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Stimuli-Responsive Polymers for Engineered Emulsions

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Emulsions are complex. Dispersing two immiscible phases, thus expanding an interface, requires effort to achieve and the resultant dispersion is thermodynamically unstable, driving the system toward coalescence. Furthermore, physical instabilities, including creaming, arise due to presence of dispersed droplets of different densities to a continuous phase. Emulsions allow the formulation of oils, can act as vehicles to solubilize both hydrophilic and lipophilic molecules, and can be tailored to desirable rheological profiles, including "gel-like" behavior and shear thinning. The usefulness of emulsions can be further expanded by imparting stimuli-responsive or "smart" behaviors by inclusion of a stimuli-responsive emulsifier, polymer or surfactant. This enables manipulation like gelation, breaking, or aggregation, by external triggers such as pH, temperature, or salt concentration changes. This platform generates functional materials for pharmaceuticals, cosmetics, oil recovery, and colloid engineering, combining both smart behaviors and intrinsic benefit of emulsions. However, with increased functionality comes greater complexity. This review focuses on the use of stimuli-responsive polymers for the generation of smart emulsions, motivated by the great adaptability of polymers for this application and their efficacy as steric stabilizers. Stimuli-responsive emulsions are described according to the trigger used to provide the reader with an overview of progress in this field.

1. Introduction

Emulsions are mixtures that comprise of two or more immiscible liquid phases.[1,2] Typically in such mixtures, one liquid is dispersed as small droplets within the other. Emulsions can take various forms, for example oil-in-water (o/w) or water-in-oil (w/o). In more complex systems, oil-in-water-in-oil (o/w/o) or water-in-oil-in-water (w/o/w) multiple emulsions can also be formed.[3,4] These systems all suffer from thermodynamic instability which can manifest through several physical processes, including coalescence, flocculation, sedimentation/creaming, Ostwald ripening, and breaking.[5] The process of coalescence, where separate droplets merge, causing a reduction of the interfacial area and ultimately phase separation, is one of the most commonly encountered emulsion instabilities.[5,6] Flocculation, the aggregation of droplets forming porous clusters, occurs when attraction between droplets is present, but a short-distance repulsion prevents coalescence. Sedimentation and creaming are comparable phenomena in which droplets come together at the bottom (sedimentation) or surface (creaming) of the continuous phase, depending on the densities of each phase.[5] Ostwald ripening arises, usually with an increase in temperature, and results in the dissolution of the dispersed phase from the interface of the droplets. Smaller droplets dissolve into the continuous phase and then merge onto the surface of larger droplets. As a result of the large droplets, the emulsion may then coalesce or phase invert.[5,7] The exposure of an emulsion to temperature variations can lead to the interfacial layers between the dispersed and continuous phases being destroyed, resulting in phase separation or breaking.[5,8]

Despite their tendency for instability, emulsions are prevalent in a wide array of products and formulations. Industries such as cosmetics, pharmaceuticals, food production, oil recovery, and chemical processing rely on the unique properties of emulsions.[2] In cosmetics, emulsions allow for the formulation of oil containing products, such as perfumes, whilst also benefitting from the desirable shear-thinning rheology of emulsions.[9] Emulsions are frequently present in food products, where any instability can affect organoleptic properties. For example, the mouthfeel of food products containing emulsions relies upon the rheology and particle size of the emulsions.[10] In chemically enhanced oil recovery, oil fields are flooded with surfactant to stabilize and extract oil; the resulting emulsion must then be destabilized to recover the oil.[11,12] Chemical processing often occurs in a heterogeneous reaction medium, requiring a strong understanding of emulsion science, for example

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in emulsion polymerization.[13,14] Additionally, emulsions can be utilized as a platform for the synthesis of advanced nano-/mesostructured materials, for example, emulsions have been employed in drug delivery systems, particularly as external/topical applications.[15,16] Such systems can improve the solubility of hydrophobic drugs by partitioning drugs between the oil and the water phase; this method of administration is faster than the disintegration and absorption procedures required for oral dosage forms such as tablets and capsules.[6]

Emulsion choice is dependent on multiple factors: intended use, component properties, compatibility with solubilized compounds (e.g., drugs, nutrients), and the desired characteristics of the final product. Several factors such as emulsion type, droplet size, continuous/dispersed phase volume ratio, and emulsion stability must be considered during the emulsification process. Crucial to all these parameters is the ability to adequately stabilize the emulsion through the use of surfactants. Surfactants are amphiphilic species such as small molecules, nanoparticles, polymers, and microgels.[17–19] These species absorb at the oil/water interface, hindering the merging of emulsified droplets through electrostatic and/or steric repulsion forces.[20] When employed to provide a barrier to the instabilities that emulsions often encounter, surfactants may also be denoted as emulsifiers.

Polymers are a particularly attractive class of emulsifiers because of their structural adaptability. In addition to being used as traditional emulsifiers, polymers can also act as responsive systems to impart additional functionality. Stimulus-sensitive polymeric surfactants have the potential to produce emulsion-based materials which undergo physicochemical changes in response to external factors such as mechanical stress, pH, light, temperature, or biological stimuli.[21–24] On-demand demulsification and sol-gel transitions, for example, have been achieved using stimuli-responsive polymers.[12,25] Additionally, emulsions that respond to external stimuli have been developed for a variety of drug delivery platforms (e.g., injectables, topical, vaginal, and ocular applications).[7,15,26–28] Due to advances in polymer science, it is feasible to create an emulsion that can be both highly stable and undergo on-demand breakdown or phase inversion.[29] Such systems are typically complex, requiring polymers capable of imparting stimuli-responsive behavior to stabilize emulsions with oils of widely varied polarity, droplet size and oil/water ratio as well as varied emulsification techniques.[30]

This review discusses the generation of "smart" (i.e., stimuli-responsive) emulsions using polymeric emulsifiers, focusing on pH, temperature, and salt-responsive systems due to their relative abundance in the literature. The underpinning behavior of polymer systems is discussed, followed by progress in the generation of responsive emulsions organized by stimulus. The behaviors of emulsion gels has been reviewed by Wan et al. and may serve as a supplement to this review.[31] Alternative approaches to generating responsive emulsions include the use of small-molecule surfactants and particles as "Pickering" emulsifiers, which have been reviewed by Brown et al.[32] and Tang et al.[20] The current review focuses on polymeric surfactants; for a broader overview of the literature on responsive emulsions, readers are directed other recent reviews.[33,34]

2. Stimuli-Responsive Polymers

Modern polymer synthesis techniques have enabled the creation of polymers with sophisticated structures and bespoke behaviors.[35] The incorporation of sensitive chemical moieties whose responsiveness enables modulation of properties, coupled with the intrinsic ability to control polymer properties through modification of architecture and inclusion of co-monomers, has resulted in polymers becoming valuable tools for developing stimuli-responsive systems.[36] Materials of this nature are often influenced by similar processes in biological systems.[37,38] For instance, certain plants such as wheat awns and pinecones respond to changes in humidity, by expanding or contracting to disperse their seeds.[37] Another common stimuli-response is the interaction of signal molecules and receptors producing physiological responses in animals. Single-celled organisms such as bacteria can sense and respond to environmental factors such as pH, light, temperature, and nutrients. The cis-trans isomerization of retinal in response to light, which enables vision, is another instance of a stimuli-responsive behavior.[37] Natural biopolymers, such as proteins and nucleic acids, are all stimuli-responsive components of living organic systems and may be isolated or chemically adapted to utilize in healthcare applications.[39,40] These "natural" stimuli-responsive polymers have formed the basis for the development of numerous synthetic polymers that mimic their adaptive responses.[36]

In synthetic polymers,[41] stimuli-responsive behavior typically arises from alterations in the physicochemical structure, driven by functional groups that are amenable to a change in character (e.g., charge, polarity, and solvency). Based on the nature of stimuli, responsive behavior can be categorized into three major types: physical stimuli (mechanical stress, electrical/magnetic field, ultrasound, light, temperature, UV); chemical stimuli (electrochemical, pH, ionic strength, redox potential, H_2O_2); and biological stimuli (enzymes/receptors, biomolecules, antigens, ligands and other biochemical agents).[42,43] Invoking such changes can trigger consequential shifts in the macroscopic material properties, leading to outcomes such as modifications in chain length, color, secondary structure, solubility or degree of intermolecular interaction.[36,44,45] In most cases, these responses are caused by the presence or disruption of secondary forces (hydrogen bonding, hydrophobic effects, electrostatic interactions, and so on), simple reactions (e.g., acid-base reactions) of moieties linked to the polymer backbone, and/or osmotic pressure variations.[36,44,45] Smart polymers may be capable of producing multiple stimuli-responses and/or exhibit reversibility of these modifications.[36,46,47] There is well-established evidence that not only are the responsive units responsible for the environmental sensitivity of the polymers, but their location, specific distribution, and molecular topology (morphology, molecular bond arrangement/cleavage and molecular motion)[48] also contribute to the behaviors of smart materials.[41] Additionally, responsive behavior can be initiated by changes in polymeric structure, such as polymer degradation caused by bond breakage in the polymer backbone or at pendant cross-linking groups in response to a particular stimulus, however these responses are typically irreversible.[49,50] Since stimuli-responsive behaviors can occur in aqueous solutions, polymers of this nature are gaining popularity in biotechnology and medicine for applications such as

biosensors, "switch on-off" drug release, drug delivery systems, affinity precipitation, enzyme and cell immobilization, tissue engineering, and artificial muscles.[51,52]

2.1. Engineering Emulsions with pH-Responsive Polymers

Due to modern synthesis techniques, polymers with sophisticated structures can be produced, which make it possible to fine-tune emulsion qualities to satisfy the demands of varied applications.[53] Due to steric hindrance and multipoint irreversible anchoring at the oil-water interface, branched polymers can offer stronger emulsion stability than their linear counterparts.[54] For example, Weaver et al. produced a range of branched copolymer surfactants (BCSs) that gave substantially higher emulsion stability than their linear analogues.[54–56] Not only did Weaver and colleagues achieve greater stability, but they were able to utilize a one-pot synthesis established by Sherrington and co-workers.[57] With this method, precise manipulation of hydrodynamic particle size and polymer chain ends is possible without the requirement of labor-intensive multi-step synthetic procedures. A large literature base is present in the area of pH-responsive BCSs, due to the large contribution that Weaver and co-workers have made to the area. As such, this section first describes their contributions to the field, which have clear overlap of concepts, before reporting systems which were not studied by this group.

Using their one-pot method, Weaver and co-workers were able to prepare pH-responsive branched amphiphilic copolymers.[57] The synthesis used pH-responsive monomer 2-(diethylamino) ethyl methacrylate (DEA) and hydrophilic macromonomer poly(ethyleneglycol) methacrylate (PEGMA) whilst introducing branches with ethylene glycol dimethacrylate and hydrophobic chain ends with an alkanethiol. It was discovered that the apparent pKa of the polyamine residues systematically varied with the degree of branching, providing tunability for various triggered-release applications. In basic pH aqueous solutions, the copolymers formed well-defined micellar structures with hydrodynamic diameters ranging from 16 to 46 nm (**Figure 1**). When the pH was reduced, the branched copolymers undergo hydration and swelling, similar to pH-responsive self-assembled materials based on tertiary amine methacrylates. This behavior is comparable to the swelling and deswelling behavior of pH-responsive shell cross-linked micelles and microgels.[58,59] In addition to this, the copolymers were reported to undergo pH-triggered uptake and release of a model hydrophobe. Fluorescence experiments were used to demonstrate the pH-dependent uptake and release of pyrene. The extent of release could be fine-tuned by adjusting the degree of branching, hydrophobicity, and concentration of the chain transfer agent. This novel approach to synthesizing copolymers represented a new and commercially viable method for preparing pH-responsive core-shell polymeric nanostructures with various applications.

Weaver and researchers have since used their template to create a new class of responsive polymeric surfactants capable of producing stable and functional micrometre-sized emulsion droplets.[54] The surface functionality of these droplets was designed to allow for reversible hydrogen-bonding interactions, enabling the controlled trapping of droplets in specific geometries (**Figure 2**a). Referred to as "emulsion engineering," this concept utilizes responsive polymeric surfactants to precisely mediate interactions between droplets. Importantly, these inter-droplet interactions are reversible, allowing the engineered emulsions to be easily disassembled back into stable individual droplets by adjusting the pH. The surfactants used in this study were amphiphilic branched copolymers synthesized from methacrylic acid (MA) and PEGMA with hydrophobic dodecane chain ends. These monomers provided simultaneous steric and electrostatic stabilization in basic conditions and were able to form multiple hydrogen bonds under acidic conditions. The branched architecture of the surfactants ensured multiple points of attachment to the droplet surface, while the dodecane chain ends mimicked the oil phase. Disassembly of the engineered emulsions was achieved by raising the pH of the continuous phase, leading to the rapid decomplexation of hydrogen bonds and electrostatic repulsion of anionic MA residues on the droplet surfaces. This disassembly resulted in reversion to conventional, dispersed, and non-interacting emulsion droplets (Figure 2b–d). The integrity of the individual emulsion droplets was confirmed through light microscopy, which showed that the droplets retained their structure without any demulsification observed after the disassembly process.

It was also discovered that the assembly of the droplets could be controlled by variations in the composition of the BCS (**Figure 3**). When the pH responsiveness of BCSs with differing ratios of MA and ethylene glycol (EG) residues (1:2 MA/EG and 1:1 MA/EG) were tested, there was no change in droplet dispersion observed at basic pH. This was attributed to simultaneous electrostatic and steric stabilization. At acidic pH, the droplets stabilized with 1:1 MA/EG BCS showed evidence of assembly whereas the 1:2 MA/EG BCS-stabilized droplets remained well dispersed. This behavior at acidic pH was attributed to the steric contribution of additional PEGMA residues in the 1:2 MA/EG BCS, preventing inter-droplet hydrogen bonding between MA and EG. Hence there is an opportunity to control the hydrogen bonding interactions in the emulsions by tuning the BCS structure. This study presented a novel strategy for the reversible assembly of stable and functional emulsion droplets into robust liquid structures. Engineered emulsions of this nature hold significant potential for applications requiring encapsulation and controlled delivery of large payloads.

Further work from Weaver and co-workers demonstrated that engineered emulsions with increased morphological and compositional complexity could be prepared using glucono-δ-lactone (GδL) while maintaining reversibility.[60] These systems used the homogenous lowering in pH caused by the hydrolysis of GδL in an aqueous solution as a trigger to create significant quantities of functional and responsive emulsion droplet assemblies. This switch was reversible, and the surface-functional emulsion droplet retained their structural integrity during the assembly/disassembly processes. Unlike conventional acidification methods, this approach enabled the monitoring of engineered emulsion kinetics using rheology, providing valuable insights. These advancements have the potential to facilitate the widespread utilization of this versatile encapsulation and reversible assembly process.

In 2011 it was reported that stable polymer-functionalized o/w emulsion droplets could be prepared with precise surface

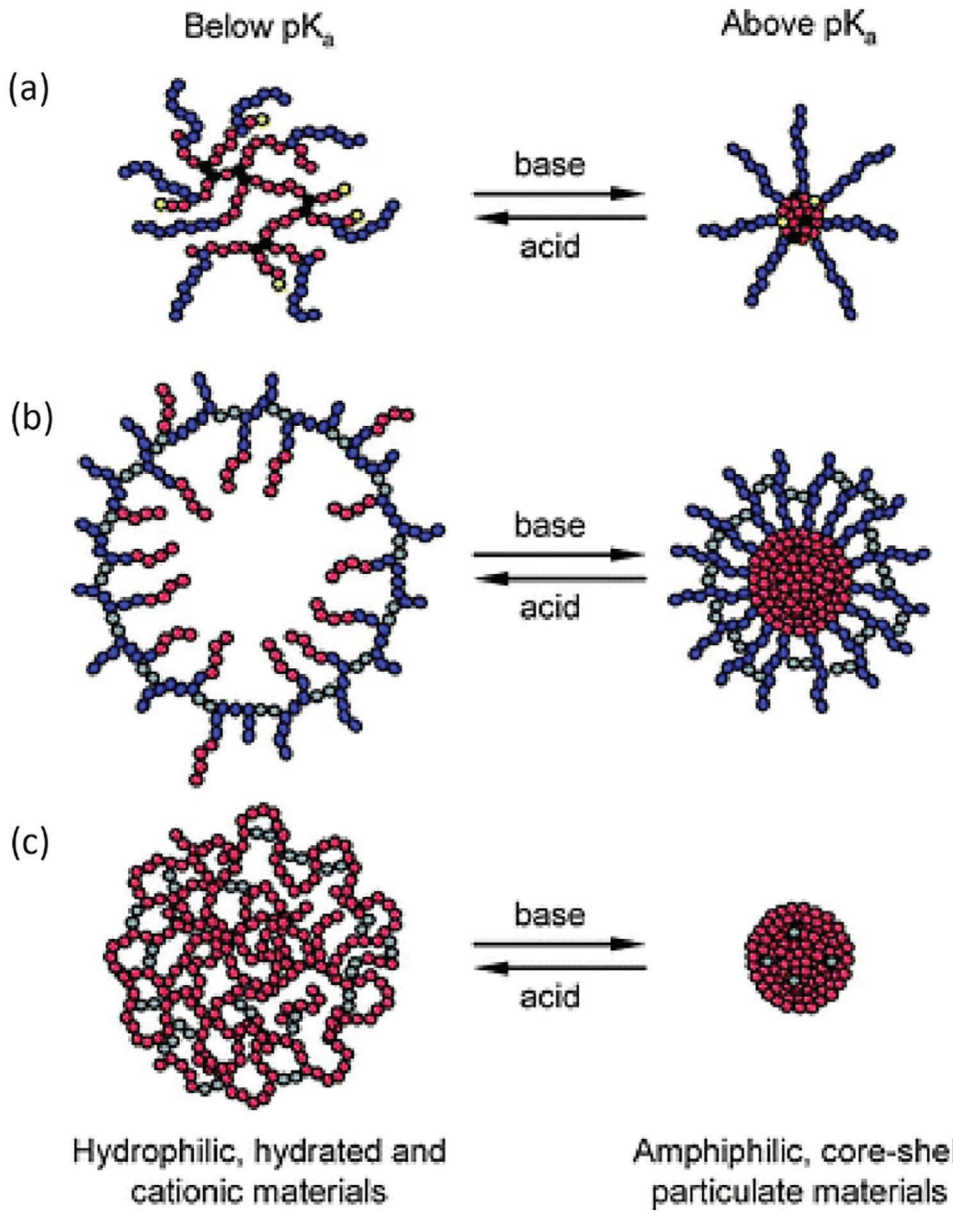

Figure 1. Schematic representing the behavior of pH responsive, tertiary amine-based a) branched copolymer nanoparticles; b) shell cross-linked micelles; c) microgels above and below their pKa in aqueous environments. Reproduced from Weaver et al.[57] with permission from The Royal Society of Chemistry.

compositions defined by branched copolymer surfactants.[55] The influence of composition, specifically the ratios of methacrylic acid (MA) to ethylene glycol (EG), on acid-triggered inter-polymer/inter-droplet hydrogen-bonding interactions was investigated. A series of branched copolymer surfactants with controlled compositions of methacrylic acid and PEGMA were prepared using a one-pot method. These copolymers were found to be highly efficient emulsifiers for stable o/w emulsions at basic pH. It was demonstrated that by varying the EG:MA ratio, the kinetics of inter-droplet interactions could be controlled, effectively switching between aggregated gel or dispersed liquid mediated by changes in pH.[55] BCSs with equimolar ratios of EG:MA promoted the fastest aggregation, whereas those with excess MA component retained droplet aggregation, but at slower rates. BCSs with excess EG residues prevented inter-droplet hydrogen bonding, eliminating droplet aggregation at acidic pH. Rheology studies showed that BCSs with higher MA content on droplet surfaces resulted in stiffer aggregated emulsion gels, with maximum structural integrity observed at stoichiometric EG:MA ratios. Hence, the study highlighted that the emulsion droplets stabilized with structurally similar branched copolymers, even with subtle functionality variations, can effectively control triggered inter-droplet interactions.

[56]Woodward and colleagues described the utilization of BCSs to stabilize emulsion droplets that served as templates for creating surface functionalized colloidal particles.[61] In these systems

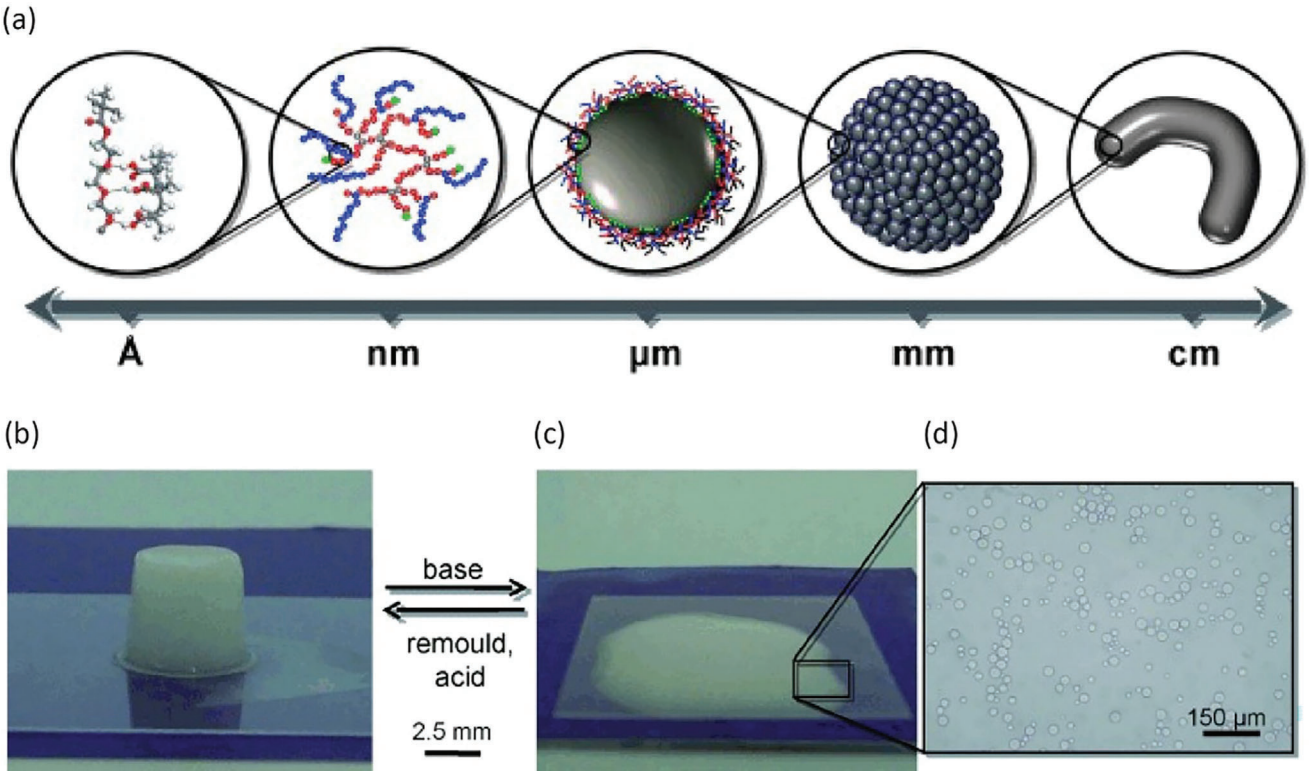

Figure 2. a) Schematic representing reversible hierarchical emulsion droplet assembly; b) templated monolithic assembly; c) disassembled monolith after addition of base; d) light micrograph of disassembled monolith. Reproduced with permission.[54] Copyright 2009 John Wiley & Sons, Inc.

the oil phase was a mixture of poly(methyl methacrylate) in ethyl acetate in which the emulsion droplets served as a template for the formation of poly(methyl methacrylate) colloids upon evaporation of ethyl acetate. The copolymers used had pH-responsive surface functionality that controlled their solution behavior, giving poly(methyl methacrylate) colloids which could disperse or aggregate to form macroscopic monoliths. The assembled colloids could be rehydrated and remained stable in aqueous acidic environment but disassembled at basic pH (**Figure 4**).[61] The colloids were capable of encapsulating hydrophobic molecules and forming macroscopic monolithic aggregates with controllable internal porosities. With further optimization, these structured biological scaffolds have potential for regenerative medical applications.

In a study conducted by Garcia-Tunon and co-workers, BCSs consisting of methacrylic acid (MAA) and PEGMA, were used for in situ surface functionalization of oil droplets. The systems consisted of smart organic particles of aluminium oxide (Al_2O_3) and silicon carbide (SiC) that could disperse or aggregate when triggered by pH (**Figure 5**).[62] Attachment and functionalization was achieved by three processes: 1) interactions between the hydrophobic chain ends (DDT) and the surfaces, 2) electrostatic interactions between the carboxylic anions in the MAA residues ($COO-$) and the positively charged particle surfaces, and 3) formation of chemical covalent bonds between the carboxylic residues and the metal oxides present on the particle surfaces. BCS functionalization enhanced the wettability of the surface of the ceramic particles resulting in an increased contact angle with water. The segregation of the amphiphilic polymer at the oil-water interface, caused flocculation at acidic pH and stabilization in basic conditions. This system could be used in a wide range of applications, such as injection moulding and tissue engineering due to their potential to fabricate highly porous materials and increase the strength of lightweight materials.[62]

Maçon et al. described the use of emulsion droplets as model-functionalized materials using electrostatic forces to induce the reversible synthesis of engineered emulsions.[63] Two distinct BCSs with polymers of 2-(sulfobenzoic acid) ethyl methacrylate (SHEMA) or poly(*N,N*-dimethylaminoethyl methacrylate) (DMAEMA) were independently synthesized, then blended. PDMAEMA was positively charged at acidic pH, whereas SHEMA was permanently negatively charged. It was shown that by altering the chemical composition of these BCSs, inter-droplet assembly can be driven by electrostatic forces. The aggregation of dispersed emulsion droplets was found to switch in a reversible manner when pH was increased or decreased with respect to the pKa of PDMAEMA. Due to their compact monomolecular structure and the presence of multiple hydrophobic anchoring sites, the BCSs demonstrated remarkable efficiency in maintaining the integrity of their associated emulsion droplets. There was no coalescence or separation of the droplets during the processes of aggregation and disaggregation. This innovative interaction mechanism observed in engineering emulsions holds significant promise as a model for investigating naturally occurring phenomena that involve dynamic electrostatic forces.

Molecular bottle-brushes (MBBs) formed from a polymethacrylate backbone with side chains of copolymerized pH-responsive poly(2-(N,N-diethylamino)ethylmethacrylate)

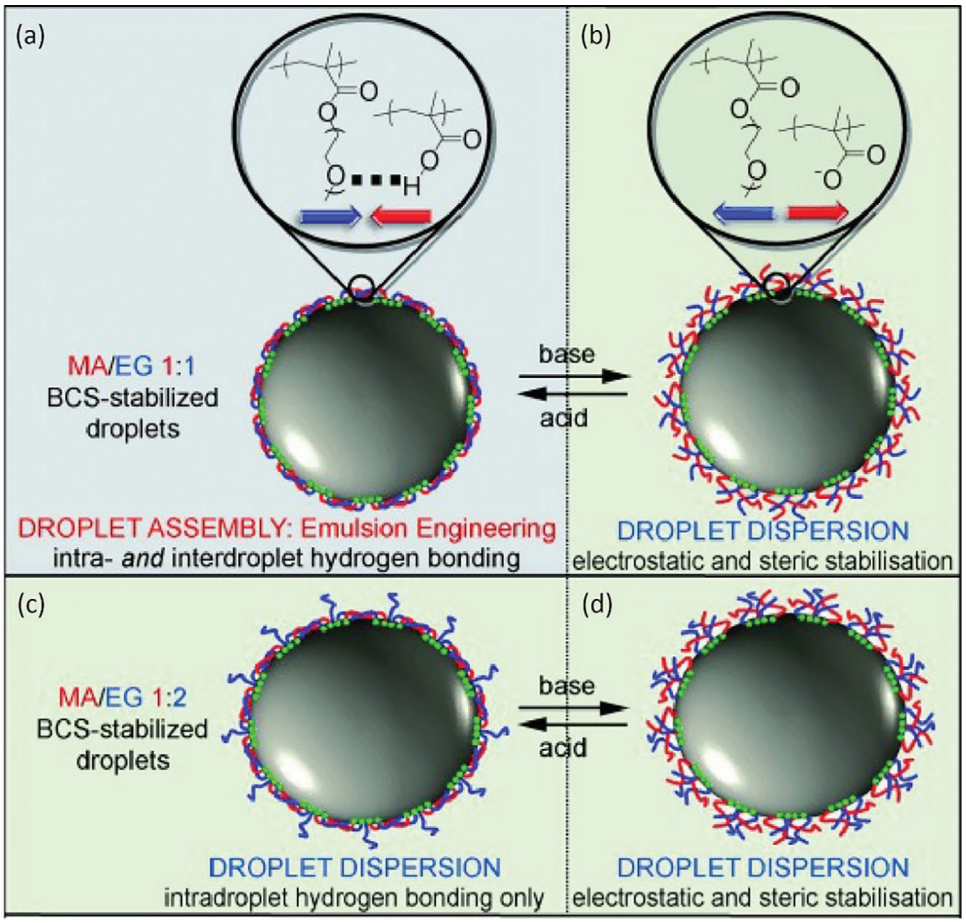

Figure 3. Impact branched copolymer surfactants (BCS) composition can have on inter-droplet interactions. a) Intra- and inter-droplet hydrogen bonding occurs at low pH for 1:1 MA/EG droplets, causing inter-droplet attraction and assembly; b) steric and electrostatic stabilization occurs at basic pH, inter-droplet repulsion occurs; c) additional steric contribution from 1:2 MA/EG prevents inter-droplet hydrogen bonding, inter-droplet repulsion therefore dominates at acidic pH; d) steric and electrostatic stabilization occurs at basic pH, inter-droplet repulsion occurs. Reproduced with permission.[54] Copyright 2009 John Wiley & Sons, Inc.

(PDEAEMA) and hydrophobic poly(n-butyl acrylate) are efficient pH-responsive emulsifiers at DEAEMA mole fractions of 0.2–0.5.[64] Water-in-toluene emulsions with excellent long-term stability were formed at pH 4 using the MBBs, in a condition where the DAEAEMA groups of the MBB were positively charged by the formation of a tertiary ammonium cation. In this state, the MBBs were believed to align at the water/toluene interface to allow access of protonated DEAEMA to the aqueous phase and n-butyl acrylate to the toluene phase. Elevating pH to 10.0 lead to demulsification, believed to be due to the reduced hydrophilicity of DEAEMA above its pK_aH which allows better MBB-toluene mixing and coalescence of oil droplets. The formation and

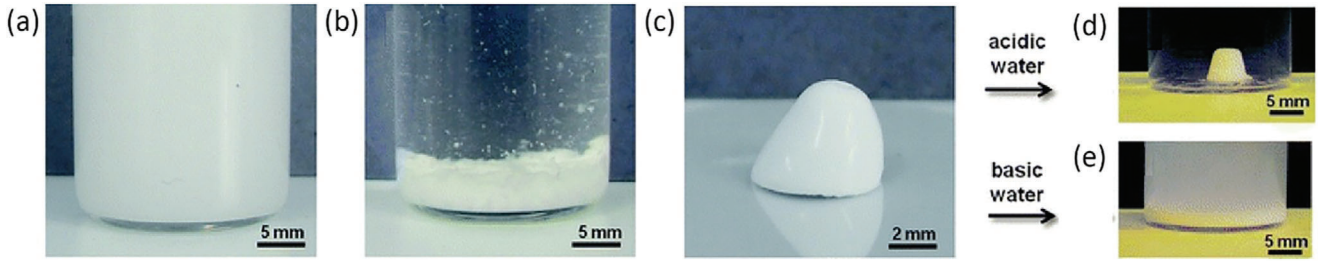

Figure 4. Images showing pH-responsive reversible colloid aggregation and monolith preparation. a) Surface-functionalized colloids dispersed at pH 10; b) aggregation and sedimentation 24 h after acidification of (a); c) monolith formed by centrifugation of (b); d) colloid monolith retaining its structure in water at acidic pH; e) monolith dispersed in water at basic pH. Reproduced from Woodward et al.[61] with permission from The Royal Society of Chemistry.

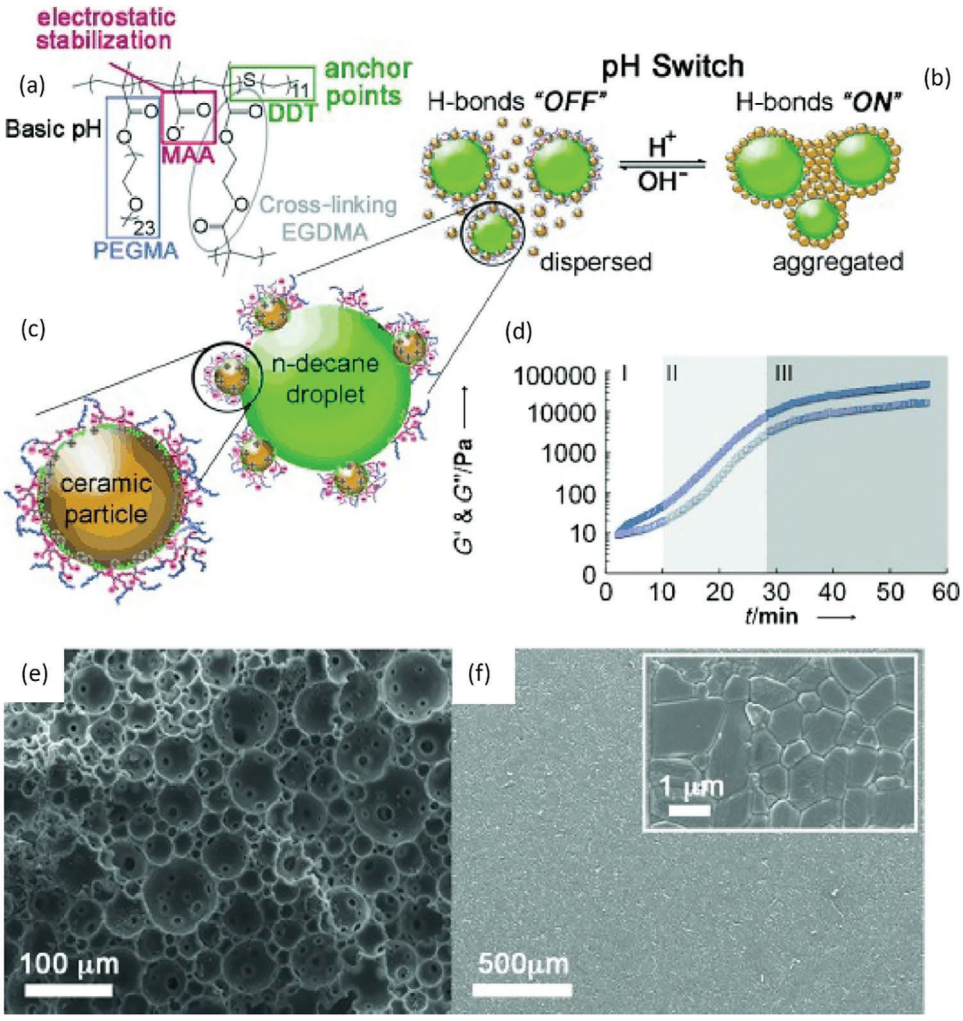

Figure 5. a) Structure of BCS, showing functionalities of each branch; b) schematic representing the assembly of BCS-functionalized ceramic particles in an o/w emulsified suspension, triggered by pH; c) enlarged view of BCS-particle-droplet and BCS-particle interactions; d) graph showing change in viscoelastic (G′,G″) properties of the emulsified suspension in response to change in pH. Particles and droplets are sterically and electrostatically stabilized at basic pH, with the MAA branches in anionic form, and the hydrogen bonds "OFF." When the pH becomes acidic, the MAA branches are completely protonated with the hydrogen bonds "ON." This allows functionalized particles and droplets to bond, forming a network; G′ (filled symbols) and G″ (open symbols) reach values above 20 kPa. e,f) Images of ceramic structures formed by pH-responsive self-assembly (e) porous SiC from an emulsion and f) sintered highly dense alumina obtained from a suspension). Reproduced with permission.[62] Copyright 2013, Wiley-VCH.

breaking of emulsions was repeated 10 times by switching from acidic to basic conditions, without detriment to the MBBs.

In 2017, Yunhua and researchers presented a method for the reversable assembly of emulsion micro-droplets stabilized by a graphene oxide/polyvinyl alcohol (GO/PVA) hybrid.[65] This was achieved by regulating the hydrogen bonding interaction between the two materials, which was controlled by the ionization of COOH groups on the GO surface. By injection moulding, the assembled emulsion droplets in an acidic state could be shaped into various macroscopic objects with a high degree of morphological control. Under basic pH condition, the assembled emulsion aggregates could be disassembled back into dispersed droplets due to reversible hydrogen bond interactions. The macroporous composite hydrogel produced by utilizing GO/PVA o/w stabilizer demonstrated biocompatibility and controlled release of doxorubicin (DOX) over a period of 10 h. At pH 7.4, a slower release profile of DOX was observed compared to the release profile at pH 4.0. The release properties exhibited potential as a carrier to deliver anti-neoplastic agents as most of the drugs can retain within the hydrogel at normal physiological pH conditions, while effectively releasing in acidic medium.[65]

pH-responsive emulsions stabilized by xanthan gum and shellac have been studied by Patel and co-workers.[66] Here, a reversible mechanism of transition between a flocculated and a stable state at acidic and neutral pH were reported (**Figure 6a**). The solubility of shellac is pH-dependent, a feature that has been used widely in the pharmaceutical sector to develop enteric release systems. Shellac can be dissolved at alkaline pH due to the presence of a significant number of hydroxy fatty acids in the resin, but it is practically insoluble at acidic pH. Because of shellac's acid resistance, colloidal particles generated at neutral to alkaline pH display instant aggregation in acidic medium. Considering the

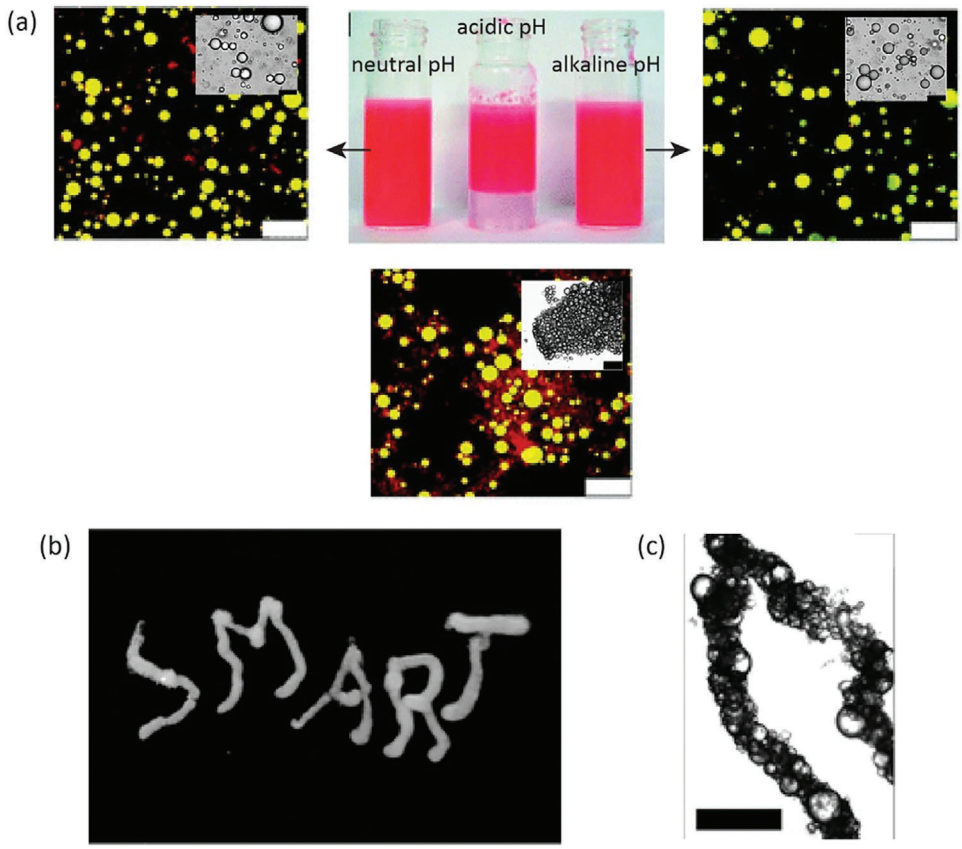

Figure 6. a) Confocal microscopy images of emulsion (10 wt% oil stabilized using a 1:1 w/w XG:SL mixture). *Left*: stable emulsion prepared at neutral pH. *Middle*: flocculated emulsion after acidification. *Right*: stable emulsion neutralized back to neutral pH (scale bars = 50 μm); b) photograph of concentrated emulsion extruded using a syringe and needle in an acidic environment (60 wt% oil stabilized with 1:1 w/w XG: SL mixture); c) microscopy image of extruded strand showing emulsion droplets (scale bar = 400 μm). Reproduced from Patel et al.[66] from The Royal Society of Chemistry.

pH-dependent solubility profile of shellac, the o/w emulsion was stabilized by colloidal interaction of Xanthan gum (XG) and shellac (SL) at the oil-water interface. The stable emulsion prepared at neutral pH showed instant flocculation on changing the pH to acidic (≈1.2); neutralizing the pH back to 7.2 resulted in switching the emulsion back to the stabilized colloidal state (Figure 6). Acidification caused the XG : SL network to undergo phase separation, resulting in the flocculation of the emulsion. However, upon restoring the pH back to neutral, the XG : SL became redispersed in the bulk phase, thereby stabilizing the emulsion and leading to the formation of distinct oil droplets. The ability of these emulsions to undergo pH-dependent flocculation was exploited to control the assembly of oil droplets into desired shapes by extruding the emulsion using a syringe and needle in an acidic medium (Figure 6b,c). Thus, this study demonstrated a straightforward way to utilize pH-triggered flocculation of emulsions to produce soft structures with controlled shapes.[66]

High Internal Phase Emulsions (HIPE) are concentrated emulsion systems with a large volume fraction (>0.74) of dispersed phase.[67] HIPEs are both kinetically and thermodynamically more unstable than conventional dilute emulsions. However, metastable emulsion systems of this nature that show no variation in appearance and properties over a lengthy period have been produced.[67] In 2010, Ngai and colleagues reported emulsion inversion from standard o/w emulsion to w/o HIPE at oil:water ratios of 23:73. This inversion was mediated by pH-responsive colloidal particles made from a polystyrene and poly(methacrylic acid) copolymer.[68] At a constant oil:water ratio, the inversion from o/w to w/o could be easily initiated by lowering the pH or the addition of salt.

Core cross-linked star (CCS) polymers of PDMAEMA have been employed as emulsifiers for the fabrication of gelled o/w HIPEs.[2] CCS polymers, consisting of small central cores attached to hydrophilic polymer "arms," have been shown to decrease the interfacial tension between water and oil in a pH-dependent manner.[69,70] An et al. synthesized pH-responsive PDMAEMA CCSs which were used to manufacture gelled HIPEs at high oil volume fractions, ranging from 80 to 89 vol%. The emulsion properties such as oil droplet size, long-term stability and rheology were all found to be influenced by pH. At low pH, the PDMAEMA CCSs are heavily protonated and exist as distinct entities, at high pH (>8.0) the degree of protonation of the polymer decreases and the CCSs are present as loose aggregates. This switch results in complete demulsification of the HIPEs upon addition of base to the system. Stable emulsions can be reformed by returning to acidic pH (2.0) and re-applying a shearing force. It was postulated that CCS polymers could serve as a link between linear polymers and colloidal particles.[70]

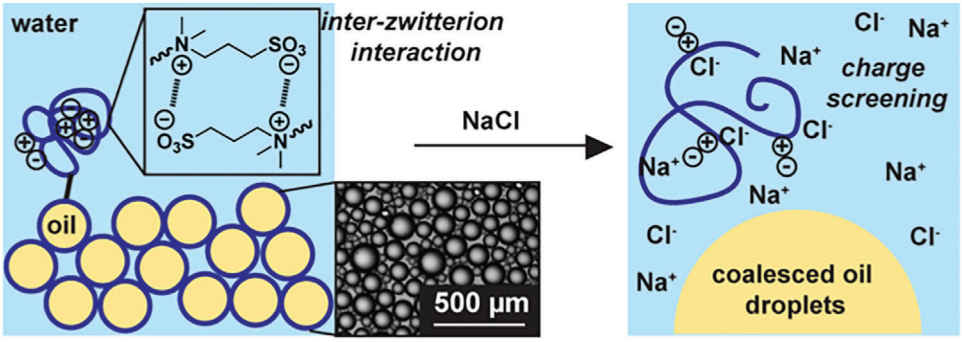

Figure 7. Schematic illustration of oil-in-water emulsion stabilized by polySBMA in pure water and their destabilization upon the addition of salt. Adapted with permission from Macromolecules 2015, 48, 21, 7843–7850. Copyright 2015 American Chemical Society.

2.2. Salt-Responsive Polymers in Emulsion Engineering

The ability to switch from unionized to ionized forms underpins the behavior of pH-responsive emulsions, however ionized polymers may also be used to give salt-responsive phase changes, particularly in zwitterionic systems. Polymer zwitterions are characterized by their covalently linked cationic and anionic functionalities that give charge neutrality throughout the polymer chain.[71] Furthermore, zwitterion-zwitterion pairing can occur between the oppositely charged groups of zwitterions in close proximity, giving rise to intra- and inter- molecular associations which can ultimately dictate physical properties of a system. However, the ionic nature of these associations makes them prone to dissociation in the presence of salt solutions which screen charge. Ultimately, resultant effects include improved solubility and intrinsic viscosity through expansion of the polymeric zwitterion chain.[72]

Chang et al. described the synthesis and interfacial fluid behavior of sulfobetaine methacrylates (polySBMA) with and without grafted alkene/alkyne functionality onto the zwitterionic subunits (**Figure 7**).[73] PolySBMA was able to stabilize emulsions simply by shaking an aqueous solution of PolySBMA in the presence of 1,2,4-trichlorobenzene to afford an oil-in-water dispersion. The addition of 0.1 mL of 1 M NaCl to emulsion droplets stabilized by polySBMA caused coalescence within 1 h. Direct attachment of alkene and alkyne groups to the zwitterionic moiety allowed the incorporation of up to 50 mol % functionality without hindering salt-responsive behavior. Furthermore, capsule formation was enabled by reaction of the alkene/alkyne units post-emulsion formation using 2,2′-(ethylenedioxy)diethanethiol with UV irradiation.[73]

Chalarca and co-workers exploited salt-responsive aggregation in polymer zwitterion stabilized o/w droplets, which were amenable to processing into macroscopic, supracolloidal fibers by extrusion into aqueous media (**Figure 8**).[74] The polymer zwitterions were hydrophilic, biocompatible, and non-interacting. The droplet-based materials exhibited responsiveness, such as disaggregation when the salt concentration was increased, and rheology controlled by salt concentration and polymer composition. The ability to translate polymer zwitterions' solution properties to fluid–fluid interfaces, supracolloidal fibers, and bulk soft materials was demonstrated. It was anticipated that such soft assemblies could be employed as model systems to better understand how different stimuli affect self-interacting soft objects like tissues or cell aggregates.[74]

2.3. Thermoresponsive Polymers as Emulsifiers

Thermoresponsive polymers are stimuli-responsive macromolecules that modify their physical properties in response to temperature. Typically, the solubility of some of the constituent units varies with temperature, promoting polymer-polymer interactions only at specific temperatures. This phenomenon is considered to be related to the ratio of hydrophilic to lipophilic moieties on the polymer chain and is governed by the thermodynamics of mixing.[75] Thermoresponsive polymers can be classified into two groups based on their temperature response type: lower critical solution temperature (LCST) and upper critical solution temperature (UCST). LCST-type polymers that are insoluble above a critical temperature, and UCST-type polymers precipitate or become insoluble below a critical temperature.[76]

UCST phase separation is driven primarily by attractive enthalpic factors, whereas LCST phase separation is driven by the entropy of the system. At the LCST, a positive change in the entropy of water molecules in the system occurs as they adopt a less ordered arrangement, this increase in entropy surpasses the enthalpy associated with water molecules hydrogen-bonded to the polymer.[76] Since temperature alterations shift the entropy of solvation of the polymer chains in an aqueous solution, LCST-type polymers exhibit rapid, sharp, and reversible phase transitions.[77] Polymers of this nature are fully soluble in water below the LCST; usually the solvated polymer chains adopt random coil conformations due to hydrogen-bonding interactions between hydrophilic polymer moieties and surrounding water molecules. Above the LCST, hydrogen bonds between the polymer and solvent are broken, and the hydrophobic effect dominates. The hydrophobic clustering of polymer chains leads to phase separation, which enables polymers to self-assemble and aggregate in aqueous solutions.[78] Macroscopically, a polymer solution at the LCST undergoes a phase transition from clear to cloudy (on the condition that the aggregates formed are sufficiently large to scatter light), this is also referred to as the clouding temperature or cloud point (Tc). In contrast a UCST-type polymer solution will exhibit a change from a turbid suspension to a transparent solution at the critical temperature point.[79]

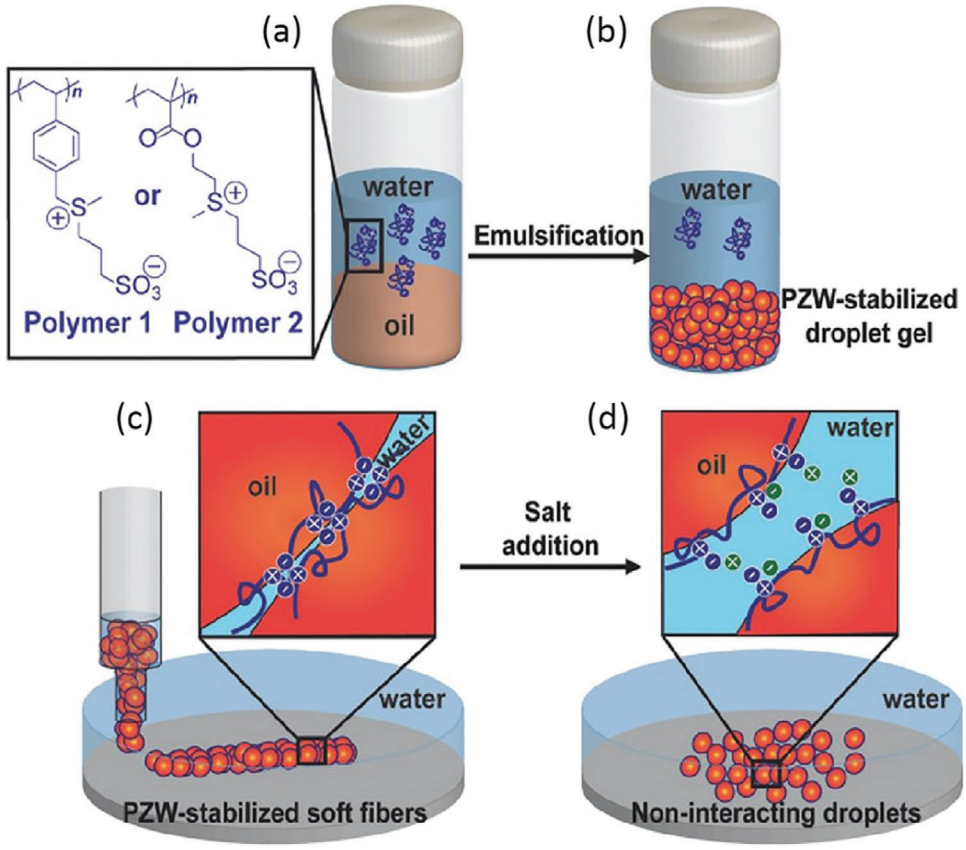

Figure 8. Schematics of the process for creating soft fibers using PZW-stabilized droplet extrusion; a) polymers 1 and 2 dispersed in water and mixed with oil; b) following emulsification and sedimentation, a PZW-stabilized droplet gel is produced; c) after discarding the supernatant, the droplet gel is extruded through a syringe and needle into water to produce supracolloidal fibers; d) the addition of salt triggers fibre disaggregation. Reproduced from Charlaca et al.[74] Copyright 2018, Wiley-VCH.

Thermoresponsive polymers have various applications; in recent years their potential for use in drug delivery systems has garnered much attention.[80–82] Polymers that exhibit thermoresponsiveness within the human physiological temperature range (≈37 °C) are particularly useful for in vivo drug delivery applications.[75] LCST polymers can be used for both sustained and/or targeted drug delivery systems.[83,84] Below the LCST, a LCST-type polymer will be hydrated and swollen, creating a mesh-like structure that hinders drug diffusion. As the temperature increases above the LCST, the hydrophobic effect becomes dominant and the polymer structure collapses. As a result of the loss of the mesh-like structure, drug molecules are released. Mechanisms of this nature enable precise, temperature-controlled drug release rates. Additionally, polymers with a LCST above body temperature can be utilized for rapid drug release at a target site. In these systems, localized hyperthermia techniques, such as infrared irradiation or microwaves, can be applied to trigger a precise local release from a drug-loaded polymer.[85,86] This feature allows for spatiotemporal control over drug delivery, which is highly advantageous for targeted therapy. Another important factor to be considered when using polymers in vivo is the excretion pathway, toxicity, and degradation characteristics. An ideal polymer would be non-toxic, biodegradable, and, if non-biodegradable, have a size and structure that would allow for renal excretion.[87,88] Hence, the aqueous compatibility of LCST-type polymers is also considered to be advantageous for drug delivery applications. LCST polymers are typically water soluble below the LCST, this simplifies their administration as they can flow through needles and plunged through applicators.

Whilst LCST polymers are used more frequently for drug-delivery applications, UCST polymers can also be used, offering their own unique applications and advantages. For example, since UCST polymers often have better solubility in organic solvents compared to water, organic solvents may be used to trigger phase transitions in UCST polymers. This characteristic provides an alternative triggering mechanism for drug-release.[89] Another notable feature is the compatibility with hydrophobic drugs. Since UCST polymers are hydrophobic in their insoluble state, they can effectively encapsulate and deliver hydrophobic or lipophilic drugs that are poorly soluble in aqueous environments.[90,91] Despite these attractive properties, the use of UCST polymers is currently limited for drug delivery applications due to several factors. First, the UCST is often above the physiological temperature range; this presents a challenge for in vivo uses and requires an external heat source.[91,92] Second, UCST-type polymers often lack physiological relevance and have limited biocompatibility.[93,94] UCST polymers also face challenges in their formulation and stability; below the UCST, UCST-type

polymers exist as two phases, these biphasic mixtures can result in aggregation or precipitation of drug-polymer formulations which may lead to premature drug release.[95] Compared to LCST polymers, there are fewer UCST polymers available with well-defined and controllable UCST values. This limits the design flexibility and choices for UCST-based drug delivery systems and wider utilization of LCST polymers in drug delivery applications.

Polymer solutions that are capable of transforming to a gel state with an elevation of temperature above a critical point (T_{gel}) are termed as "thermoreversible gels" or "thermogelling materials."[96] A sol-gel transition occurs after heating a thermoreversible gel beyond a critical temperature, affected by an overall increase in hydrophobic units above the LCST, triggering self-assembly processes and physical interaction which increases the viscosity of the system.[97] Prior literature has divided these materials into two types: the first class depends on a hydrophilic/hydrophobic balance and the second depends on a temperature-responsive polymer component.[97] Factors such as polymer architecture, molecular weight, additives, and polymer concentration are crucial in tuning the gelation properties of LCST-exhibiting thermoreversible gels.

Verbrugghe et al. developed temperature-responsive poly(*N*-vinylcaprolactam) (PVCL)-based graft copolymers and studied their emulsifying properties.[98] It was discovered that below the cloud point temperature, the copolymers acted as amphiphilic stabilizers however, above the LCST the emulsions broke down due to the copolymers no longer being able to stabilize the emulsion. Koh and Saunders further reported the behavior of emulsions stabilized by a thermoresponse graft copolymer, PNIPAM-*co*-PEGMA, which instead of emulsion breaking, led to temperature-triggered gelation.[99] It was proposed that the mechanism for emulsion gelation involved flocculation triggered by the collapse of the adsorbed PNIPAM-*co*-PEGMA layer at temperatures above the solution LCST. Higher temperatures led to stronger flocculation due to a decrease in copolymer layer thickness. The collapse of the adsorbed layer created a rigid interface that prevented coalescence of the flocculated droplets. The reversibility of the gelation process was attributed to the interpenetration and entanglement of interfacial copolymer chains. Hence, the use of PNIPAM-*co*-PEGMA graft copolymers enabled temperature-induced reversible gelation of o/w emulsions switching from a liquid emulsion to a highly viscous gel.

Following this study, Koh and colleagues studied temperature sensitive emulsions stabilized with poly(N-isopropylacrylamide)-*co*-poly(ethyleneglycol methacrylate) (PNIPAM-*co*-PEGMA) graft polymers, then performed a rheological analysis on the emulsions to assess thermo-reversibility.[100] When heated, the viscosity of the emulsions decreased and then significantly increased at 48 °C, exhibiting gelation due to flocculation between neighboring droplets, forming a network that entrapped the aqueous phase. The strength of the network increased with temperature and the emulsion gelation was both reversible and sensitive to shear. The reversible gelation phenomenon was observed for various oil phases such as toluene, poly(dimethylsiloxane) and perfluorodecalin and had significant technological implications in transforming fluid emulsions into gels using temperature as the trigger. This study provided a comprehensive rheological investigation of temperature-induced gelation in o/w emulsions stabilized by PNIPAM-*co*-PEGMA, revealing its unique behavior and potential applications in the field of emulsion technology.

Using poly(ethylene oxide) (PEO) star polymers as emulsifiers synthesized via atomic transfer radical polymerization (ATRP), Saigal et al. formed stable emulsions with temperature-sensitive microstructure and rheology.[101] When heated above the cloud-point then cooled to room temperature, the emulsions contained mostly flocculated droplets and showed gel-like rheological activity with rises in both the viscous and elastic moduli compared to the original emulsion. Emulsions made at the same high temperature and cooled to room temperature behaved differently, with non-flocculated droplets, more liquid-like rheology, and lower viscous and elastic moduli than emulsions made at room temperature.

Feng et al. synthesized di(ethylene glycol) methacrylate (DEGMA) and PEGMA thermoresponsive surfactants via ATRP where the LCST could be tuned between 90 and 28 °C by altering the molar ratio of the monomers. A copolymer with a molar ratio of 8% PEGMA and 92% DEGMA, displaying a LCST of 34 °C, was selected for further studies. It was discovered that below the LCST the surfactants were able to stabilize the emulsion for up to 4 months. Above the LCST, a viscous immiscible phase was formed at the oil-water interface due to the collapse of the hydrophilic block of the surfactants.[29]

In a study conducted by Iwasaki et al., an o/w emulsion was stabilized by the addition of poly[2-isopropoxy-2-oxo1,3,2-dioxaphospholane] (PIPP) functionalized cellulose nanocrystals (CNCs).[102] Studies of the CNC-g-PIPP stabilized emulsions found that different concentrations of grafted particles resulted in different droplet sizes. Additionally, studies showed that the emulsions exhibited superior stability against coalescence compared to those stabilized with unmodified CNCs. Since PIPP exhibits thermoresponsive behavior, the systems were examined over a range of temperatures. At 4 °C stable heptane-in-water emulsions were formed due to strong adsorption of CNC-g-PIPP at the oil-water interface. However, the emulsions disintegrated rapidly at 45 °C, as the hydrophobized CNC-g-PIPP desorbed from the interface (**Figure 9**). This thermally-induced reversible emulsification/demulsification showed a promising alternative for controlling emulsion stability in response to temperature, especially for biomedical applications.

Combining the concept of "engineered emulsions" and HIPE gels, it was demonstrated by Chen and co-workers that altering the amount of nanogel particles used can change the mechanical strength of HIPE hydrogels.[103] The HIPE hydrogels were synthesized from aqueous PNIPAM nanogel dispersions and were non-covalently crosslinked by 2-ureido-4[1H] pyrimidinone (UPy) quadruple hydrogen bond groups. The addition of UPy hydrogen bonding crosslinks resulted in HIPE gels with thermoresponsive activity. By using injection moulding, it was shown that the HIPE hydrogels could be formed into reconfigurable shaped objects. Furthermore, because of the PNIPAM's LCST behavior, the structures could shrink significantly at high temperatures, permitting triggered delivery of guest molecules.In 2022, Da Silva and co-workers reported a new generation of thermoresponsive engineered emulsions stabilized with BCSs.[104] The BCSs consisted of thermoresponsive PNIPAM, hydrophilic PEGMA, an ethylene glycol dimethylacrylate (EGDMA) crosslinker, and a hydrophobic chain transfer agent 1-dodecanethiol

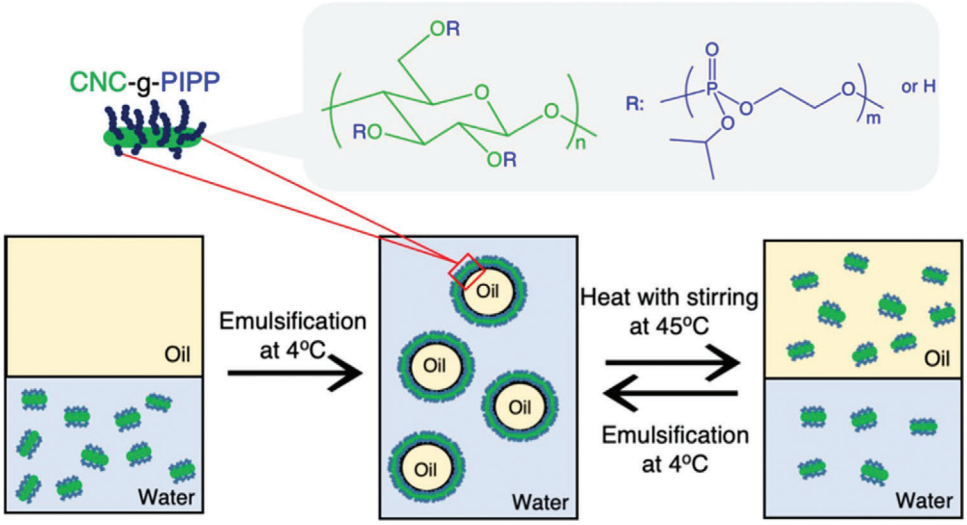

Figure 9. Schematic showing hypothesized mechanisms for reversible emulsification/demulsification of CNC-g-PIPP-stabilized emulsion. Reproduced from Langmuir 2019, 35, 35, 11 443–11 451.[102] Copyright 2019, American Chemical Society.

(DDT). The BCSs were found to effectively stabilize o/w emulsions whilst also exhibiting thermoresponsive behavior, undergoing a switch to non-flowing gels upon heating. The thermorheological properties of the emulsions stabilized with these BCSs were studied using shear oscillatory rheology. Small angle neutron scattering (SANS) and neutron reflectivity (NR) techniques were employed to investigate the nanoscale morphology of the BCSs above and below the transition temperature. Above its LCST, PNIPAM transformed from a swollen to a collapsed coil structure, resulting in a change in the thickness of the emulsions. The influence BCS molecular weight had on this behavior was also investigated. It was determined that addition of BCSs with low number average molecular weight (M_n) resulted in emulsions which thinned above the LCST (≈32 °C), those with higher M_n (>7.0 kg mol^{-1}) were found to thicken irreversibly. At 45–50 °C, a second thickening event occurred, which was attributed to the BCS phase separation. SANS and NR experiments indicated that BCS micelle-like aggregates were present in the aqueous phase alongside a layer of BCS at the oil/water interface. A mechanism for gelation in thermo-thickening engineered emulsions was hypothesized, which involved the collapse of PNIPAM above its LCST. This collapse resulted in polymer-polymer interactions causing aggregation of BCS clusters (**Figure 10**). In emulsion systems, these polymer-polymer interactions also occur between the nanoaggregates within the emulsion bulk and the polymer present at the interface, forming bridges that contribute to the elastic properties of the gel. These emulsions demonstrated successful thermoreversible gelation; however, the gel state was relatively weak, with a storage modulus (G′) of ≈30 Pa.

BCS with poly(diethylene glycol methyl ether methacrylate) (poly(DEGMA)) thermoresponsive moieties have been developed in an attempt to access new BCS architectures with preferable properties relative to PNIPAM systems (Figure 9).[105] It was found that poly(DEGMA) BCS-stabilized emulsions gave the desirable thermoreversible sol-gel transition (**Figure 11**) but that linear equivalents (i.e., without branching) could not elicit the sol-gel transition. The importance of the BCS architecture was also demonstrated by switching hydrophobic (and tensioactive) dodecyl chain ends with hydrophilic termini by the use of 2-mercaptoethanol in place of dodecanethiol, which led to a loss of thermoresponsive sol-gel events. Furthermore, *Mn* was vital for the stiffness of the gel, with G′ exceeding 300 Pa in the highest molecular weight systems (≈21 kg mol^{-1}). Interestingly, the poly(DEGMA) BCS system forms nano-aggregates that have the shape of oblate ellipsoids (akin to a flying saucer) and grow anisotropically, largely in the equatorial direction, upon heating.

Poly(DEGMA) BCS can not only elicit gelation, but also temperature-triggered emulsion breaking, dependent upon composition.[106] The PEGMA component (indicated in blue on the schematic, Figure 10) controls this function. Short PEGMA chains (<500 g mol^{-1}) lead to emulsion breaking whereas a longer chain (950 g mol^{-1}) allows gelation due to the greater stability of the system when a larger hydrophilic stabilizing block is present. Furthermore, the PEGMA/DEGMA ratio can tune gelation temperature. It was also found that these poly(DEGMA) BCS emulsions could be improved by the addition of methylcellulose, which extended the temperature range over which the gel phase was stable and greatly improved stability.[107]

Recent advances in the understanding of connectivity between emulsion droplets stabilized by PNIPAM microgels behavior further support mechanistic models of BCS systems.[108] Rey et al. demonstrate that stimuli-responsive emulsion breaking in o/w emulsions stabilized by PNIPAM microgels is primarily determined by interactions between interfaces rather than laterally across the interface. Cry-SEM and Brownian dynamics simulations illustrated important duality in microgel systems as a function of cross-linking density. “Hard” microgels with high cross-link densities with limited deformability formed core-corona structures which stabilized emulsions even above the volume phase transition temperature. Linear PNIPAM, however, produced emulsions which were unstable at all temperatures due to a weak interface. A balance of polymer/colloid behaviors can be observed in microgels with low cross-linking densities, which have the stabilizing power of a colloid, with the deformability

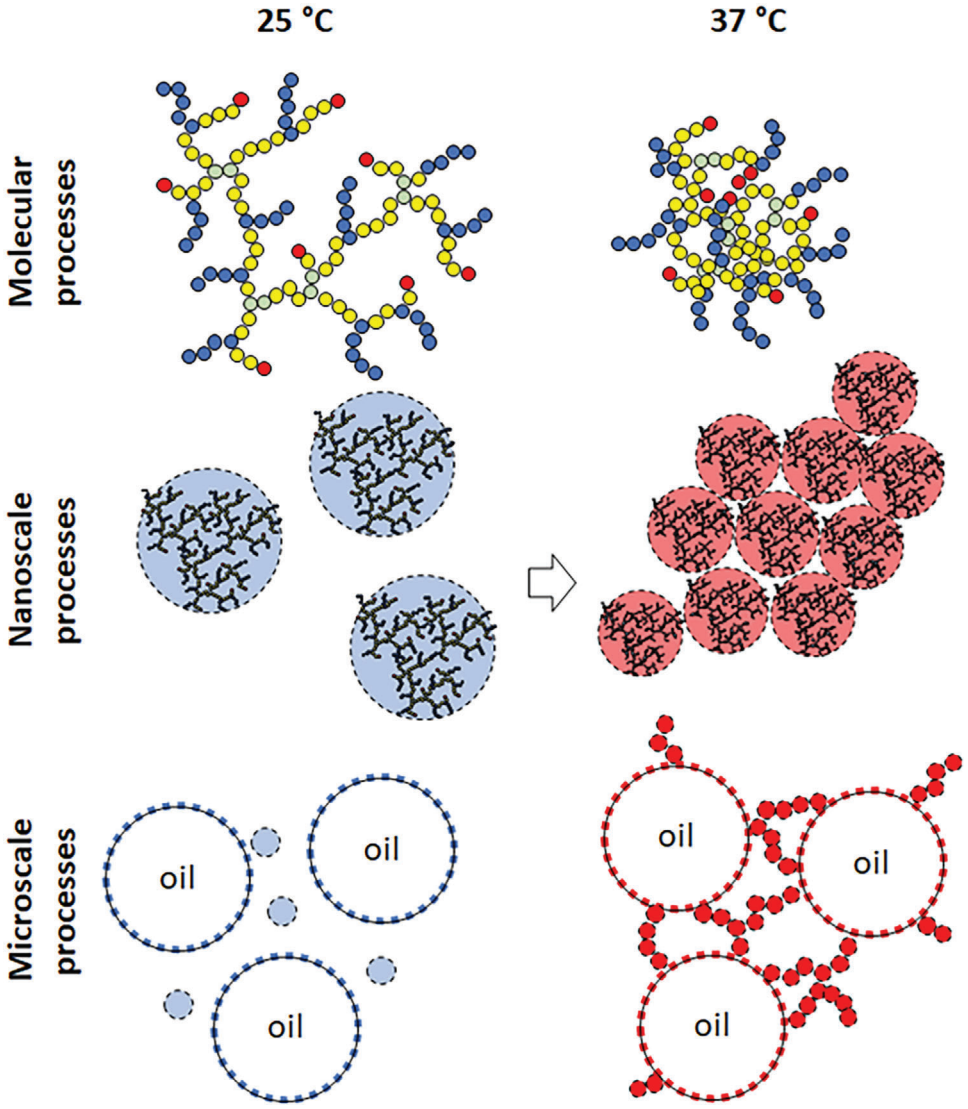

Figure 10. A hypothesis on the mechanism of gelation in thermoresponsive engineered emulsions stabilized with BCSs. Reproduced with permission.[104]

of polymer systems. Above transition temperature, flattened microgels collapse into a thin film, which is insufficient to prevent coalescence, permitting thermoresponsive breaking of the emulsion. Simulations show an negative osmotic pressure even for two microgels in this condition, that is, that there is an attraction vertically between interfaces. Indeed, for flocculated emulsions, it was demonstrated that microgels shared by two interfaces in a floc induce an attractive force above transition temperature, leading to coalescence.

Thermoresponsive emulsions exhibiting sol-gel transitions can also be exploited to generate nanodispersions in polymer solids. Chen and Doyle demonstrated an innovative concept of dissolving drug (fenofibrate) in anisole prior to dispersion in hydroxypropylmethylcellulose (HPMC) to form a nanoemulsion which is then heated, inducing a sol-gel transition which sterically stabilizes the emulsion as the system dries (**Figure 12**).[109] The resultant film contained up to 63 wt% drug by mass in the most stable polymorph, but with drug domain sizes of ≈600 nm. A result of this nanodispersion is a large increase in the dissolution rate, which is linked to improved rates and extents of absorption in vivo. The concept has also been extended to core-shell structures by inclusion of calcium chloride in a thermogelling methylcellulose (MC) emulsion which is then dripped into hot aqueous alginate solution to induce MC gelation (due to heat), with concomitant coating with an alginate shell due to the diffusion of Ca^{2+} ions from the matrix.[110]

2.4. Dual Responsive Emulsions

Dual-stimuli responsive systems combine two stimuli to give further control points over material behavior. Whilst these behaviors are scientifically interesting and open up the toolbox of materials available to scientists, they do pose significant challenges. For

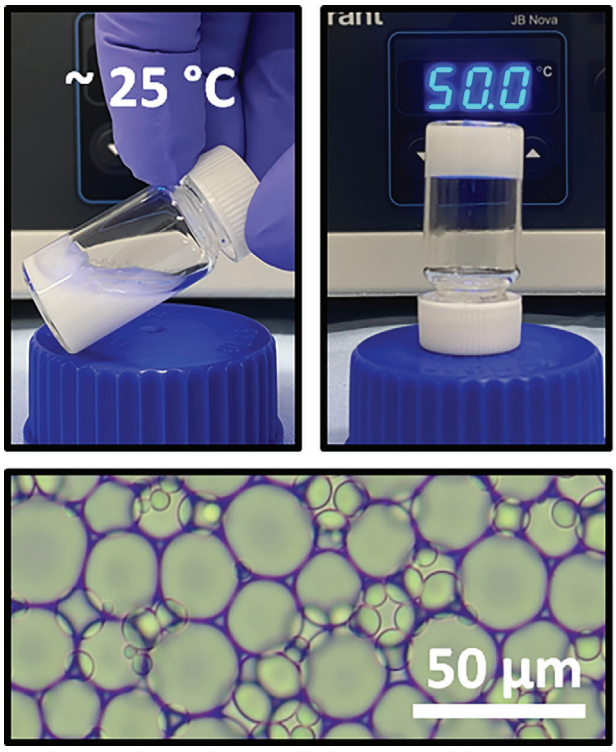

Figure 11. Poly(DEGMA) BCS can stabilize emulsions which then have a sol-gel behavior upon heating (top), without coalescence of emulsion droplets (bottom). Reproduced from Rajbanshi et al.[105]

example, combining pH-response with thermoresponsive behavior leads to a system with a two-factor behavior space for each material composition, meaning that exploration and precise control becomes complex. There are, however, specific applications where the ability to induce two separate behaviors with different triggers is desirable for emulsion systems.

In 2008, Brugger and colleagues explored the stability and effective break-down of PNIPAM-*co*-MAA microgel-stabilized emulsions to identify dually responsive emulsions.[17] In these systems, polarity of the oil determined how the emulsion responded to changes in pH and temperature. The emulsions were destabilized only when both the pH was reduced and the temperature increased to well above the volume phase transition temperature of PNIPAM. Rheology results showed that the interface was extremely elastic at low temperature and high pH, and thus the emulsion was stabilized. A transition from a highly elastic to a less elastic interface at pH 5 indicated that weakly acidic MAA groups played a significant role in the elastic properties. Successive increases in temperature and decreases in pH value led to the break-down of the emulsion, resulting in destabilization. The water/oil ratio and microgel concentration were found to affect the stability and type of emulsion formed, with o/w being the favored stable form for PNIPAM-*co*-MAA microgel-stabilized heptane-water emulsions.

Yamagami and researchers synthesized micrometer-sized, monodisperse, non-spherical poly(methyl methacrylate)/poly(styrene-2-(2- bromoisobutyryloxy)ethyl methacrylate)-graft-poly(2-(dimethyl amino)ethyl methacrylate) (PMMA/PS-BIEM-g-PDM) Janus particles for use as emulsifiers.[111] Particles obtained in the 5-wt% PS-BIEM system had a closed mushroom-cap-like PDM layer that reversibly responded to temperature and pH (**Figure 13**). With control over the hydrophilic/lipophilic balance, the dual stimuli non-spherical particles effectively acted as a particulate surfactant, resulting in a solid 1-octanol-in-water emulsion. At pH 5.5, the opened mushroom-cap was so hydrophilic that the particles could not adsorb at the interface and the emulsion was destabilized. However, the PDM phase had a strong affinity for 1-octanol at pH values of 5.8 and 6.0, resulting in the particles acting as particulate surfactants. By further increasing the pH to 6.5 the droplets collapsed, indicating the necessity of appropriate hydrophilicity. In addition to pH, the PDM phase became lipophilic with the rise in temperature above

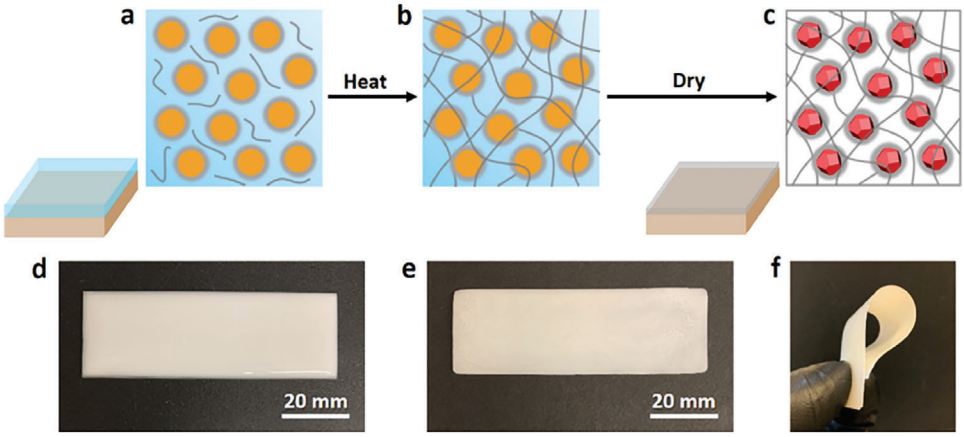

Figure 12. Film-forming process based on a thermogelling nanoemulsion. a) Nanoemulsion loaded on a glass slide at room temperature bearing drug-loaded oil domains in an HPMC solution. b) Heating the system induces gel formation and stabilizing the emulsion against coalescence. c) Drug domains remain in the nanodispersion after drying into the HPMC matrix. (d) Nanoemulsion on a glass slide prior to drying. e,f) The oral film detached from the glass slide post-drying. Reproduced with permission from Attia, L., Chen, L. H. & Doyle, P. S. Orthogonal Gelations to Synthesize Core–Shell Hydrogels Loaded with Nanoemulsion-Templated Drug Nanoparticles for Versatile Oral Drug Delivery. Adv. Healthc. Mater. 34, 11, 2301667, (2023). Copyright 2023 American Chemical Society.

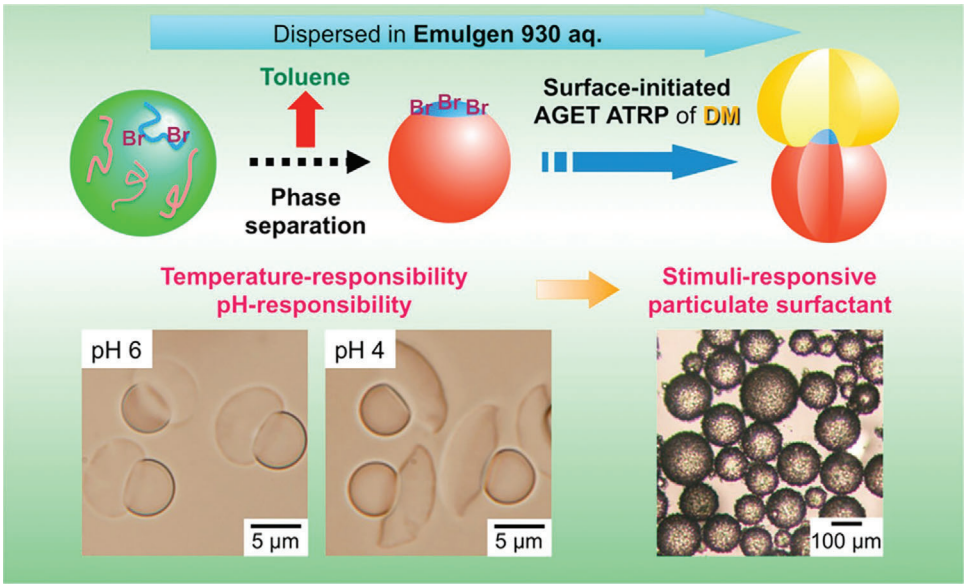

Figure 13. a) Schematic representing the preparation of mushroom-like PMMA/P(S-BIEM)-g-PDM Janus particles. Initially a macroinitiator particle was obtained by slow release of toluene from homogeneous PMMA/P(S-BIEM)/toluene droplet dispersed in an aqueous environment. Next, particles were prepared using surface-initiated activator generated electron transfer (AGET) ATRP of 2-(dimethyl amino)ethyl methacrylate (DMAEMA). Based on their dual stimuli-responsive characteristics, the particles functioned effectively as particulate surfactants. This led to the formation of a stable emulsion of 1-octanol in water at optimal temperature and pH. The emulsion could be destabilized by controlling the particles, allowing for fast destabilization of the emulsion. Reproduced with permission.[111] Copyright 2014, American Chemical Society.

the LCST. This indicated that the temperature and pH could be adjusted to control the emulsion's stability.

Zhao et al. 2015 employed a general method to make dually sensitive Janus composite nanosheets that can serve as surfactants to stabilize emulsions.[112] ATRP was used to selectively graft pH sensitive 2-(dimethylamino)ethyl methacrylate (DMAEMA) and thermally responsive NIPAM onto corresponding sides of silica Janus nanosheets. By adjusting the pH or temperature, the wettability of each side could be adjusted between hydrophilic and hydrophobic separately. The composite nanosheets could act as a sensitive solid emulsifier, allowing emulsions to be stabilized by adjusting pH and/or temperature. Janus nanosheets with dual responses could be useful in phase transfer catalysis.

Ngai and co-workers demonstrated that by utilizing an aqueous dispersion of PNIPAM-*co*-MAA microgels, o/w HIPE gel structures with internal phases of up to 90% could be generated.[113] It was suggested that hydrogen bond interactions cause the hydrogel-like continuous phase to form. Later in 2010, Ngai improved on this method for assembling HIPE-gels by employing core-shell particles with a polystyrene core and a microgel polymer outer shell and designed HIPEs using pH- and temperature-responsive microgels.[68,114]

In research by Li et al., dual responsive Y-shaped amphiphilic PS-$(PDMAEMA)_2$ miktoarm star copolymers were synthesized.[115] Depending on the volume ratio, the star copolymers could stabilize both o/w and w/o emulsions with toluene as the oil phase. Demulsification could be achieved by changing pH, and phase inversion from an o/w to an o/w/o emulsion could be attained by increasing the temperature with stirring.

An and colleagues reported dual responsive CCS copolymer emulsifiers comprising of 2-methoxyethyl acrylate (MEA) and poly(ethylene glycol) acrylate (PEGA) of varying compositions.[116] Heating o/w HIPEs over the LCST of the CCSs "arms" resulted in demulsification (**Figure 14**). The inclusion of kosmotropes and chaotropes, which are solutes that increase or decrease the structure of water molecules, could be used to adjust the stability of the emulsion and demulsification efficiency. The kosmotropes decreased the cloud point and improved demulsification efficiency, whereas the chaotropes increased the cloud point and improved the thermal stability of the emulsion.

Phase inversion may also be triggered by pH-switch. Besnard et al. demonstrated that copolymers of poly(styrene) (PS) – *b* – *(PS* – *ran* – (PDMAEMA)) could give multi-responsive emulsions.[117] Temperature and pH controlled the phase of the emulsion, however pH gave larger effects due to the relative strength of Coulombic interactions. In the protonated regime, at pHs below the pK_aH of DMAEMA (≈6.4), o/w emulsions were formed, however at pHs above the pK_aH, w/o emulsions were formed. The presence of multiple emulsions was even established at the boundary between these two phases.

3. Conclusions

Stimuli-responsive emulsions have emerged as a promising drug delivery platform with significant implications for pharmaceutical applications. Continued research and development in the field of stimuli-responsive emulsions holds the promise of expanding their applications, enabling controlled drug release strategies, and revolutionizing drug delivery paradigms. By exploiting external stimuli such as temperature, pH, magnetic, and salt concentration, emulsions offer a new dimension of control over drug

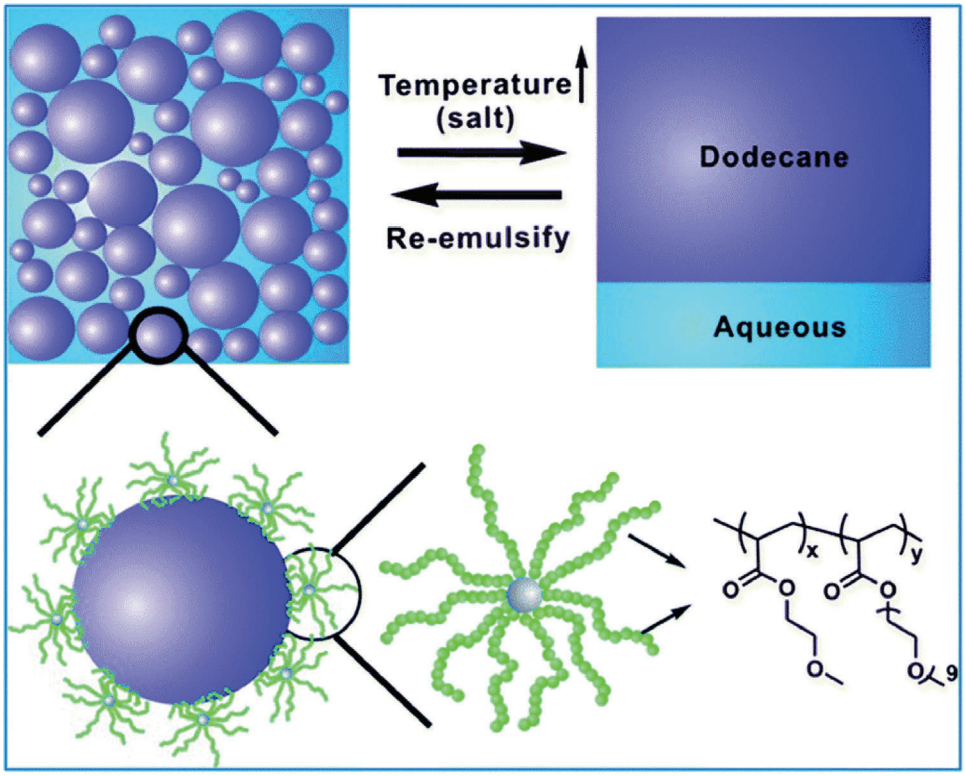

Figure 14. Schematic representation of responsive HIPEs stabilized by CCSs comprising of 2-methoxyethyl acrylate (MEA) and poly(ethylene glycol) acrylate (PEGA). Reproduced from Chen et al.[116] with permission from The Royal Society of Chemistry.

release kinetics or site-specific delivery through sol-gel mechanisms. Their capacity to encapsulate a diverse range of hydrophobic and hydrophilic compounds underscores their adaptability, making them an attractive choice for delivering a wide range of therapeutic agents. There are, however, many questions that still remain. The complexity of these systems is such that careful optimization is required for each application, and indeed the sensitivity of the polymeric stabilizers such that mild environmental changes, such as salinity of water, room temperature, or dissolution of atmospheric gasses may affect their function. The current literature base suggests that these materials are sufficiently understood to allow new explorations of applied sciences based on the frameworks presented. Key questions for the scientists remain. What are the highest value applications for these materials? What level of toxicological understanding is required before translation? And of course, what are the potential environmental impacts of these emulsions, good or bad. Current frameworks for pharmaceutical regulation are such that translation opportunities are more likely to be found outside of medicines, however, current initiatives such as the FDA's PRIME programme may offer new opportunities to accelerate the introduction of these novel excipients.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

cosmetics, creams, dispersions, pharmaceuticals, smart materials

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