players and their customers access to new markets, product differentiation, improved performance, compatibility and stability with other products, reduced costs, and enablement of new, higher-performance actives. In order to better protect valuable actives in such formulations, the development of advanced encapsulation strategies remains an active area of research.[2] As part of the strategy for encapsulation of actives, methods are also needed to effect the release of the active from its encapsulated state at the desired location and time of action. One such method is the employment of triggers to induce active release upon a specific stimulus. Significant academic research efforts and associated dollars have been spent on development of triggered-release chemistries and applications, though little has translated for industrial use.[3] In 2011, The Dow Chemical Company (Dow) announced a $250 million investment in academic research projects at major American universities to support breakthrough technologies in areas of industrial relevance.[4] As part of these funds, a program was created at the University of Illinois to explore the development of novel trigger release chemistries, mechanisms, and systems. This review results from interactions between Dow and the University of Illinois, offering our joint perspective on the state of triggered release technologies and their potential for adaptation to industrial formulations and applications.

For triggered-release chemistry to find success in industrial applications, there are several critical criteria that must be satisfied. The single most important criterion for the vast majority of applications is that the addition of new chemistry to the system cannot add an appreciable cost to the final product. The exact tolerance for this additional cost is determined by the application space and the typical profit margins that the market can command. To minimize costs, the chemistry typically must be simple, uncomplicated to synthesize, and scalable to industrially relevant quantities. The chemistry must be stable

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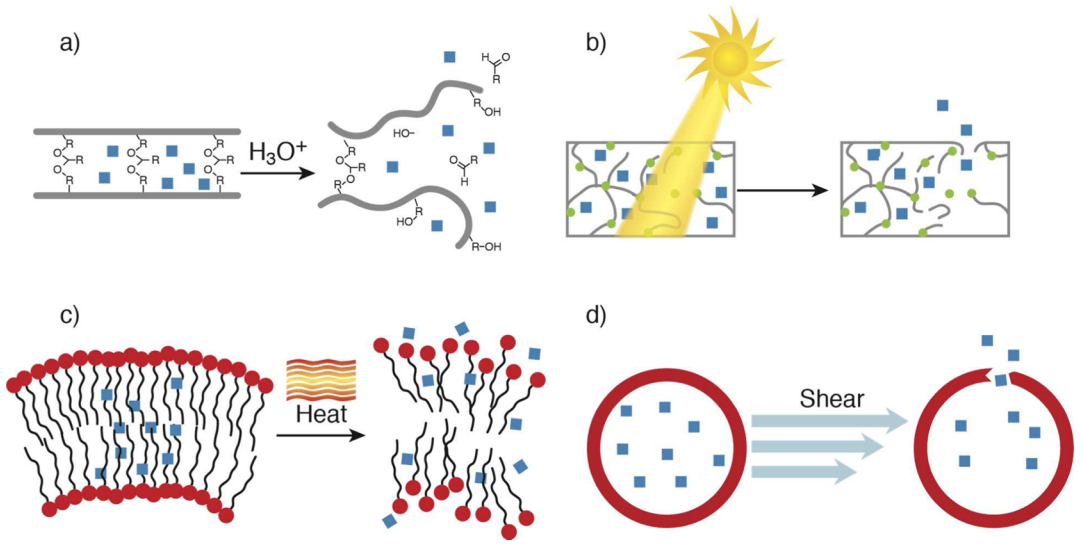
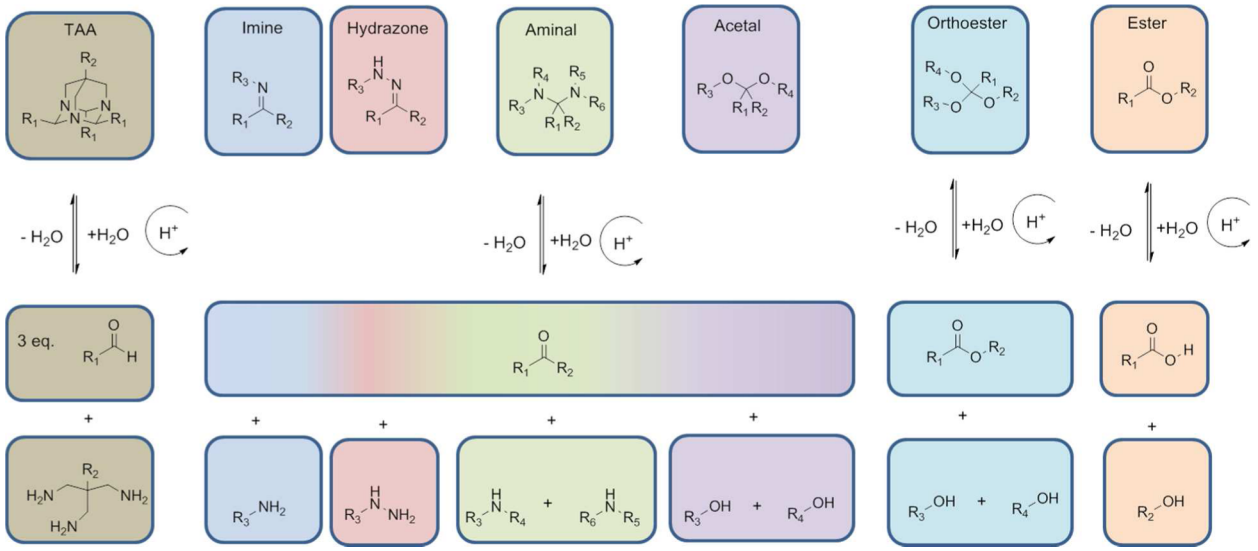



**Figure 1.** Example mechanisms of triggering. (a) pH-induced hydrolysis of an acid-labile cross-linker; (b) photolysis of photocleavable linkers in a polymer matrix; (c) thermal destabilization of a bilayer membrane by heat; (d) shear-induced cracking of an encapsulant shell.

**Scheme 1. Acid-Catalyzed Bond Cleavage Routes and Products**




in the formulation prior to triggering. For some formulations this means stable to processing conditions (i.e., melt extrusion), whereas for others it could be physical stability from effects by other ingredients such as surfactants. Additionally, the trigger chemistry must also enable the desired release profile for the application, be it rapid burst or slow release following the trigger event. The specific requirements for encapsulation are beyond the scope of this review and instead are discussed in another review by our groups.[2] Rather, in this review, we focus on four triggers for release of encapsulated materials that we believe have the most potential in industrial applications: pH, light, heat, and shear. One common feature among these four triggers is the existence of many industrial systems that already utilize them as part of their normal mode of operation, meaning the resource barriers for adopting new systems with these features are surmountable with potential to translating to lower overall cost and higher profitability.

We have broken this review into three sections, building from fundamental chemistries of the most industrially relevant triggers to how trigger chemistries are built into materials. Ultimately, examples of the use of these materials in polymeric assemblies for encapsulation and delivery applications are provided. Our hope is that, through this review, you, the reader, will better understand some of the challenges facing industrial encapsulation and delivery, enabling you to better allocate your research efforts and funding toward applications more likely to gain adoption within the industrial arena.

## 2. TRIGGER MECHANISMS

**pH Triggers.** The use of pH as a trigger requires the modulation of hydronium concentrations to induce chemical reactions or changes in material properties. In the majority of academic work on the subject, pH changes are designed to occur over a range commonly found in biology, namely, the shift from physiologically neutral pH (7.4) to a more acidic pH found in certain subcellular compartments such as the endosome (pH as low as 5) or in diseased tissue (e.g., cancer, with pH around 6.5−6.8).[5,6] Industrially, pH is already used as a trigger to target oral pharmaceutical delivery to different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regions of the digestive tract, where pH rapidly shifts from highly acidic in the stomach to progressively more neutral pH in the upper regions of the intestines. Evonik's Eudragit line of pharmaceutical excipients leverages this phenomenon. However, less explored are opportunities for harnessing pH shifts in nonpharmaceutical formulations to trigger release and development of enhanced properties. For example, many coatings formulations contain ammonia, whose volatilization during film cure drops the pH and could be used to trigger additional properties. Many home care and industrial concentrates (detergents, fabric softeners, etc.) are formulated at non-neutral pH, and the shift upon dilution toward neutral could be used to trigger release. Two-pack systems could also be employed to trigger a pH shift upon combination, releasing an active of interest.

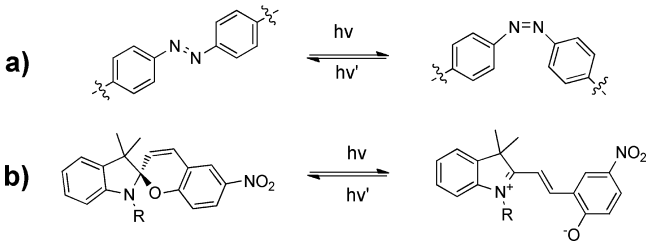
The most common chemical strategies for using pH change as a trigger generally fall into two categories: acid/base-catalyzed covalent bond cleavages and hydrophilicity/phobicity changes by variation in protonation states. The use of the most common types of acid-labile covalent bonds—including acetals, orthoesters, imines, hydrazones, and esters—in degradable polymers has been recently reviewed by Binauld and Stenzel.[7] The cleavage of acid-labile bonds in an encapsulating material can lead to structure fragmentation, depolymerization, or polarity change, translating to enhanced permeation and release of encapsulated cargo (Figure 1a, Scheme 1).[8−10] In the cases of cationic and anionic polymeric encapsulants, variations in pH alter the degree of ionization through protonation or deprotonation, leading to changes in electrostatic interactions and hydrophilicity. A ketal-containing cationic poly($\beta$-amino-ester) nanoparticle developed by Almutairi and co-workers demonstrates an interesting application of both acid-catalyzed bond cleavage and acid-induced change in protonation state.[8] Prepared from a copolymer of ketal and aminoester monomers, the nanoparticles exhibit a burst release profile in acidic media. The swelling effect from secondary amine protonation enhances the uptake of acidic water, resulting in accelerated ketal cleavage throughout the nanoparticles. Aminals, amine analogues of the oxygen-based acetal structures, are less commonly encountered in synthetic soft materials compared to acetals, most likely because of relatively lower stability. However, for a special type of cyclic aminal structure, 1,3,5-triazaadamantane (TAA), the stability is substantially higher owing to their three-dimensional, diamond-like structure. Synthesized by a condensation of a 1,1,1-tris(aminomethyl) compound with three aldehydes, TAAs are tuned by substituent effects to degrade at different rates and have been derivatized by Zimmerman and co-workers for use in acid-responsive materials such as hydrogels and dendritic structures.[11−14]

Compared to acid-triggered release, which has dominated the current literature largely as a result of strong interest in cancer drug delivery research, base-triggered release has received relatively less attention and is most often realized by anionic polymeric encapsulants.[15] Under a higher pH environment, anionic polymers such as those based on polyacrylic acids, undergo ionization through increased deprotonation, causing the encapsulants to swell or disintegrate.[16,17] Nevertheless, a novel degradable polymeric encapsulant capable of incorporating a variety of triggers, such as base, acid, or light, through a modular synthetic approach, has recently been reported.[18,19] This type of flexible synthetic design represents a new popular trend in the field of fully degradable polymers. More details on this new design concept and its implementation in triggered release will be discussed in later sections.

**Photochemical Triggers.** Scientific interest in using photochemistry for triggered release is dominated by the ability to readily implement both spatial and temporal control of the triggering event, a feature not as easily attained in other modes of triggered release.[20] While precise, remote application of phototriggers is possible thanks to modern optical technology, photoenergy in the form of natural sunlight, which already plays a pivotal role in maintaining natural processes, serves as an essentially unlimited source from which energy can be tapped for industrial and agricultural use.[21] Chemical plants could in theory be modified to accommodate light sources to trigger reactions during manufacture. However, given the high cost barriers to altering plant processes, systems that are already in practice exposed to natural light are more likely to be developed for triggered release applications. Relevant areas of industrial use therefore include agriculture, exterior coatings, and skin- or hair-applied personal care items such as sunscreens.

In general, there are two types of photoregulated release systems: phototriggered isomerizations and phototriggered covalent bond modifications. One of the most widely cited examples of phototriggered isomerizations is based on azobenzenes, which switch from the thermodynamically favored *trans*-conformation to the bent *cis*-conformation upon irradiation with UV (Scheme 2).[22] In an azobenzene-functionalized

**Scheme 2. Photoisomerization of (a) Azobenzenes and (b) Spiropyrans**




encapsulant, enrichment of the *cis*-state in sufficient concentrations leads to enhanced release. Such phenomena are believed to arise from the less stable, structurally bent *cis*-form increasing structure polarity and decreasing molecular close-packing, thus leading to enhanced molecular transport across the barrier or even damage to the encapsulant structure.[23] The isomerization of azobenzene is a reversible process, which is advantageous when on/off temporal control of the triggered release is desired. In addition to azobenzenes, reversible photoreactions are also found in systems that exhibit photoinduced bond cleavages. For example, the photorearrangement reaction of spiropyrans involves the transition from a neutral, hydrophobic, ring-closed molecule to a charged, open-ring species by UV irradiation.[24] Relaxation by thermal or visible light assisted pathways restores the lower energy, nonpolar form. The ability to use photostimuli to control the relative concentrations of the chemically distinct states allows azobenzenes and spiropyrans to be utilized as photoswitches for photoregulated stepped release.[25,26] However, current systems suffer from diminishing responses as a result of photofatigue from repeated exposure cycles.

Photocleavage reactions are used to trigger either fragmentation or depolymerization of polymeric encapsulants or induce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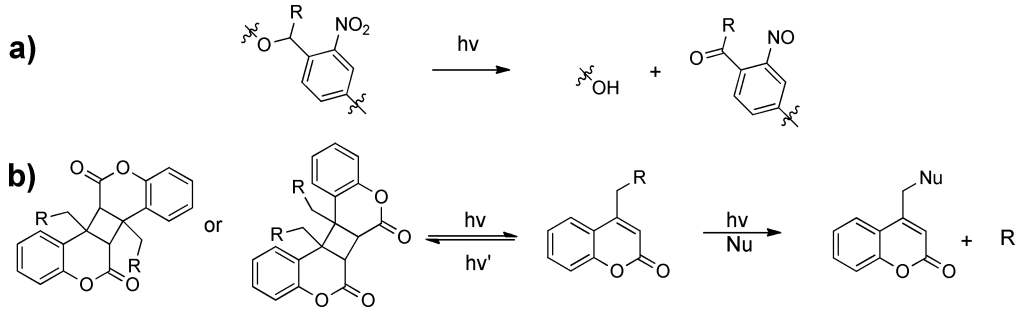
**Scheme 3. Photorearrangements of (a) Nitrobenzyl Cages and (b) Coumarin Derivatives**




hydrophobic-to-hydrophilic transition by generating polar groups (Figure 1b, Scheme 3).[18,27−30] The most well-known photocleavage reactions used in triggered release are those based on the *o*-nitrobenzyl (ONB) chemistry.[18,27,30] Additionally, other photolabile chemistries such as those based on pyrene and coumarin derivatives have been reported as well.[25,26] The mechanism of the photolysis of ONB derivatives has been suggested to involve a rearrangement reaction to form an acinitro intermediate, which cleaves the carbon−heteroatom bond at the benzylic position to generate a nitrosophenyl carbonyl compound (aldehyde or ketone) and a leaving group such as an alcohol, amine, or carboxylic acid.[31] Photolysis of coumarin derivatives is believed to undergo a heterolytic cleavage to form a coumarin cation and a leaving group anion, followed by nucleophilic attack of the coumarin cation to complete the bond cleavage.[32] Esters of ONB, coumarin, and pyrene have been incorporated in hydrophobic encapsulants as nonpolar side groups that, upon photoirradiation, cleave to generate the corresponding polar carboxylic acid groups.[25,29,30] To effect phototriggered chain scissions, depolymerization, or polymer swelling or dissolution, photocleavable compounds such as photolabile monomers, linkers, or cross-linkers have been designed.[33] In the case of polymeric materials bearing photosensitive double bonds (e.g., cinnamic acid and coumarin derivatives), the reversible photocycloaddition reactions between the olefinic moieties introduce light-regulated cross-linking and de-cross-linking.[34,35] It should be noted that coumarin-derived photosensitive materials undergo reversible [2 + 2] cycloadditions for cross-linking/de-cross-linking as well as irreversible bond scissions (through one-photon UV or two-photon NIR photolysis) as seen in coumarin ester containing micelles.[27,36]

In a final example of using light to trigger chemical changes, oxidation by photosensitizer-generated singlet oxygen has been used as an indirect method to trigger the release of materials from lipid membranes and polymer-coated nanoparticles.[37,38] In the former example, chemical attack on the membrane structure by singlet oxygen rendered the membrane damaged and leaky. In the latter case, the reactive singlet oxygen generated by sensitizer eosin oxidatively cleaved the hydrophobic 9,10-dialkoxyanthracene from the polymer to expose a polar alcohol chain, resulting in a hydrophilic polymer that releases the encapsulated drug. It should be noted that both examples respond to visible green light because of the presence of photosensitizers. Although UV is not required, which has advantages compared to phototriggerable release systems such as azobenzene, the intensity of visible light used was high (500 mW/cm$^2$) and thus could pose a challenge to adoption in industrial applications.

Recently, there have been significant developments focusing on the use of IR light as a triggering source,[39,40] primarily because the longer wavelengths allow for enhanced penetration depths and minimal harm to irradiated materials, especially mammalian tissues. However, current systems usually require dopants or a high power laser source to efficiently and sufficiently apply IR radiation for triggered release.[41] At least in the near term, such requirements are inconvenient and come with additional implementation costs that render the adoption of IR-based systems less likely in commercial applications beyond those in highly specialized medical therapeutics.

**Thermally Induced Triggers.** Heat is a widely available trigger in a range of chemical application spaces. Chemical reactors and materials processing equipment typically have heating functionality built in, and many application spaces are subject to thermal changes and/or fluctuations. These applications include oil recovery, commercial and residential washing appliance use, pharmaceutical administration, adhesive application, coatings and film formation, thermal printing, and food preparation. Since most academic research has focused on pharmaceutical delivery, typically explored temperature ranges have been between ambient and body temperature, though some materials have been developed to produce higher temperatures *in situ*.[40,42,43] Expansion of thermally responsive material concepts beyond pharmaceuticals should enable development and leveraging of chemistries active across a wider temperature range.

A thermal stimulus for triggered release generally manifests its effects in phase changes, structural disruptions, enhanced diffusion, or a combination of these effects (Figure 1c). Inspired by the discovery of thermoresponsive properties of acrylamide-based polymers, significant efforts have focused on using these polymers to engineer thermoresponsive soft materials. In the area of triggered release, thermoresponsive materials based on polyacrylamides such as poly(*N*-isopropylacrylamides) (PNIPAAMs) have found ways to demonstrate thermally regulated release of encapsulated materials. The most common strategy utilizes the inherent change in hydrophilicity when PNIPAAM undergoes temperature-triggered coil-to-globule transition in order to control permeability or solubility of encapsulant materials.[44,45] Other systems take advantage of the contraction and expansion associated with the coil−globule transition as temperature-regulated gating materials for porous encapsulants.[46] Because a temperature gradient is necessary and sufficient for spontaneous heat propagation and dissipation, efforts to more precisely control thermal stimuli have led to the development of coupled triggering events that involved other triggers such as light and magnetism. Photothermosensitive triggered release systems enable localized heating through incorporation of metal nanoparticles that, upon photo-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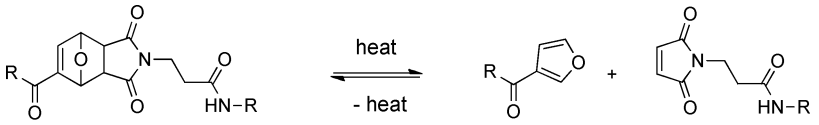
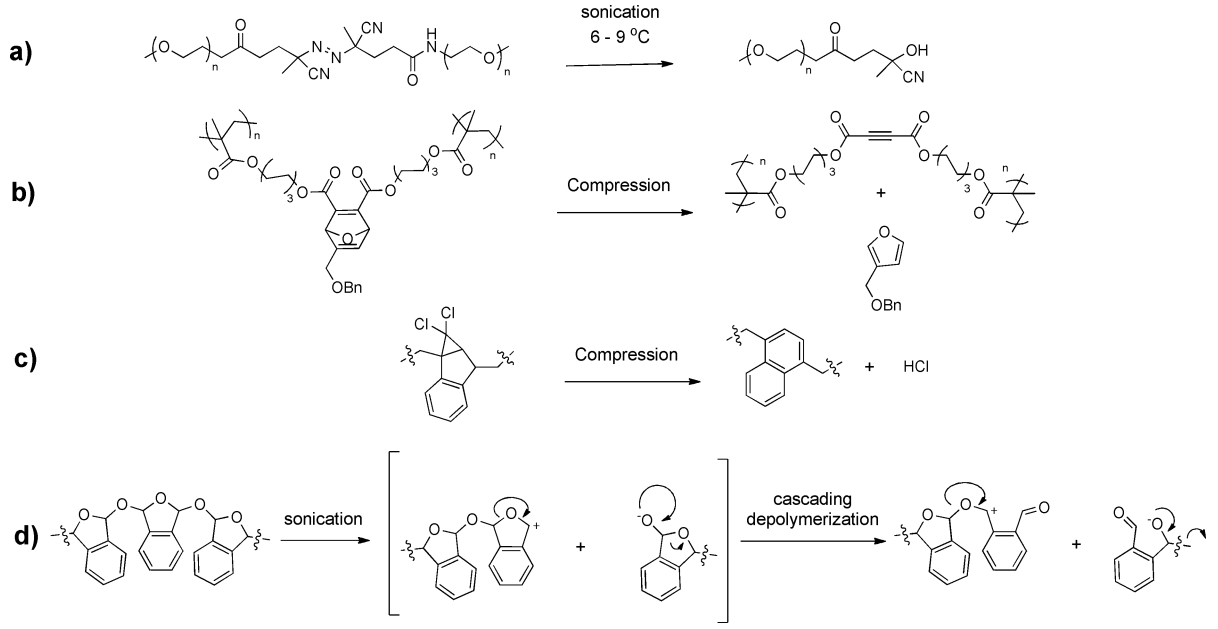
**Scheme 4. Retro Diels–Alder Fragmentation of a Furan–Maleimide Adduct**




**Scheme 5. Mechanically Triggered Chemistry**[a]




[a](a) Azo-cleavage of a PEG copolymer. (b) Compression-induced retro-DA liberation of a furan. (c) Compression-induced liberation of HCl. (d) Sonication-induced depolymerization of a polyacetal.

irradiation, generate heat by plasmonic resonance.[40] Analogously, magnetothermosensitive encapsulants rely on magnetic particles that convert the magnetic energy into heat when subject to an oscillating AC magnetic field.[47] In essence, the coupling of light or a magnetic trigger to a latent thermal source introduces spatiotemporal control that is otherwise not attainable with the thermal trigger alone. However, as previously discussed, despite the benefits of enhanced control, the additional need of supplying the thermal generator and the associated remote energy sources will make coupled thermal-triggered release less attractive for practical applications, at least in the foreseeable future.

Thermally triggered covalent bond modifications for encapsulant degradation and triggered release remain comparatively underexplored. While thermally reversible Diels–Alder (DA) reactions have been widely studied for use in heat-activated rehealable materials, DA-based materials for triggered release applications have received increased attention only in recent years. In general, for most DA adducts, efficient bond cleavage requires a temperature exceeding 100 °C. However, the more labile furan-based DA adducts dissociate at temperatures as low as 80 °C and thus are becoming the choice for many triggered release and degradable polymer systems (Scheme 4).[48−51] Bowman and co-workers developed a PEG hydrogel containing pendent maleimide–furan DA adducts which underwent faster release of the furan-terminated peptide at 80 °C than at 37 °C, owing to the retro-DA reaction being favored at a higher temperature.[52] By varying the loading of pendent maleimide in the hydrogel polymer, the rate of peptide release is modulated, presumably as a result of varying statistical binding events between the furan-peptide and the maleimide.

**Shear/Mechanical Triggers.** Release by mechanical shear has been widely adopted in industrial applications and continues as a very applicable triggered release method. In many application settings, ranging from "scratch and sniff" fragrances to self-healing applications,[53] triggered release occurred by shear functions without sophisticated equipment or agents, such as a laser source or chemical additives (Figure 1d). Shear is often applied to chemical systems through process extrusion (applications in polyurethanes, foams, and plastics), spraying (agriculture and industrial coatings), or mechanical damage. Shear is typically a physical rather than chemical mechanism and, as such, has not received as much attention in recent chemical literature. However, scientific interest in developing practical shear-triggered release systems is found in several recent reports. For example, Zumbuehl and co-workers reported a way to tune self-assembled liposomal structures for low shear-triggered release.[54] More specifically, compared to typical spherical liposomes, lenticular liposomes prepared from synthetic 1,3-diamidophospholipid exhibit enhanced stiffness and the ability to undergo burst release by shear generated from shaking the vesicle solution. Whereas Zumbuehl and co-workers discovered a way to render self-assembled structure susceptible to destabilization by shear, Routh and co-workers actually strengthened an enzyme-loaded, self-assembled colloidosome with a $CaCO_3$ sealant to achieve enhanced stability while maintaining the ability to undergo rupture by shear in a laundry machine.[55] These examples of distinct chemical approaches to achieve effective shear-triggered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release from self-assembled encapsulants demonstrate the contribution of creative chemical designs to the development of shear-triggered release systems.

In addition to physical breakage or structural destabilization by mechanical force, mechanically activated chemical reactions also show potential for use in triggered release applications. Chemical reactions that are triggered by mechanical input fall under the subject of "mechanochemistry", which encompasses mechanically driven chemical phenomena ranging from phase transitions to covalent bond modifications (Scheme 5).[56] The discovery of a variety of mechanochemically induced organic reactions in the past decade has expanded the mechnochemical tools for use in intelligent functional materials. To utilize mechanochemical reactions in synthetic materials, significant efforts have focused on developing mechanically sensitive chemical entities, called mechanophores, which are synthetically integrated into polymeric materials for precise, site-specific chemical transformations by mechanical activation. For example, in 2005 Moore and co-workers drew inspiration from the historically known observation of homolytic cleavage at the center of a polymer under sufficient shear stress and designed PEG polymers containing an ultrasonic shear-labile azo linker both near and away from the center of the polymer chains (Scheme 5a).[57,58] This work highlighted the possibility of mechanically activating homolytic cleavages in polymer at specific locations simply by placing sensitive mechanophores at sites of interest along the polymer chain.

In addition to controlled polymer cleavage, another potential use of a mechanical trigger is to release a small molecule. For example, Boydston and co-workers demonstrated the use of compressive stress to trigger a retro-[4 + 2] cycloaddition reaction of an oxanorbornadiene moiety embedded in a noncleavable cross-linker to release a furan molecule without chain scission; when applied to an appropriate cross-linked elastomer, stepped release through repeated compressions was achieved (Scheme 5b).[59,60] An extension of the concept of mechanically triggered small-molecule extrusion is the generation of a catalyst that helps to initiate other chemical transformations. Such a concept was realized by the recently developed *gem*-dichlorocylcopropane-based mechanical polymeric acid generator (Scheme 5c).[61] Contrary to the known thermally activated HCl elimination reaction from a *gem*-dichlorocyclopropane,[62] the acid generation reaction is assisted by aromatization of the indane moiety, allowing mechanical compression to trigger the elimination. In 2014, Moore and co-workers developed a degradable low ceiling temperature polyacetal that fully depolymerized upon ultrasonication; experimental evidence as well as computational studies suggested a less common mechanically initiated heterolytic bond dissociation was responsible for cleaving the polymer chain into a highly unstable zwitterionic pair that then separately undergoes rapid depolymerizations (Scheme 5d).[63] Admittedly, from a practical point of view, the aforementioned mechanochemical systems face challenges such as long-term stability, synthetic complexity, stringent operating conditions (e.g., molecular weight restrictions, need for sonication or high pressure compression, etc.), and/or low efficiency. Nevertheless, these recent examples of synthetic polymers using mechanistically distinct, mechanically activated reactions to demonstrate site-specific chemical transformations, small-molecule/catalyst release, and full depolymerization represent an important step toward better understanding and control of mechanochemistry for potential use in novel triggered release applications.

## 3. TRIGGERS BUILT INTO POLYMERS

Trigger-cleavable polymers comprise a class of polymers whose structures contain metastable trigger-responsive motifs. Without external stimuli, these polymers can retain their structures; however, upon trigger exposure, the trigger-responsive motifs engage, resulting in degradation of the polymeric material. Generally, trigger-cleavable polymers are classified into five main categories based on the chemical location of the triggerable moieties within the polymer: (1) a single group located at the polymer terminus; (2) a single group at the chain center of homopolymers or the junction of block copolymers; (3) multiple groups built into the side chain of polymers; (4) multiple groups in the main chain of polymers; and (5) multiple groups distributed in cross-linking units of network polymers (Figure 2). How a polymer triggers can greatly

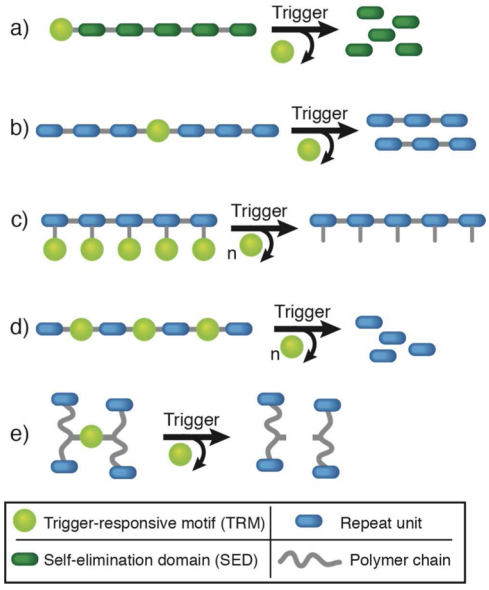


**Figure 2.** Schematic illustration for different trigger-responsive cleavable polymers with trigger-responsive moiety located at (a) terminal, (b) chain center or junction, (c) side chain, (d) main chain, and (e) cross-linked point of polymeric materials and their degradation processes after trigger treatment.

influence the resulting profile of active release (i.e., burst or a slower controlled release), so the choice of how a trigger is built into a system is vital to matching the needs of the application. In this section, we describe these polymer structures and discuss the typical effects of trigger cleavage on the polymers.

A single trigger-cleavable moiety located at the terminus of a polymer is capable of triggering the degradation of the polymer into small-molecule monomers. Self-immolative polymers (SIPs) utilize a terminal protecting group capable of temporarily stabilizing otherwise kinetically unstable polymers, resulting in a dormant polymer chain responsive to a stimulus dictated by the protecting group. Exposure to that stimulus leads to triggering of a head-to-tail depolymerization of the polymer main chain.[64] The combination of selective and environmentally sensitive responsiveness and spontaneous degradation has made SIPs an attractive and versatile new tool for small-molecule release upon depolymerization, signal


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amplification, and trigger-release applications.[65−70] Specifically, stimuli-responsive depolymerization has been used to irreversibly degrade hydrophobic components of micelles,[71] vesicles,[72] microcapsule shells,[19] and solid patterned plastics.[73,74] These degradable platforms may find application in areas including drug delivery, self-healing materials, and lithography. For example, Moore and co-workers incorporated SIPs into microcapsules resulting in microcapsule shells that were responsive toward acidic or basic media, using either Boc- or Fmoc-protection groups, respectively.[19] Exposure of the microcapsules to either 4 M HCl or 5% piperidine initiated the respective deprotection reaction, triggering depolymerization of the polymer shell and release of the encapsulated contents.

A single trigger-cleavable moiety at the middle site of a homopolymer chain backbone is an efficient way to cut long polymer chains into two shorter chains under trigger conditions. Typically, there are two routes employed for synthesis of a homopolymer with the trigger-cleavable moiety at the center of the chain: (a) a trigger-cleavable motif containing a bifunctional initiator that can be used to polymerize a monomer via controlled polymerization[75,76] or (b) a trigger-cleavable motif containing a bifunctional compound that can be conjugated with monofunctional homopolymers.[77,78] For example, Turro and co-workers designed and synthesized a UV-responsive atom-transfer radical-polymerization (ATRP) bifunctional initiator. ATRP polymerization of *tert*-butyl acrylate (tBA) yielded a PtBA−ONB−PtBA homopolymer with the light-cleavable ONB derivative in the middle. When exposed to UV light, the polymer undergoes scission into two PtBA segments. Bielawski and co-workers prepared a mechanical responsive poly(methyl acrylate) (PMA) grown from a cycloaddition adduct of maleimide with furan containing two polymerization initiators.[79] The resulting material was subjected to ultrasound irradiation and degraded into the two low molecular weight PMA segments. This is also the synthetic approach taken by Moore and co-workers, as discussed earlier, for designing cleavable PEG polymers.[58]

Compared to homopolymers, block copolymers (BCPs) bearing a trigger-cleavable junction linking two different polymers have more diversity for trigger-controlled degradation and related applications.[80,81] When the appropriate trigger condition is applied to the cleavable moiety at the junction of two polymers, the block copolymer undergoes scission into two different homopolymers. In addition, block copolymers are able to self-assemble into different nanostructures both in solution and in the solid state,[80] enabling the building of smart trigger-responsive polymer nanostructures. The Moon group first reported the synthesis of a poly(ethylene glycol)-*b*-poly(styrene) (PEG−PS) BCP with an ONB linker.[82] Nanoporous PS films with controlled pore sizes were obtained from annealed PEG−ONB−PS films through UV irradiation and photocleavage of the PEG block. Burdick and co-workers developed a novel strategy for synthesizing BCPs that allows for the incorporation of a variety of functional groups at the junction of the two blocks.[83] PEG−ONB−PCL with ONB located at the junction between PEG and poly(ε-caprolactone) (PCL) blocks was prepared by a modular synthetic route in which a PEG was end-capped with a protected, triggerable amino acid followed by deprotection and subsequent coupling of a second polymer block. Upon stimulus, the blocks cleaved from each other, allowing for structure disassembly.

Side chain bond cleavage is another route to triggering structure dissociation. A common strategy to this end is the use of acid or amine functional groups built into side chain functional polymers to alter the hydrophilicity/phobicity by variation in the protonation states, a topic that has been thoroughly reviewed elsewhere.[84−89] In this section, therefore, we will focus on covalent bond cleavage-related trigger-responsive side chain functional polymers. Trigger-cleavable moieties have been incorporated into the block copolymer structure as side groups of the hydrophobic block, ultimately enabling a change in polarity upon stimulation.[90] In the instance of BCP aggregates in solution, the amphiphilicity of the block copolymer is changed, and the hydrophobic block may no longer be hydrophobic enough to retain the nanostructure association, instead dissolving into the solution. For example, block copolymers containing pyrene,[28] *o*-nitrobenzyl,[30] and coumarin[29] (meth)aryl esters as photochromic side groups have been prepared. Exposure to light cleaves the photochromic moieties and converts the hydrophobic polymer into a hydrophilic one through the liberation of carboxylic acids. These changes of the amphiphilic BCP structures to more hydrophilic ones are able to destabilize the BCP structures, inducing cargo release from the nanostructures. Irvine and co-workers developed ONB-protected acrylic random copolymers that upon light deprotection exhibited pH-dependent solubility, offering a material subject to two triggers in a sequential fashion.[91]

In self-immolative polymers, or other polymers containing single triggerable domains, the sensitivity to a stimulus relies on a single triggering event leading to self-elimination reactions. However, if the triggering is not very efficient, then not all polymer scissions will occur. In principle, a polymer with trigger-sensitive moieties in the chain backbone should degrade more efficiently and into smaller fragments upon exposure to the trigger conditions, therefore increasing the responsiveness of a polymer and allowing for faster release. Polymers of this type, with a trigger-cleavable group in each repeating unit of the chain backbone, are achieved by means of condensation polymerization using a trigger-responsive domain (TRD) containing monomers.[8,27,92,93] Upon polymer exposure to the trigger condition, the polymer degrades into small molecular weight segments, a feature that can be leveraged to disrupt the structure of polymer nanoaggregates and induce the release of encapsulated cargo.[8,27,92,93] To further bind actives into a polymer matrix and avoid diffusion-controlled release, Cheng and co-workers developed a strategy in which the active is covalently conjugated into the triggerable polymer backbone.[18] This strategy affords precise control over both active loading and active release by incorporating a TRD and bis-functional actives into the A/B (TRD/active) condensation polymerization process, building trigger-responsive degradable polymers containing the active compound.[94] The release of actives was precisely controlled by the adjacent TRD; application of an external trigger would activate the TRD, subsequently inducing chain-shattering degradation of the polymer and release the active from the polymer.

Trigger-responsive moieties in polymer networks provide a cleavable point between polymer chains and facilitate de-cross-linking reactions to break up cross-linked polymer networks into soluble polymers or small molecular segments. For example, the Turro group reported a photodegradable polymer network prepared from ONB containing star polymers by using copper-free click chemistry for *in situ* cross-linking.[95] This


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network was degraded into low molecular weight polymer fragments upon UV irradiation. Positive-working photoresists are another example of triggered cross-link degradation.[96] Upon light irradiation, the cross-linker junction groups were triggered by light directly or by conditions resulting from the light exposure. The de-cross-linking reactions resulted in the cross-linked nonsoluble polymeric network becoming soluble.

There is growing interest in the controlled release of compounds from hydrogels, microgels, or other cross-linked polymeric networks that disassemble or degrade in a controlled fashion upon application of an external stimulus.[97−102] In the case of hydrogels, various responsive cross-linkers with triggers such as pH,[11,103,104] enzyme,[105] redox,[99,106,107] and light[106] have been developed. Recently, the Cheng group reported a new strategy for preparation of trigger-responsive cross-linked networks by development of poly($\beta$-aminoester) (PBAE) gels synthesized from diacrylate macromers containing multiple acid-sensitive ketal bonds or reduction-responsive disulfide bonds.[76] The degradation capability of hydrogels was enhanced by increasing the number of trigger-responsive, degradable domains in the backbone of the PBAE, and the encapsulated protein release profiles were tuned by external trigger conditions, such as different pH and redox conditions.

## 4. TRIGGERED RELEASE FROM AGGREGATE SPECIES IN SOLUTION

Encapsulation is utilized in industrial formulations for the preservation, sequestration, and, in most cases, ultimately, release of active ingredients. Polymer capsules have been widely used in industry, and triggered release from them has been previously reviewed.[108] Utilized far less frequently in industry is encapsulation using block copolymer aggregates in solution, such as micelles, liposomes, and polymersomes. These encapsulating materials are simple to assemble, remain in solution, and can be designed with specific triggers for release (Figure 3). In the coming section, we review recent advances in the design of triggerable polymersomes and other block copolymer aggregates that we believe offer promise for translation and adaptation for high-performance industrial formulations.

Micelles and polymersomes are formed through the aggregation of amphiphilic BCPs in solution. Formation in both aqueous and organic solvents is possible,[109−111] though aqueous systems are far more common. The structure and properties of self-assembled BCPs have been thoroughly reviewed by Mai and Eisenberg.[112] While micelles and polymersomes can encapsulate cargo, they are also inherently leaky, allowing cargo to release from their structure over time in a passive manner.[112] Environmental stressors such as solvent,[113] surfactants,[114] shear,[115] and osmotic pressure[116] have been shown to alter the permeability of aggregates, and as a result, many strategies have been explored to enhance the stability of these materials.[2] Generally, we expect that polymersomes and BCP micelles will be most applicable to aqueous formulations, generally those with minimal surfactant presence, such as agriculture, pharmaceutical, water treatment, or home and personal care formulations. Concepts shown in the following section, however, can be applied to other encapsulation systems, such as capsules and matrices, to improve other areas of industrial need.

**Change in Membrane Properties.** The nature of the aggregate membrane is an important feature for triggered and controlled release. Changes in membrane properties allow for

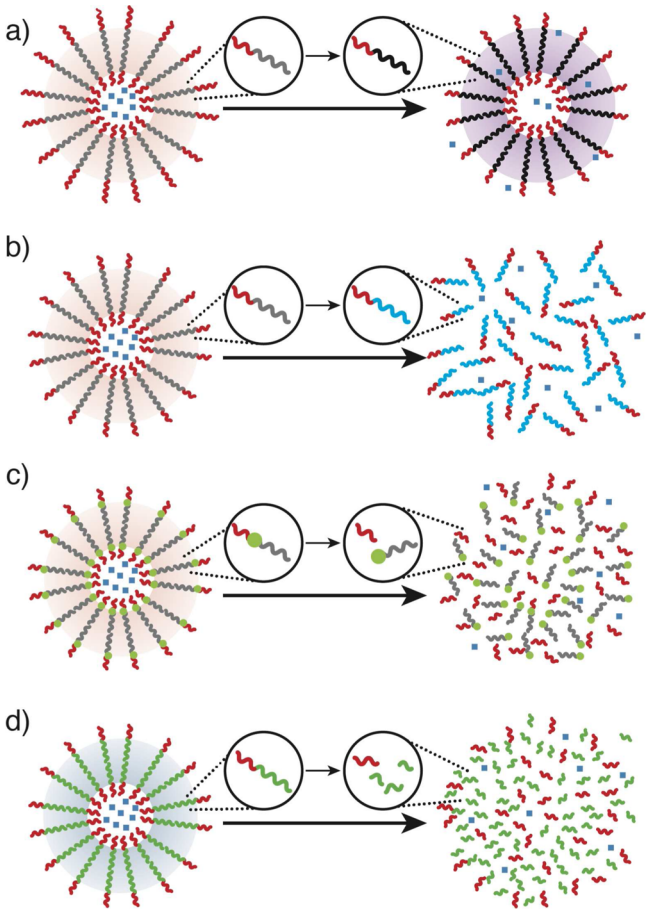


**Figure 3.** Schematic representation of triggered release from polymersomes utilizing different triggering mechanisms: (a) change in membrane permeability, (b) change in polymer polarity, (c) cleavable linkers between blocks of diblock copolymers, and (d) degradation of the main polymer backbone.

alterable permeability, whereas changes in the structure of the membrane alter the stability of the aggregate structure, both resulting in the delivery of a payload. The introduction of channels into a membrane bilayer alters the membrane morphology and enables the release of cargo where the membrane would otherwise be impermeable. Channels, or pores, are incorporated into the aggregates through multiple methods such as in the initial preparation of the aggregate,[117] the incorporation of enzymes into the membrane,[118] or through the use of blends of copolymers where certain blocks are more stable than others.[119−121] Polymersomes formed from a blend of poly(lactic acid)-*b*-poly(ethylene oxide) (PLA-*b*-PEO) and poly(butadiene)-*b*-poly(ethylene oxide) (PBD-*b*-PEO) have been shown to form pores over time through the hydrolysis of the polyester polymer block. This results in polymersomes with size exclusion properties.[119] It has also been demonstrated that micelles formed from PLA-*b*-PEO and PLA-*b*-PNIPAM form PEG channels when exposed to temperatures above the LCST of PNIPAM, altering the release profile of the micelle.[120] Micelles formed from poly(caprolactone)-*b*-poly(asparagine) and PCL-*b*-PNIPAM were used to create charged channels through the micelle which suppressed the release of similarly charged actives relative to neutral actives.[121]

The use of cross-linking is a common technique to alter the membrane properties and stability of block copolymer


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aggregates. Irreversible cross-linking is commonly used to impart stability in otherwise unstable aggregates but can alter the ability of aggregates to release cargo. Polymersomes have been demonstrated utilizing hydrophobic blocks containing the pH-sensitive poly(diethylaminoethyl methacrylate) (PDEAEMA) and the photo-cross-linkable 2-hydroxy-4-(methacryloyloxy) benzophenone.[122] Through photo-cross-linking, these structures are shape persistent, but when pH is lowered, significant swelling is observed resulting in enhanced cargo release. Vesicles formed from BCPs whose hydrophobic layers consist of statistical copolymers of pH-sensitive PDEAEMA and trimethoxysilyl group-containing poly(3-(trimethoxysilyl)propyl methacrylate) are capable of self-cross-linking in aqueous solution while also having alterable permeability based on the pH of the system.[123] Although cross-linking often increases the stability of aggregates, it cannot always limit the rate of cargo release. To further slow release in a cross-linked system, Talelli and co-workers demonstrated covalent attachment of a drug to the scaffold of cross-links within a micelle, binding it to the assembly until cleavage of the cargo−scaffold bond.[124]

Reversible cross-linking has also been used for triggered release of actives. Cross-linking imparts stability and increases the retention of actives, whereas the de-cross-linking allows the release of cargo or the disassembly of the aggregate. Zhao and co-workers have shown that incorporating coumarin side groups into PEO-*b*-PMMA BCPs allows cross-linking to occur through the photodimerization of the coumarin groups.[36] Cross-linking hindered the release of dye, while subsequent photocleavage of the coumarin dimers was able to reverse some of the process and resume leakage.[36] The same concept has been applied to poly(ethylene oxide)-*b*-poly(2-(2-methoxyethoxy)ethyl methacrylate-*co*-4-methyl-(7-(methacryloyl)oxyethyloxy)coumarin) polymer micelles which are stable to temperature changes but form a nanogel particle below the LCST of the methoxyethoxy methacrylate block.[125] It was shown that the covalently cross-linked nanogels had a slower rate of release than non-cross-linked micelles.[125] Reversible cross-linking has also been demonstrated with dynamic covalent hydrazone bonds which were triggered with acidic pH.[126] While cross-linking is primarily used to impart stability and limit release of actives, Liu and co-workers recently reported a system in which cross-linking allows for the release of cargo.[127] Using poly(ethylene oxide)-*b*-poly(2-nitrobenzyloxycarbonylaminoethyl methacrylate) polymers, which contain photolabile carbamate-caged primary amines, stimulation caused the amines to deprotect and subsequently cross-link the material. This cross-linking stabilizes the polymersome, but it also alters the polarity of the membrane allowing the polymersome to release both hydrophilic and hydrophobic cargo. Because amines are generated, this polymersome system also can be used for triggering both the release and scavenging of molecules in solution.

**Change in Polarity of Polymers.** The change in the physical properties of BCPs, such as polarity and solvent interactions, can lead to the destruction of aggregate species and the release of cargo. The use of physical and chemical stimuli to alter the state of polymers has been demonstrated in the literature and was reviewed by van Nostrum and co-workers in 2007.[128] While other reviews have appeared since, there has been little focus on the mechanisms of triggering, which we hope to address here.

One of the simplest ways to alter the physical properties of BCPs is through temperature. Altering the temperature of the system changes solvent−polymer interactions and can therefore change polymer hydrophobicity and mobility. For example, Chung and co-workers demonstrated that the incorporation of PNIPAM into the hydrophilic block of BCPs results in the hydrophobic collapse of the micelles and cargo release when the temperature is increased above the LCST of PNIPAM.[129] This same polymer has also been incorporated into the hydrophobic block of vesicles; destabilization and cargo release is observed when the temperature is decreased below the LCST.[130] As an example of changing solvent−polymer interactions, vesicles of PS-*b*-PAA polymer in THF/$H_2O$ mixtures were shown to transition to micelles when the temperature was elevated above 50 °C, allowing the vesicles to release their cargo.[131]

Polymers with pH-dependent polarity have also been successfully incorporated into polymer aggregates and used for triggered release. It has been demonstrated that vesicles containing polymers with both a polyacid and a polybase block, such as PAA-*b*-PS-*b*-P4VP[132] and PGA-*b*-PLys,[133] inverted the structure of their membrane with altered pH. Liu and co-workers studied how the location and degree of incorporation of pH-sensitive poly(dimethylacrylamide) (PDMA) in the membrane can alter the pH at which the polymer is triggered.[134] They found that increasing the block length of the PDMA block required a higher pH to trigger the destruction of vesicles, while the location of the block within the membrane or the use of a statistical copolymerization can also alter the triggering pH.

Protecting groups along a BCP chain are also used to trigger a switch in polarity. Zhao and co-workers utilized a coumarin-protected acrylic acid polymer to form micelles that are triggered to release cargo upon the cleavage of the coumarin moiety with an UV or NIR stimulus.[29] Thayumanavan and co-workers demonstrated that a tetrahydropyranyl (THP) protected poly(hydroxyethyl methacrylate)-containing BCP can form micelles but will release cargo as the THP protecting groups are removed when exposed to low pH.[10]

Altering the oxidation state of polymers is yet another way to induce polarity changes and release cargo. Triblock copolymers of PEO and poly(propylene sulfide) assemble into vesicle structures that when exposed to oxidative stress, such as $H_2O_2$, are oxidized to poly(propylene sulfoxide) then poly(propylene sulfone).[135] Poly(propylene sulfone) is more hydrophilic than poly(propylene sulfide), and its presence causes the disassembly of the vesicle structure. Large compound vesicles formed from BCPs containing tetraaniline as their hydrophobic block have been show to disassemble when exposed to voltage because of the altered oxidation state of the tetraaniline.[136]

As discussed earlier, photoisomerizable units can induce changes in molecular packing resulting in the disruption of BCP aggregates and release of cargo. Nassoy, Li, and co-workers demonstrated that the incorporation of azobenzene units into a single side of an asymmetrical vesicle membrane allows an UV stimulus to rupture the membrane through the isomerization of the azobenzenes.[137] Alteration of the shape of the azobenzene units resulted in changes to the packing on one side of the polymersome membrane and the resulting stress causing the membrane to burst within milliseconds. The azobenzene functional group has also been incorporated into micelles, where the change in polarity of the functional group upon photoisomerization results in destabilization of the micelles in


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an hour.[138] Similarly, light has been harnessed to induce differential membrane stress in composite porphyrin−polymer polymersomes.[139,140]

**Cleavable Linkers between Blocks of Diblock Copolymers.** Another location in which triggerable linkers are incorporated is between the hydrophilic and hydrophobic blocks of amphiphilic copolymers. By providing the relevant stimulus, the linker is cleaved, resulting in the separation of the blocks and loss of amphiphilicity. Polymer aggregates formed from these polymers likewise are triggerable to disassemble and release their payload. Hubbell and co-workers demonstrated that vesicles formed from BCPs composed of PEG and poly(propylene sulfide) linked through a disulfide bond could be triggered by reducing agents such as cysteine and dithiothreitol providing release within hours.[141] These disulfide linkers have also been applied to micelles, with longer release over days demonstrated.[10] Photocleavable linkers have also been incorporated into BCPs. There are multiple instances of linkers between blocks for both polymer vesicles[83,142,143] and micelles,[142] which upon UV irradiation are cleaved, resulting in the destruction of the aggregate and release of cargo. Other photocleavable motifs have been introduced into BCP aggregates such as $\alpha$-truxillic acid derivatives.[144] In the case of BCPs linked by azobenzene units, enzymatic reactions have been used to cleave the diblocks.[81] In lieu of covalently attached junction linkers, the use of supramolecular connections, such as in the case of the voltage triggerable cyclodextrin ferrocene supramolecular polymersome system reported by Yin and co-workers, has also been demonstrated.[145] One of the distinct challenges of using cleavable linkers between blocks is that the hydrophilic block is removed and freely dissolves in solution, whereas the hydrophobic block likely remains aggregated in solution.[27] This phenomenon was independently demonstrated by Meier and Burdick and their co-workers when, upon UV irradiation, vesicles with photocleavable linkers between blocks degrade into nanoparticles.[83,142] Although vesicle structure is destroyed releasing hydrophilic cargo, the release of hydrophobic cargo from vesicles is likely incomplete because of polymer aggregation and precipitation.

**Degradation of the Main Polymer Backbone.** The degradation of polymer blocks is also a triggered release mechanism in BCP aggregates. As with linker triggers, the breakdown of one of the blocks of the amphiphilic BCP similarly results in the loss of polymer amphiphilicity and therefore leads to the destruction of aggregate structures. This method is beneficial over other methods as it may result in the complete breakdown of a polymer into small molecules that are more easily dispersed and flushed from the system. Random chain scissions of the polymer backbone, especially of the hydrophobic block, lead to the destruction of polymer aggregates as the polymer is broken into polymer fragments, oligomers, and small molecules. Due to their biocompatible nature, polyesters such as PLA and PCL have been widely studied and have been incorporated into BCP aggregates.[119,146,147] These polyester polymers are susceptible to hydrolysis of their backbone, which is catalyzed through low pH to achieve release over a time period of days. Polymers with a polyacetal backbone, such as poly(ethyl glyoxylate) (PEtG), have been incorporated into micelles through the use of PEG-*b*-PEtG-*b*-PEG triblock copolymers.[148] At pH 4 the rate of cargo release, due to the breakdown of PEtG, is increased relative to pH 7.4.[148] Breakdown through random chain scissions is useful for the delivery of actives, but to achieve quick, highly controlled release, polymers must be more strategically designed.

Rapidly induced release has been specifically designed through the incorporation of triggerable groups in the backbone of the polymer, as stabilizing units along the polymer, or as end-caps. These fully degradable polymers offer the potential for a material that does not produce large particulate waste. Zhao and co-workers demonstrated the incorporation of repeated photobreakable ONB motifs into the backbone of BCPs and the destruction of micelles and release of cargo within seconds with an UV stimulus.[27] They also demonstrated the incorporation of dithiol groups in addition to the ONB units, imparting a second triggered release profile on a longer time scale of hours.[149] Acid-labile polycarbonates containing trimethoxybenzylidene acetal stabilizing groups have been incorporated into both micelles and polymersomes allowing for the pH-dependent release of actives over days.[150] Polycarbamate polymers stabilized with labile end-caps have been incorporated into BCP nanoparticles, and the release has been shown to be time dependent based on the length of the polymer.[71] Liu and co-workers recently reported the first polymersomes utilizing self-immolative BCPs which can be triggered to release cargo by the removal of an end-cap, resulting in the head-to-tail cascade depolymerization of poly(benzyl carbamate).[72] The self-immolative block was caged with visible light-, UV light-, or reduction-responsive terminal groups. The BCPs depolymerized into water-soluble compounds upon removal of the caging moiety when triggered by the appropriate stimulus.

## 5. CONCLUSION

With increasing consumer demands and the introduction of higher-performance industrial actives, development of innovative, advanced formulation technologies is necessary to help maximize product performance. Incorporation of triggered release functions into materials is one approach to address industrial encapsulation and delivery challenges but at present remains an area of continued need for further innovation. A wide variety of chemical mechanisms, functional polymers, and smart assemblies have been developed to control the release of cargo, though to date most research has focused on the applications of drug release in biomedical applications. Through this review, we have attempted to highlight some of the promising chemistries and materials approaches that could be applicable beyond biomedical applications, leading to eventual adaptation in the chemical industry. Ultimately, any adaptation will require the proper balance of performance improvements coupled to cost tolerance for the application. To that end, the more simple the chemistry and the more easily incorporated into the standard processes, the more likely any innovation will find success. The chemistries and materials highlighted here are those that we believe begin to address some of these criteria and with further development could ultimately find their way into the industrial formulations of the future.

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### Notes

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