Stimuli-Responsive Polymers

Modern polymer synthesis techniques have enabled the creation of polymers with sophisticated structures and bespoke behaviors. 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. Materials of this nature are often influenced by similar processes in biological systems.

For instance, certain plants such as wheat awns and pinecones respond to changes in humidity, by expanding or contracting to disperse their seeds. 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.

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. These “natural” stimuli-responsive polymers have formed the basis for the development of numerous synthetic polymers that mimic their adaptive responses.

In synthetic polymers, 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). 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.

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.

Smart polymers may be capable of producing multiple stimuli-responses and/or exhibit reversibility of these modifications. 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) also contribute to the behaviors of smart materials.

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. 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.

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. Due to steric hindrance and multipoint irreversible anchoring at the oil-water interface, branched polymers can offer stronger emulsion stability than their linear counterparts. For example, Weaver et al. produced a range of branched copolymer surfactants (BCSs) that gave substantially higher emulsion stability than their linear analogues. 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.

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. 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. 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.

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. with permission from The Royal Society of Chemistry.

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. 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** 2a).

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.

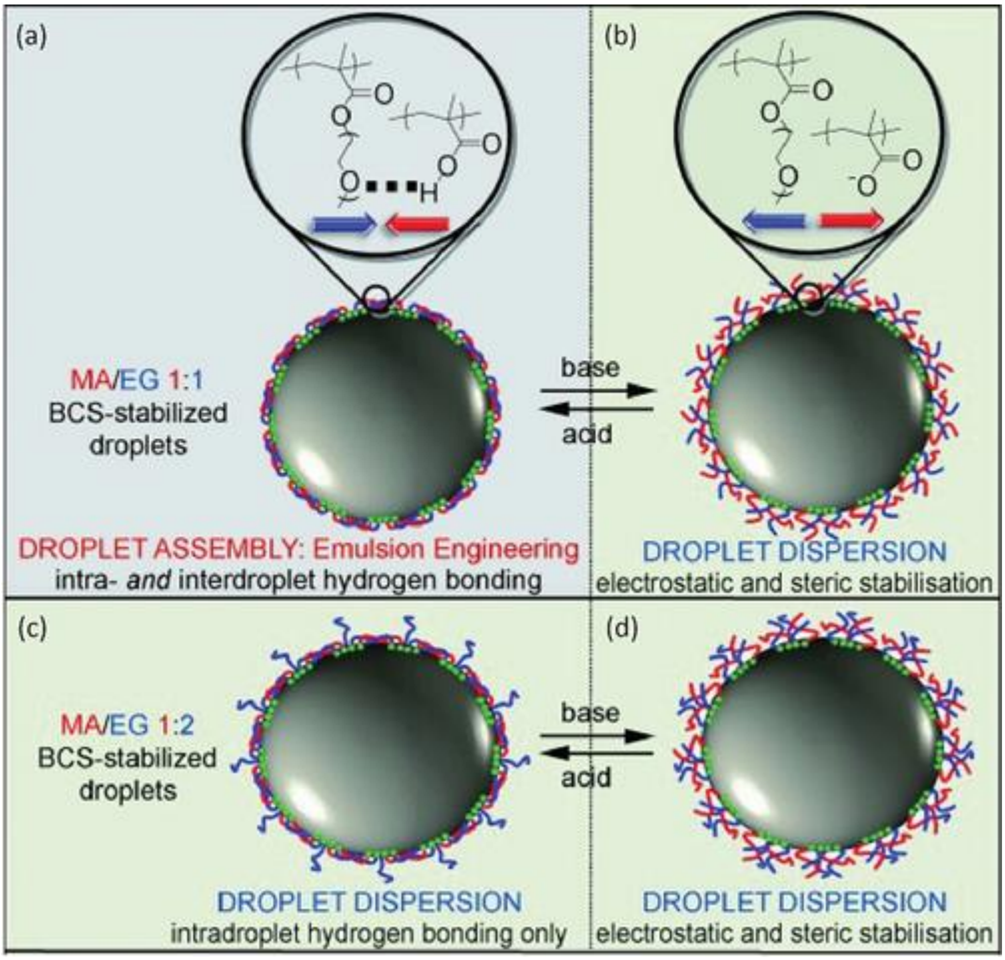

Figure 3

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.

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.

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 compositions defined by branched copolymer surfactants. 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 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.

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

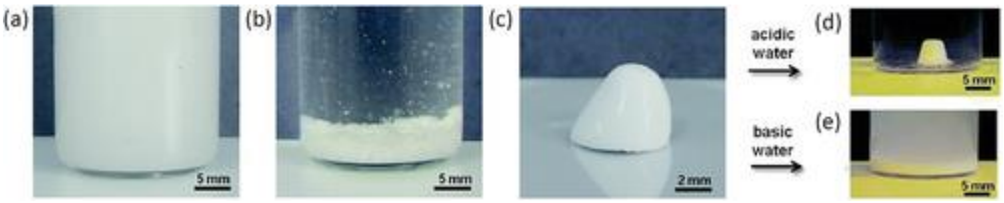

Figure 4
Images showing pH-responsive reversible colloid aggregation and monolith preparation. a) Surface-functionalized colloids dispersed at pH 10; b) aggregation and sedimentation 24 h after acidification of (a); c) monolith formed by centrifugation of (b); d) colloid monolith retaining its structure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

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). 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.

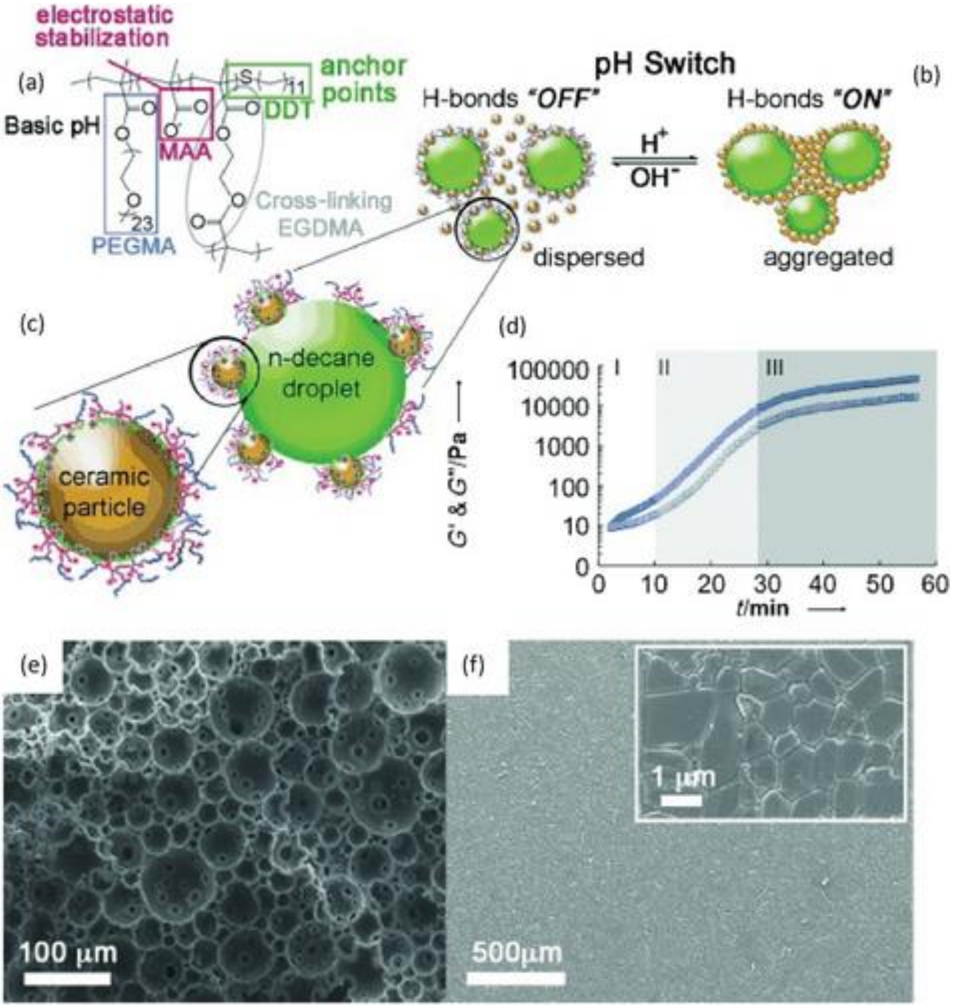

Figure 5

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. Copyright 2013, Wiley-VCH.

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) (PDEAEMA) and hydrophobic poly(n-butyl acrylate) are efficient pH-responsive emulsifiers at DEAEMA mole fractions of 0.2–0.5. 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 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. 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.

pH-responsive emulsions stabilized by xanthan gum and shellac have been studied by Patel and co-workers. Here, a reversible mechanism of transition between a flocculated and a stable state at acidic and neutral pH were reported (**Figure 6**a). 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 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 re-dispersed 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 6 b,c). Thus, this study demonstrated a straightforward way to utilize pH-triggered flocculation of emulsions to produce soft structures with controlled shapes.

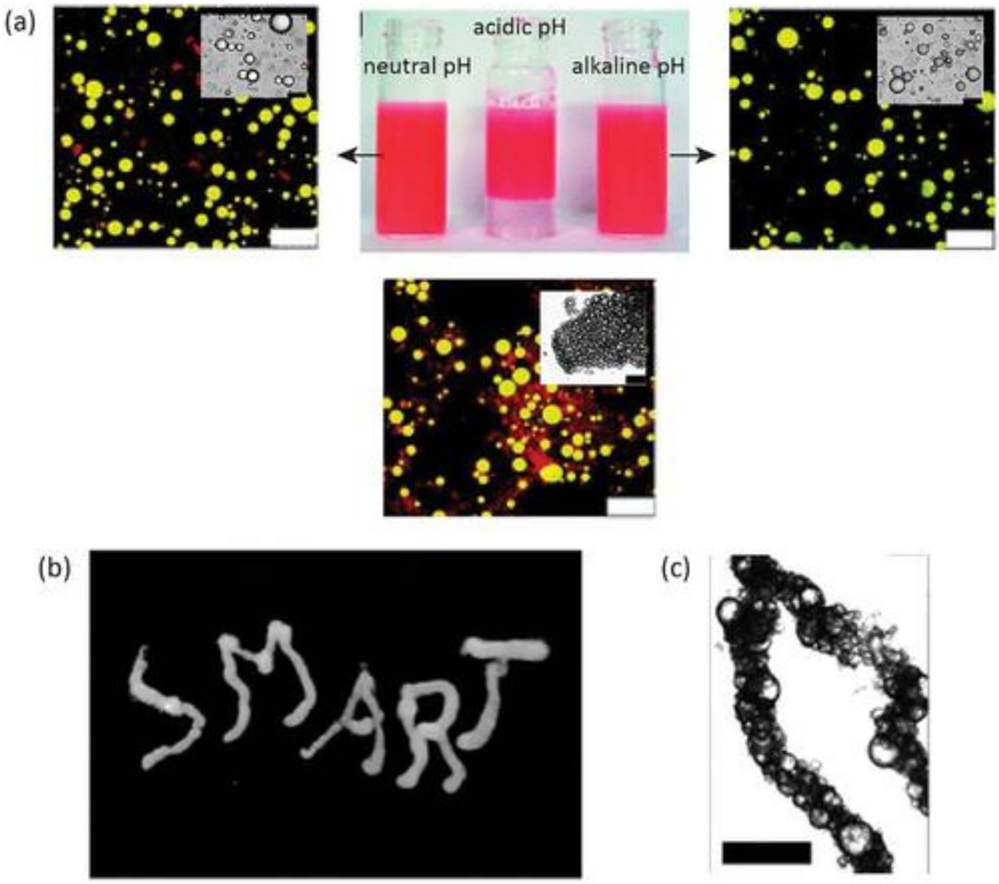

Figure 6

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.from The Royal Society of Chemistry.

High Internal Phase Emulsions (HIPE) are concentrated emulsion systems with a large volume fraction (>0.74) of dispersed phase. 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. 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. 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. 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. 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.