

# New Frontiers for Encapsulation in the Chemical Industry

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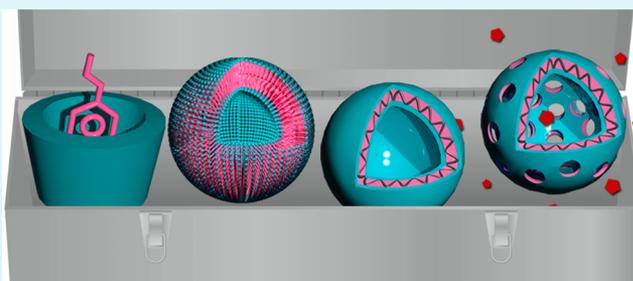
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**ABSTRACT:** Encapsulation of actives comprises an area of exploration undergoing rapid growth in both academic and industrial research settings. Encapsulation processes are employed as a part of product synthesis processes for improved efficiency, enhanced stability, active ingredient compatibility, increased safety, targeted delivery, and novel performance of the end product. Such technical benefits enable producers to offer products with increased formulation complexity, access new markets, differentiate products, and improve compatibility and stability, while meeting consumer demands with improved performance, reduced costs, and new actives. In this review, we highlight several emerging academic areas of encapsulation that we believe have specific relevance to industrial formulation, with a focus on three primary areas: supramolecular encapsulation, aqueous self-assembled systems, and emulsion-based capsules. The goal of this review is to help identify the major challenges facing encapsulation technology adoption in the chemical industry, bringing focus and maximizing the potential value of ongoing research efforts.

**KEYWORDS:** encapsulation, controlled release, self-assembly, interfacial polymerization, supramolecular interaction, vesicle, capsule



materials, such as fragrances or low molecular weight compounds that would otherwise evaporate from the product.<sup>3</sup> By increasing the amount of AI retained for release during actual use, product performance increases. Encapsulation may also allow for a synergistic reaction to occur at the point of use, which is unlikely without encapsulation. Highly reactive materials, like bleaches or other oxidizers that are intended to react only upon application, are common examples of improved efficacy. These effects typically lead to cost reduction by requiring a lower concentration of the AI to achieve the desired performance. Similarly, other aspects of encapsulation, such as targeted delivery and optimized active release, can reduce overall active costs.

## 1. INTRODUCTION

Encapsulation of actives comprises an area of exploration undergoing rapid growth in both academic and industrial research settings. Typical encapsulation processes require the isolation, stabilization, delivery, and controlled release of an active ingredient (AI) from a particle or capsule. There are many reasons for adding encapsulation processes to product synthesis including improved efficiency, enhanced stability, AI compatibility, increased safety, targeted delivery, and novel performance.<sup>1</sup> For relatively pristine systems, such as those containing only the AI, water, and a buffer, the primary concern is AI delivery to the target destination and release via an appropriate mechanism. Formulated liquid products, however, are typically complex combinations of solvents, surfactants, buffers, defoamers, fragrances, and a host of other additives that improve formulation behavior, performance during use, or function of the final application.<sup>2</sup> These additives often place significant chemical stresses on the AI, hence requiring its encapsulation and protection. The encapsulating material itself must maintain an effective barrier to preserve AI stability despite the myriad of destabilizing formulation additives.

Improved AI efficiency is possible when encapsulation provides a decrease in AI loss during product preparation, storage, or use. Examples include encapsulation of volatile

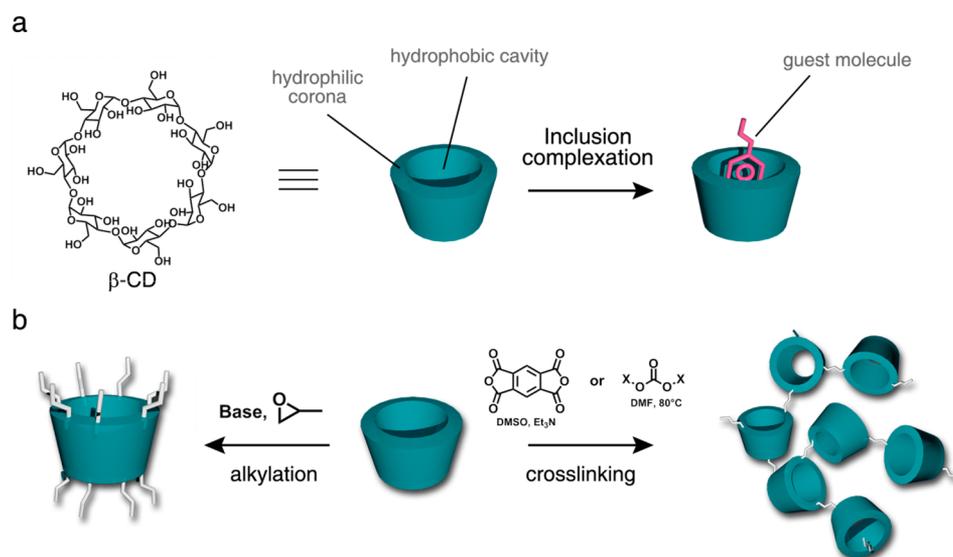
materials, such as fragrances or low molecular weight compounds that would otherwise evaporate from the product.<sup>3</sup> By increasing the amount of AI retained for release during actual use, product performance increases. Encapsulation may also allow for a synergistic reaction to occur at the point of use, which is unlikely without encapsulation. Highly reactive materials, like bleaches or other oxidizers that are intended to react only upon application, are common examples of improved efficacy. These effects typically lead to cost reduction by requiring a lower concentration of the AI to achieve the desired performance. Similarly, other aspects of encapsulation, such as targeted delivery and optimized active release, can reduce overall active costs.

Encapsulation is a strategy to isolate actives that otherwise would detrimentally impact formulation stability. Interactions with key formulation components (dispersants, rheological modifiers, etc.) may reduce additive effectiveness, diminish shelf life, and adversely affect product behavior. For example, highly reactive AIs, such as antimicrobials intended to inhibit biological growth in a coating application, could oxidize any

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**Figure 1.** (a) Chemical structure of  $\beta$ -cyclodextrin ( $\beta$ -CD) with a schematic representation of an inclusion complex. (b) Schematic representation of  $\beta$ -CD modification and cross-linking.

number of the additives required for stability of the coating formulation, resulting in reduction of the antimicrobial activity and the product quality.<sup>4</sup> Safety considerations are also addressed through AI encapsulation, reducing unintended user exposure or improved chemical stability during handling prior to final application of the AI. For actives such as pesticides, which are often harmful to the user at high concentrations, this feature expands available markets by increasing safe product use by nonprofessionals as well as enables development of more concentrated products (with lower exposure risk), again reducing overall costs or improving profit margins. Reduction of the environmental impact from accidental exposure is also possible, making the product safer in residential areas. Finally, encapsulation enables novel product performance and offers numerous advantages to the end-user. For example, synergistic interactions between two actives are maximized when one or both are encapsulated until their interaction is desired.

The above factors illustrate some of the fundamental advantages of encapsulation, though detailed, product-specific advantages are also significant. These include aspects like increased formulation complexity, access to new markets, product differentiation, improved compatibility/stability, meeting consumer demands, improved performance, reduced costs, and enabling of new actives. In 2011, The Dow Chemical Company (Dow) announced a \$250 million investment in academic research projects at major American universities to support breakthrough technologies in areas of industrial relevance.<sup>5</sup> To that end, recognizing the need for improved encapsulation, a program was initiated between Dow and the University of Illinois to focus on novel encapsulation technologies. Through our interactions, Dow has provided the university new focus areas, problem statements, and guidance for research relating to the encapsulation of actives beyond pharmaceuticals, areas for which government funding might not be readily available but of which there is significant commercial need and space for breakthrough technologies. In return, Dow has received direct access to pioneering, higher-risk work than what is typically tolerated within the industrial research setting, providing a technically derisked initial path

toward new and next-generation technologies. Building on our interactions, we have prepared this review, in which we highlight several emerging academic areas of encapsulation that we believe have specific relevance to industrial formulation. Rather than being comprehensive, we focus our review on the aspects and attributes of emerging polymeric encapsulation technologies specifically relevant to the industrial arena. We focus on three primary areas: supramolecular encapsulation, aqueous self-assembled systems, and emulsion-based capsules. For this review, we highlight technical approaches to encapsulating materials of interest. Equally important to encapsulation of materials is their subsequent release, a complex and challenging area of research in its own right. In the interest of conciseness, rather than inclusion in this review, discussion of AI release is the focus of a second review prepared by our groups to which we refer the interested reader.<sup>6</sup> Our goal is that the reader, through our review, will identify the major challenges facing encapsulation technology adoption in the chemical industry to bring focus and maximize potential value.

## 2. SUPRAMOLECULAR ENCAPSULATION

The inclusion of small molecules within structural cavities is part of a field known as supramolecular chemistry. Organic cavities typically consist of macrocyclic oligomeric materials, while inorganic structures are based on metal–organic frameworks (MOFs) or mesoporous silica.<sup>7–12</sup> This mode of encapsulation is often driven by a combination of enthalpically weak intermolecular interactions and a favorable entropy resulting from the liberation of solvent from molecular compartments.<sup>13</sup> As this review is focused on organic encapsulating materials, we focus our discussion on macrocyclic oligomers. The most notable supramolecular macrocycle utilized in the food, pharmaceutical, and chemical industry today is cyclodextrin (CD, Figure 1a).<sup>14</sup> CDs are cyclic oligomers of D-glucopyranose and exist in multiple sizes, the three most common and readily available being  $\alpha$ -,  $\beta$ -, and  $\gamma$ -CDs, having six, seven, and eight  $\alpha$ -D-glucopyranoside units linked 1–4, respectively.  $\beta$ -CD is the most commonly used and studied and is the most economical, though other forms are

also used.<sup>15,16</sup> CDs facilitate encapsulation through their unique structural properties. Whereas the CD exterior is hydrophilic, the interior consists of a hydrophobic cavity (approximately 6–6.5 Å in diameter for  $\beta$ -CD) that allows encapsulation of less polar molecules (such as essential oils) through hydrophobic interactions. Consequently, typical guests include small drug compounds, flavonoids, and volatile aroma compounds that require stabilization and solubilization in aqueous systems.<sup>16</sup> Small aromatic compounds recently studied include vanillin,<sup>17</sup> etodolac,<sup>18</sup> and usnic acid.<sup>19</sup> Inclusion complexes of small molecules with CD also alter the physical state of volatile organics, enabling improved shelf stability and eased material handling, such as is observed with the potent antiripening agent, 1-methylcyclopropene.<sup>15</sup>

CDs are produced from starch through an enzymatic process with postsynthetic modifications typically made to the structure to tune solubility and/or to impart specificity for the targeted application.<sup>16</sup> The most widely used modified CDs are the (2-hydroxypropyl)  $\beta$ - and  $\gamma$ -CDs commercially available and marketed by Ashland under trade names Cavitron and Cavasol, respectively. Cavitron and Cavasol are found in a variety of products from pharmaceutical formulation to odor elimination products. Other synthetic modifications have been explored for CDs, such as alkylation, which are useful for producing amphiphilic CD structures for systems of higher complexity.<sup>20</sup>

Another trend in using CD as an encapsulating material is immobilization onto or within polymeric structures to enhance the stabilization of the complexes, such as CD nanosponges (NSs) (Figure 1b).<sup>21</sup> CD-NSs consist of CDs that are highly cross-linked with small multifunctional linking units, including hexamethylene diisocyanate (HMDI), carbonyldiimidazole (CDI),<sup>22</sup> diphenyl carbonate,<sup>23</sup> and pyromellitic anhydride,<sup>21</sup> producing a dense matrix of CDs. For example, Gallo and co-workers demonstrated that CD-NSs cross-linked with CDI outperformed HMDI-cross-linked CD-NSs for encapsulating antioxidant apple phenols (rutin, phloridzin, and chlorogenic acid).<sup>22</sup> The authors attributed this feature to the small spacing provided by the CDI linker within the polymer matrix that has less flexibility and higher density of CDs when there is a lower CDI to CD ratio (1:3). Supramolecular encapsulation of CDs has been used extensively in industry, and the development of NSs could open up the uses of CDs in other areas provided the cross-linking methodologies are robust enough to withstand processing.

Other classes of supramolecular macrocycles have received similar attention to CDs. Cucurbit[*n*]urils (CBs), like CDs, have a hydrophobic barrel-like cavity capable of hosting and transporting hydrophobic AIs through aqueous systems. Unlike CDs which have truncated cone geometry, however, CBs have identical diameter openings at either end with their carbonyl groups pointing toward the center. Although CBs have been shown to sequester cations,<sup>24</sup> organic dyes from wastewaters,<sup>25</sup> and are actively being investigated in drug delivery applications,<sup>26</sup> there is still an ongoing need to improve their synthesis and functionalization to reduce their cost and make them a viable option for use in industrial formulations.<sup>13</sup>

Core-shell dendritic polymers comprise another emerging class of vehicles for molecular encapsulation that has strong potential for industrial adaptation.<sup>27</sup> Core-shell dendritic polymers are highly branched polymers with low polydispersity and well-organized functionalities that grow from a branched core in stages. Terminal groups can then be cross-linked to impart additional encapsulation performance. A dendritic

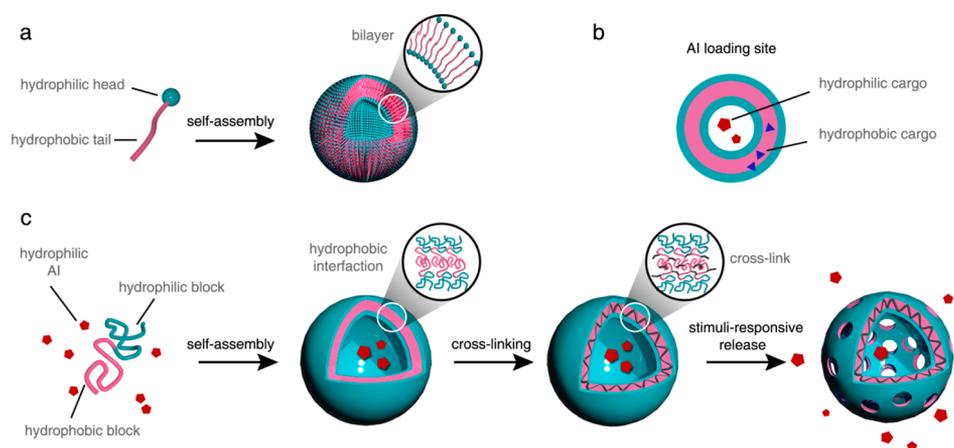
polymer that has been used extensively as the core for this type of encapsulation is the hyperbranched polyglycerol (HPG).<sup>27,28</sup> Appealingly, HPGs are available through a facile, one-step synthetic procedure, an anionic ring-opening polymerization of glycidol in basic conditions. This approach produces low dispersity polymeric nanoparticles with terminal hydroxyl groups that can be further functionalized to tailor the encapsulating properties of the final product.<sup>29</sup> Once the core HPG is synthesized, a host of synthetic modifications can be achieved on terminal and interior hydroxyl groups. In core-shell structures, secondary polymerizations are initiated from functionalized terminal groups to create layers with distinct chemical properties.<sup>30</sup> For example, Kurniasih and co-workers engineered an amphiphilic core-shell HPG with a biphenyl-functionalized core and polyethylene glycol (PEG) chain outer shell.<sup>31</sup> The biphenyl moieties could  $\pi$ - $\pi$  stack and encapsulate aromatic guests within the polymer core, while the PEG provided colloidal stabilization. For 20 mol % of biphenyl per HPG, they observed as many as 11 to 12 pyrenes encapsulated within the particle core by diffusion in Milli-Q water solution.

One strategy that was employed by Zimmerman and co-workers to achieve encapsulation using HPG particles was the intramolecular cross-linking of alkene-functionalized HPGs.<sup>32,33</sup> With the alkene-terminal functional groups, ring-closing metathesis (RCM) was used to intramolecularly seal the neighboring alkenes to form a covalent barrier around the HPG particle surface. This strategy yielded multiple encapsulating HPGs that could serve as ionophores and dye encapsulating particles. Oxidation of the alkene bridge enabled increased water solubility of the particles. The primary observation of this study was that binding properties were dependent on the loop size of the RCM products. In particular it was found that smaller loops had a stronger affinity to guest dyes. Collectively, CDs, dendrimers, and hyperbranched polymers offer unique properties for intimate association with AIs, providing enhanced AI stability and novel formulation performance.

### 3. VESICLE ENCAPSULATION

Beyond the self-assembly process inherent in host-guest interactions, encapsulating molecules also have the ability to self-assemble themselves forming higher-order structures capable of encapsulating cargos. For water-soluble AIs requiring stabilization in aqueous systems, vesicles present a promising structural motif for encapsulation. In a vesicle, amphiphilic encapsulants, most commonly lipids or block copolymers, self-assemble to form a bilayer membrane structure with an aqueous core enclosed (Figure 2a).

Designed by and inspired from biology, liposomes, assembled from phospholipids, stearylamine, and in some cases plant and animal cell extracts, have been utilized for encapsulation and protection of aqueous actives in aqueous media.<sup>34</sup> Various liposome architectures such as unilamellar (0.02–1  $\mu\text{m}$ ), oligolamellar, multilamellar, and multivesicular structures are produced depending on the mode of fabrication, enabling variable structure stability and active release profiles. Unilamellar structures are formed through sonication, extrusion, freeze-drying, and electroformation. Sonication usually leads to smaller liposomes, whereas freeze-drying forms larger structures.<sup>35</sup> Giant unilamellar liposomes (GULs) are typically formed by electroformation, which utilizes electrical current to swell a lipid film from a silicon plate. A more recent technique for GUL formation utilized agarose films in salt solution leading to swelling and formation of GULs.<sup>36</sup>



**Figure 2.** (a) Liposomes with bilayer membrane structure formed from self-assembly of lipids. (b) Location of encapsulated hydrophilic and hydrophobic AIs in polymersome. Hydrophilic AI is dissolved in the aqueous core, while hydrophobic AI is located inside hydrophobic domains of the bilayer membrane. (c) Schematic illustration of polymersomes formation from polymeric amphiphiles, cross-linking of polymersome for higher stability, and stimuli-responsive release of encapsulated AIs.

Multilamellar liposomes are prepared by thin-film hydration or direct dispersion and are converted to unilamellar liposomes by sonication or extrusion.<sup>34</sup> Physical encapsulation of AIs within liposomes is achieved by mechanical or solvent dispersion. Mechanical dispersion involves sonication or high shear mixing of lipids in a solution of the desired encapsulants, whereas solvent dispersion involves injecting lipids dissolved in organic solvent directly into an aqueous solution followed by solvent extraction.<sup>35</sup> In both cases, the encapsulation efficiency is typically low.

The pharmaceutical industry is the primary employer of liposomes because they are biocompatible and tailorable to target and release drugs at a desired rate.<sup>37</sup> Other industries have been slow to adopt liposomes due to weak mechanical and chemical stability, leading to poor AI stability and limiting formulated product shelf life, though there has been some adaptation in the personal care arena.<sup>38</sup> Indeed, due to the poor stability of liposomes, even the pharmaceutical industry has adopted modified liposomes (typically through the introduction of poly(ethylene glycol) conjugates) for some drug formulations, such as the drug Doxil.<sup>39</sup> Additionally, many of the techniques described above are challenging to scale to the industrial scale. These challenges coupled with the poor encapsulation efficiency of liposomes have led to exploration of other strategies for aqueous encapsulation of actives.<sup>40</sup> One approach that is gaining traction, though yet to see commercial success to address some of these challenges, is the development of polymersomes, a synthetic analogue of liposomes, formed from the self-assembly of amphiphilic block copolymers.<sup>41–43</sup> Advances over the last two decades in controlled polymerization methods have enabled the syntheses of block copolymers with narrow polydispersity, tunable molecular weights, and predetermined functionalities, leading to different self-assembled structures with various properties and functions.<sup>44,45</sup> Depending on the fractions of hydrophobic block and hydrophilic block, the amphiphiles assemble into spheres, cylinders, or bilayer structures; polymersomes are formed by further closure of bilayer membranes.<sup>41,42</sup>

Compared to lipids, polymeric amphiphiles are typically much larger in molecular weight, leading to more robust, mechanically tougher vesicles that provide better barrier properties with lower membrane fluidity and permeabil-

ity.<sup>42,43,46</sup> Polymersomes are able to encapsulate both hydrophilic and hydrophobic AIs with their liposome-mimetic structure but thicker membrane (Figure 2b).<sup>41</sup> Many polymeric materials of industrial relevance have been used to fabricate polymersomes including polystyrene, polybutadiene, and poly-(butylene oxide) as the hydrophobic block and poly(ethylene oxide) or poly(acrylic acid) as the hydrophilic block.<sup>43,47,48</sup> Additionally, functionalization of polymer side chains provides a facile tool to alter the membrane properties of polymersomes by attaching cross-linkable, stimuli-responsive, or other functional groups, further broadening the design and application spaces of polymersomes.<sup>42,49,50</sup>

The shape and arrangement (i.e., chain stiffness or secondary interactions between chains) of each polymer block have been found to play vital roles in determining the polymersome structure and therefore its performance properties.<sup>42</sup> Dendrimersomes and hyperbranched polymer vesicles enabled systematic study of chemical structure–assembly structure relationships.<sup>51,52</sup> Polypeptides formed conformation-specific polymersomes as a result of their unique rigid  $\alpha$ -helical structure, whereas the random-coiled analogue, lacking the side-by-side alignment between rod-like helices, could not form polymersomes.<sup>53</sup> Recent work from Hammer and co-workers demonstrated the first example of synthetic proteins specifically designed to assemble into various supramolecular architectures including vesicles.<sup>54</sup> While much can be learned from the chemistries and molecular structures that enable encapsulation through these studies, due to the significantly high cost to produce protein at the industrial scale, especially compared to block copolymers, we do not envision commercial adaptation of these materials in the foreseeable future beyond highly specialized systems.

The membrane properties of polymersomes, especially the permeability, are key parameters when polymersomes are used as encapsulating agents. It is necessary to maintain enough stability to prevent cargo leakage against conditions such as the shear, salts, surfactants, or organic solvents that are often present in industrial processing and formulations. However, a mechanism by which the AI is accessible is required for the AI to have any utility in the formulation (and thereby justify the cost of its inclusion). One approach to address this challenge is

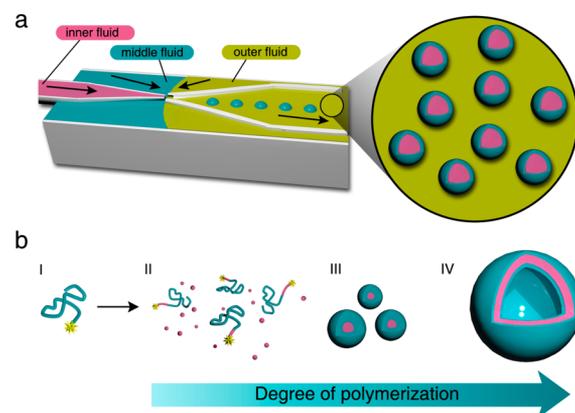
selective permeability by size or hydrophilicity such as has been accomplished with polymersome nanoreactors.<sup>55,56</sup>

To improve the stability of vesicles, polymersome cross-linking has been widely explored. Photo-cross-linking of poly(butadiene)-based vesicles greatly enhances the stability of polymersomes against dehydration and salt.<sup>57</sup> Cross-linking also effectively increases the stability of polymersomes against surfactants, which are known to disrupt polymersome structure through membrane dissolution.<sup>58</sup> More recently, cross-linking has been coupled with strategies to permeate the vesicle membrane to facilitate active transport (Figure 2c).<sup>55,59,60</sup> Voit and co-workers reported a pH-dependent swellable polymersome for controlled loading and release of small-molecule cargos.<sup>59</sup> Cross-linkable dimethyl maleimide-based monomers and pH-responsive tertiary amine-based monomers were randomly copolymerized in the hydrophobic block. Following self-assembly and photo-cross-linking in basic solution, upon exposure to acid and amine protonation the structure swelled, inducing release of the encapsulated material. The system was further tuned to exhibit pH- and pressure-dependent size-selective membrane permeability.<sup>55</sup> Another example developed by Liu and co-workers reported concurrent polymersome cross-linking and permeabilization.<sup>60</sup> The second block of the copolymer contained nitrobenzyl-protected primary amine groups that undergo deprotection with the nitrobenzyl group removable upon UV irradiation. Following UV-induced nitrobenzyl deprotection, the exposed amine groups cross-linked the polymersome via amidation that led to a change in the membrane permeability through protonation. This approach provided another controlled release platform with well-maintained polymersome structure.

Although effective to increase stability, polymersome cross-linking is limited to specialized copolymer structures because the cross-linkable groups need to be present on polymer side chains. To address this, Katz and co-workers demonstrated a simple modification of polymer end-group chemistry to enable UV-induced polymerization of the membrane.<sup>61</sup> This approach, although not as robust as complete cross-linking, was also effective to increase polymersome stability with improved resistance to surfactant disruption and decreased rate of AI release. As a more general strategy to increase the polymersome permeability, Spulber and co-workers used hydroxyalkylphenone to chemically modify the polymersome membrane.<sup>62</sup> After radical attachment of hydrophilic moieties from hydroxyalkylphenone, the membrane was altered to be permeable to hydrophilic molecules without changing the size and morphology of the polymersome structure. This method provided a simple and powerful way to render the polymersome membrane semipermeable.

Although polymersomes generally address many of the challenges presented by liposomes in terms of structure robustness, they share traditional methods for preparation, which continue to have drawbacks such as scalability, poor size distribution, low yield, and the use of organic solvents for their preparation.<sup>63</sup> Consequently, recent research in new polymersome fabrication methods is of great interest for furthering polymersome technical development for industrial applications.

In 2005, David Weitz' group first reported the fabrication of monodisperse double emulsions using microfluidic devices (Figure 3a). Unlike traditional two-step emulsification methods, the double emulsion droplets from microfluidics exhibit excellent monodispersity, and the size of the droplets is easily tuned by flow profiles of the fluids.<sup>64,65</sup> When amphiphiles were



**Figure 3.** (a) Schematic illustration of monodisperse polymersome fabrication using microfluidic devices. AIs are dissolved in aqueous inner fluid, and polymeric amphiphiles are dissolved in oil middle fluid. (b) Schematic illustration of RAFT dispersion polymerization to form polymersomes. Starting from macro-CTAs (I), the transition from soluble diblock copolymer (II) to spherical micelles (III) and vesicles (IV) is observed as the degree of polymerization of second block increase.

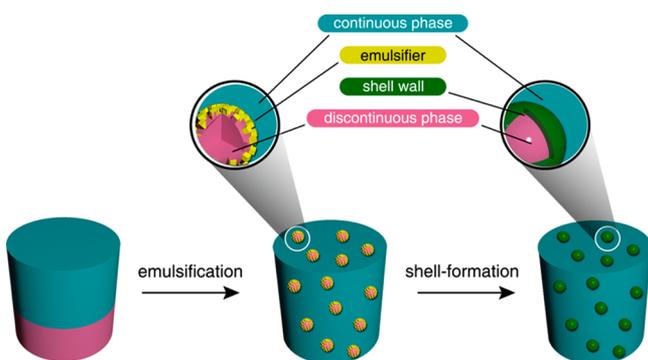
dissolved in the oil phase, the resulting core-shell droplets were used to template liposomes and polymersomes. Compared to traditional polymersome preparations, microfluidic-fabricated polymersomes exhibit finely tunable size, well-controlled monodispersity, extremely high loading efficiency (approaching 100%), and an enhanced library of polymers from which to assemble the vesicles.<sup>66</sup> Further refinement of the microfluidic design has enabled improved throughput production and complicated multicomponent polymersome structures, which could begin to pave the way for scalable devices that could be operated beyond the bench scale.<sup>67,68</sup> Microfluidic systems are still limited by the requirement for the use of organic solvents, but continued advances could address these concerns, perhaps through the use of neat liquid polymers or biphasic aqueous systems.<sup>48,69</sup>

A second approach to scalable polymersome preparation is *in situ* assembly during polymer synthesis, utilizing dispersion polymerization with a soluble macromolecular initiator or macromolecular chain transfer agent (macro-CTA, Figure 3b).<sup>70</sup> As the degree of polymerization increases, various self-assembly morphologies are observed because of the changing block composition. Among all available polymerization techniques, reversible addition-fragmentation chain transfer (RAFT) dispersion polymerization was most widely used to prepare self-assemblies.<sup>70</sup> RAFT dispersion polymerization enables polymersome preparation and formulation in one pot with potentially safer solvents and higher solid contents. The synchronized polymerization and self-assembly step avoids the use of additional solvents (i.e., DMSO, DMF, CHCl<sub>3</sub>, or THF), which is beneficial for maintaining the integrity of fragile encapsulants, lowering preparation costs, and enhancing the environmental and health profile of the formulation. Initial RAFT dispersion polymerization studies took place using a styrene/methanol system with different macro-CTAs.<sup>71–73</sup> When the polymerization time, styrene/methanol concentration, and other parameters were properly controlled, polymersomes were easily obtained. More recently, aqueous RAFT dispersion polymerization was also reported to prepare polymersomes using 2-hydroxypropyl methacrylate monomer.<sup>74,75</sup> As a result of the significant environmental and

health concerns with methanol, the aqueous medium is far more practical for industrial applications. Because these early reports only focused on morphology studies, continued study focusing on encapsulation and controlled release in the future is of great interest to potentially develop routes that offer the scalability that is desperately needed for industrial applications.

#### 4. EMULSION ENCAPSULATION

Unlike earlier discussed encapsulation techniques that are driven by inter-/intramolecular noncovalent interactions, emulsion-templated encapsulation techniques typically rely on covalent shell-wall formation that provides a particularly robust encapsulation. Emulsion-based encapsulation methods have been used extensively in many fields including microbial control,<sup>4</sup> agrochemicals,<sup>2</sup> personal care,<sup>3,38</sup> food and nutrition,<sup>76</sup> and coatings,<sup>77</sup> utilizing triggerable microcapsules,<sup>78</sup> microreactors,<sup>79</sup> synthetic cellular structures,<sup>80</sup> and self-healing materials.<sup>81</sup> Emulsion-templated encapsulation typically consists of two steps: formation of the emulsion followed by fabrication of a separation barrier (Figure 4).



**Figure 4.** Schematic illustration of emulsion-templated microencapsulation routes. Step 1: emulsification of the biphasic liquid mixture. Step 2: Formation of the shell at the emulsion drop interface.

Emulsion templates have been demonstrated to be useful for fabrication of ordered microscale and macroscale structures.<sup>82–84</sup> In typical preparations, amphiphilic species known as emulsifiers stabilize immiscible multiphase mixtures by lowering the surface tension of the discontinuous liquid. The shape and morphology of the liquid droplet precursor in the emulsion dictate the ultimate shape of the encapsulation vehicle.<sup>85</sup> Surfactants have been most extensively used as emulsifiers,<sup>84,86</sup> and macromolecular amphiphiles similarly serve as stabilizers due to their affinity to both hydrophilic and hydrophobic states.<sup>87,88</sup> However, microcapsules fabricated from small molecules or macromolecular surfactant-stabilized emulsions are limited because of the relatively weak resulting mechanical and barrier properties. In contrast, emulsions stabilized by colloidal particles, known as “Pickering emulsions”, possess inherent strength in mechanical properties and are emerging as a promising approach to the design of robust liquid-core microcapsules.<sup>89,90</sup> When stabilized by hydrophilic particles, nonpolar liquids are the discontinuous phase forming oil-in-water (O/W) emulsions;<sup>91–93</sup> water-in-oil (W/O) emulsions are referred to as “inverse Pickering emulsions” and can be generated where hydrophobic particles act as an emulsifier.<sup>93,94</sup> Various particles have been used as Pickering emulsifiers. For example, Benkoski and co-workers demonstrated the use of poly(methyl methacrylate) nano-

particles to generate O/W emulsions,<sup>95</sup> and Armes and co-workers fabricated pH-sensitive O/W emulsions using sterically stabilized poly(2-vinylpyridine) latex particles.<sup>96</sup> Stover and co-workers prepared microcapsules in which silica Pickering particles were pretreated with poly(sodium styrene sulfonate-co-2-(2-bromo-isobutyryloxy)ethyl methacrylate) to prepare O/W emulsion-based microcapsules.<sup>97</sup> Nonpolar liquids including hexadecane and perfluoroheptane were efficiently encapsulated using this method. Weitz and co-workers have also demonstrated generation of Pickering emulsion templates in flow focus conditions similar to those used to prepare polymersomes, ultimately fabricating microcapsules with selective permeability.<sup>98</sup>

Following generation of the emulsion, the major feature that differentiates emulsion-templated encapsulation from encapsulation using self-assembled interactions such as dendrimers and polymersomes is that a solid covalent or ionic network is formed as a separation barrier. Building on the precursor emulsion, different methods are utilized to deposit a shell at the emulsion interface, including layer-by-layer assembly (LBL), polymer deposition, and interfacial polymerization. LBL assembly involves layering of polyelectrolytes of alternating charge to produce a barrier.<sup>99,100</sup> Resulting microcapsules exhibit tunable permeability, compatibility with both organic and nonorganic encapsulants; however, postfabrication loading is usually necessary, and the structural integrity is often unsatisfactory. These features significantly limit LBL’s potential for adaptation in industrial production. While an area of significant academic research and with many companies recently started to develop and commercialize LBL technologies, such as Nanostrata and Svaya, due to the relatively low throughput and poor barrier properties compared to conventional systems (as discussed below), we at this time do not see rapid adoption of LBL technologies for industrial encapsulation use.

Direct polymer deposition at the emulsion interface due to phase separation of polymers is another method used to fabricate microcapsules.<sup>101–103</sup> In this process a polymer is suspended in a mixture of volatile good solvent and nonvolatile poor solvent, which is emulsified by agitation and surfactants. Upon evaporation of good solvent, the polymer phase separates, precipitates, and coalesces at the interface to form microcapsules. Polymers, including poly(styrene)<sup>101</sup> and poly(methyl methacrylate),<sup>102</sup> have been demonstrated to form shell walls using this encapsulation method. In-situ generation of the depositing polymer via polymerization is also common. For example, the encapsulation technique based on urea-formaldehyde condensation at acid pH conditions is widely utilized in both academic<sup>57,88</sup> and industrial production.<sup>104,105</sup> Interface deposition usually generates thick-shelled microcapsules with a relatively large size distribution. White and co-workers used this technique to generate double-layer microcapsules containing a self-healing reagent as the core liquid surrounded by the interfacial condensation reaction between urea and formaldehyde.<sup>81</sup>

In addition to interfacial deposition, by far the most common other approach to form covalent barrier microcapsules is emulsion-templated interfacial polymerization.<sup>106,107</sup> Typically, complementary reactive monomer units from disparate phases migrate to the interface of each droplet, where they react to form the capsule shell. To minimize the foaming and coalescence of the emulsion droplets, Pickering emulsifiers and other surfactants can be used.<sup>97,76,108</sup> The most common

interfacial reaction is between multifunctional isocyanates and amines to form a poly(urea) shell. To further improve the barrier properties, recently, Benkoski and co-workers illustrated secondary metal deposition on top of an organic barrier to form metal shell microcapsules,<sup>109</sup> enabling encapsulation and protection of moisture- and air-sensitive cargos such as isocyanates for self-healing applications. Radical polymerizations of styrene have also been explored.<sup>97</sup> Interfacial atom transfer radical polymerization (ATRP) was completed using a styrene monomer in the emulsion droplet precursor and the initiator/ligand/catalyst combination in the continuous phase. In-situ formation of a polymeric network at the interface efficiently encapsulated the core liquid. In a recent example, Klumperman and co-workers illustrated the strategy of cross-linking emulsifiers to form a shell that encapsulates a core liquid. In their system, amphiphilic amine-functionalized silica nanoparticles were used to generate and stabilize a Pickering emulsion followed by cross-linking of the nanoparticles by addition of a styrene–maleic anhydride copolymer to form a shell.<sup>110</sup> Leveraging the use of microfluidic double emulsion templating, Studart and co-workers generated water-in-oil-in-water (W/O/W) double emulsions in which the oil phase contained liquid acrylic monomer and hydrophobic silica particles. Following generation of the emulsion, UV irradiation polymerized the acrylic monomer, forming a solid shell around the inner aqueous phase.<sup>111</sup> Aside from radical polymerization, interfacial condensation polymerization has also been extensively used in emulsion-templated microencapsulation.<sup>52,112</sup> Recent collaborative work between the University of Illinois and Dow as part of the encapsulation research program combined several aspects of enhanced interfacial encapsulation to encapsulate polar aliphatic amines for one-pot epoxy applications. Inverse Pickering emulsions were generated using hydrophobically modified clay nanoplatelets as Pickering stabilizers, containing a water–amine solution in the core with a xylene continuous phase. Isocyanates were used to form a polyurea shell. It was found that the stability of the microcapsules was further improved by the addition of linear poly(allyl amine), an additive that appears to be interfacially active.<sup>113</sup> The resulting microcapsules formulated into a liquid epoxy resin yielded a stable suspension with a significantly improved shelf life. Epoxy curing could be easily induced through mechanical rupture of the capsules. These experiments demonstrate how fundamental studies and minor changes can induce significant effects toward improving the performance of encapsulated systems.

## 5. CONCLUSION

In this review, we have highlighted several of the emerging academic areas of encapsulation that we believe have specific relevance to industrial formulation. As formulations become more complex and higher performance, new technologies offering robust stability to many of the formulation additives will be required while still maintaining an acceptable cost profile. Ongoing challenges remain for development of new encapsulating materials that offer sufficient barriers for protection of the AI while maintaining a mechanism for providing the AI in its active form at the site of delivery. Better barriers are especially required for blocking small-molecule penetration (including water and oxygen) and for providing enhanced stability during formulation (such as from surfactants and salts) or processing (such as extrusion or spray drying). We hope that our review will inspire new research efforts to

maximize potential value for encapsulation in the chemical industry.

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### Notes

The authors declare no competing financial interest.

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