Formation of liquid core–polymer shell microcapsules

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Polymer shell microcapsules with liquid cores are used in a wide variety of industries, from food and flavour protection to inkless paper. There is a number of production methods, each with different characteristics and this article reviews a number of them. The methods considered are colloidosome formation, polymer precipitation by phase separation, polycondensation interfacial polymerisation, layer-by-layer polyelectrolyte deposition, polymer growth by surface polymerisation and copolymer vesicle formation. Each production method is described and the relative strength of each is outlined.

1. Introduction

This article examines different mechanisms of creating encapsulated systems. The manufactured dispersions comprise hollow particles of various sizes with an active liquid core. The shell, which stops active release and ensures the particles remain as separate entities, can be hard or soft, organic or inorganic, depending on the system. The main design criteria are the need for encapsulation, choice of compatible shell material that provides the desired release profile and the appropriate encapsulation technique. Fig. 1 shows an SEM image of 1 μm diameter particles with silica shells that display the morphology under consideration.

Why encapsulate

The manufacture of liquid-core particles is of increasing importance to many industries and is carried out for a variety of reasons; the primary one being to isolate the core from its surroundings. This can be for protection against a harsh denaturing environment, such as in protecting enzymes from denaturing by solvents[1] or shielding probiotic bacteria from high temperature food processing and passage through the digestive system.[2] It can also be applied to protect products from deteriorating effects like oxidation and moisture, especially in the food and beverage industry, as well as in the pharmaceutical industry, where drugs and vitamins are the active ingredients.[3]

Encapsulation also allows the pausing of any external chemical reactions until suitable conditions are achieved, for example in packaged baking mixes.[4] The isolation and protection allows an increase in shelf life of the active ingredient and this in turn maintains the product quality.

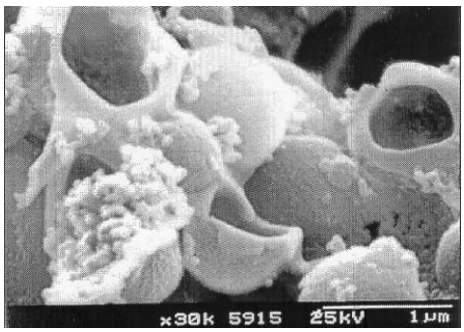

Fig. 1 SEM image of polydimethylsiloxane (PDMS) core particles with a silica shell, reproduced from the lab of Brian Vincent, with permission.

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Apart from critical protection, encapsulation allows for cellular immunoisolation and tissue growth, where the solid shell of the microcapsule acts as a rigid scaffold to support the living cells, while simultaneously providing a protected environment and allowing free diffusion of gases and nutrients. Further examples of the use of encapsulated systems include carrier systems for catalysts and as confined reaction vessels.[5]

A further reason for encapsulation is to allow for controlled and/or targeted release of the encapsulated ingredient. In pharmaceutical applications, the controlled release of an active drug species over an extended timescale is often the preferred method of treatment, and enclosing the drug inside a particle with well-defined release properties is a method of achieving this.[5] Treatments can also be targeted to particular points in the patient prior to release and combination of both mechanisms allows for the development of novel drug and vaccine delivery vehicles.

Other examples for targeted release include ink encapsulation for inkless paper, dyes for textile manufacture and perfumes for scratch-and-sniff magazine advertisements, whereby the encapsulated ingredient is generally released upon action of a stress to cause shell breakage.[4,6]

Encapsulation is also carried out to improve the handling characteristics of various materials. For example, to deliver potentially toxic materials to intended environments, such as pesticides and herbicides in agricultural and environmental applications,[7] requires a form of encapsulation, which can ensure safety in handling. This is also the case with detergents, where the delayed release in the washing cycle allows additional control. Encapsulation also allows simplification of manufacturing processes by allowing liquids to be handled as solids, especially in the food industry.[8]

Another common application for encapsulation is fragrance, flavour and colour trapping. In the food and cosmetic industries, encapsulation is typically used to either delay the release of a particular fragrance or to mask an unpleasant odour by containing the offending component.[9] It is necessary to release the active ingredient on demand, and hence these systems must release the encapsulant in response to a light shear, or some other trigger. Similar technologies are also used to delay the release of, or mask, flavours and colours.

Naturally occurring encapsulation systems

As can be seen, encapsulation is performed for a range of reasons. However, encapsulation is not a novel technology, since nature displays many cases. Three examples, over widely different length scales, of a protective shell surrounding an active ingredient are bacterial spores, plant seeds and egg shells.[9] Bacteria themselves are entities with a protective wall surrounding their core and thus, may also be considered an encapsulating system.

Release mechanisms

Depending on the application, there are a number of possible release mechanisms for microcapsules. The most dramatic release is by shell rupture through an applied shear or pressure. This requires a brittle shell and examples of such cases include inkless paper and fragrance release. The force required to break the shell is determined by the shell material and thickness, and both these parameters are controllable through the manufacturing process.

Another method of release is to dissolve the shell. This can be brought about by melting, solvent action, enzyme attack, hydrolysis, slow disintegration, chemical or photochemical reaction. The disintegration of the shell will lead to complete removal of the encapsulation and hence, total release. An example of such an application is the release of flavour from dry products like cake mixes when water is added.[9]

Shell breakage and dissolution are suitable for immediate release of the encapsulated ingredients. If gradual sustained release is preferable, whereby the core ingredient is released over an extended period of time, diffusion through a permeable shell is an option. The encapsulated ingredient will slowly diffuse through the shell, in which the diffusion rate is controlled by the shell permeability as well as the size and shape of the active.[10]

An alternative to sustained release is to employ a swellable shell, which is formed by incorporating responsive materials into the shell. Such materials undergo reversible transitions when stimulated by external conditions such as pH,[11] ionic strength,[12] light[13] and temperature.[14] Shell swelling initiates the release of the encapsulant and hence, control over the release profile is maintained by control of the relevant trigger.

2. Methods of encapsulation

Encapsulation has evolved extensively over the years. Various methods have been reported including liposomes,[9] dendrimers[5] and silica shell microcapsules.[15,16] In this article, a number of possible methods for preparation of core-shell particles is reviewed. The pros and cons of each method are examined and discussed in detail, with a preface summary attached in Table 1. The main focus is on liquid core particles, although there is a brief discussion on the use of colloidal particles as templates for the core-shell morphology.

With the range of techniques available, many different types of liquid cores can be encapsulated. The most common cores consist of organic materials, necessitated by the production methods, although aqueous cores are starting to be reported.[17,18] For biological applications, the use of an aqueous core is crucial and this necessitates production without using many solvents and monomers that are commonly employed. For aqueous systems, a self-assembly type approach is the preferred method.

Colloidosomes

Colloidosomes are microcapsules whose shells consist of coagulated or fused colloid particles. They allow a great degree of control on the permeability of the entrapped species by varying the colloid particles' size and/or degree of fusing. The production method is sketched in Fig. 2.

An aqueous suspension of colloidal polymer particles is emulsified in an organic phase, with the shear rate of the mixer governing the size of the emulsion droplets formed. The colloidal particles migrate to the oil/water interface and stabilise the water-in-oil emulsion droplets. The colloidosomes thus formed require stabilisation by locking the particle layer.

Table 1 Pros and cons of different methods of encapsulation

Methods of Encapsulation	Pros	Cons
Colloidosomes	Formation by self-assembly	Further shell stabilization stage required to ensure robust structure
	Suitable for biological encapsulation due to no contact with harsh solvents	Risk of incomplete shell formation leading to leakages and/or core contamination
	Good degree of control on shell permeability	
	Possibility of dual levels of encapsulation with gelled core	
Polymer precipitation by phase separation	More suitable for oil core encapsulation	Right wetting conditions critical for microcapsule formation
	Microcapsules with relatively thick shells obtained	Use of organic solvents required
	Narrow size distributions	Less than 100% release of active ingredients
		Large volatile organic solvent content required for aqueous core microcapsules
Polycondensation interfacial polymerization	Suitable for both oil cores and aqueous cores	Shell formation is diffusion controlled and hence slow
	Simple fabrication procedures	
Layer-by-layer polyelectrolyte deposition	More common with aqueous cores due to electrostatic attraction as driving force	Laborious fabrication procedures
	Controllable shell thickness by number of times process is repeated	Long term stability dependent on surrounding conditions
	Possible biological encapsulation due to non-use of harsh solvents	High tendency for flocculation
		Only possible with low particle concentrations
Polymer growth by surface polymerization	Ease of control over shell composition and thickness	Not feasible for liquid core encapsulation
Copolymer vesicles	More robust relative to liposomes	Other ordered structures (micelles) coexist
	Microcapillary device used, enabling uniform vesicles with high encapsulation efficiency	Stability highly dependent on copolymer composition and surroundings
		Polymersome formation limited by either dilute copolymer solution or droplet formation frequency

The easiest way to do this is to heat the dispersion, causing the polymeric particles in the shell to sinter and form a continuous shell. Alternative shell locking mechanisms include the use of coagulant or polymer adsorption once stabilised. The colloidosomes can be re-dispersed in an external fluid that is similar to the encapsulated environment. A similar but alternative production is to use colloidal particles that are initially suspended in the organic phase.

The first colloidosomes were made by Velev *et al.*[19–21] by introducing oil emulsion droplets into an aqueous suspension of micron-sized polystyrene particles, whereby the polymer particles coated the emulsion droplets, providing stability. Velev *et al.*[19–21] tailored the interparticle interactions by adsorbing surfactants to the particle surface, prior to emulsification, and this was termed 'interaction-tailored colloid assembly'. The third paper by Velev *et al.*[21] introduced

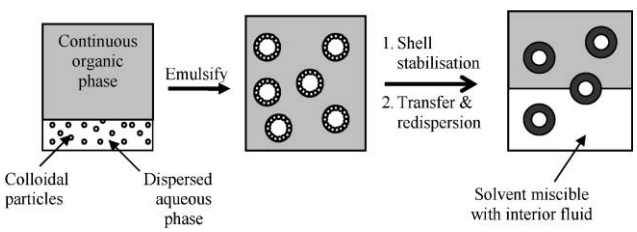

Fig. 2 General overview on the fabrication method of colloidosomes.

water-core structures that were developed further by Dinsmore *et al.*,[17] and this paper coined the phrase 'colloidosome'.

Hsu *et al.*,[22] continuing the work of Dinsmore *et al.*,[17] fabricated colloidosomes using a direct self-assembly method. The technique's success lies in the self-assembly of a particle layer at the emulsion drop surface, which in their case is due to the particle surface hydrophobicity and hence, a minimisation of the total interfacial energy. Hsu *et al.*[22] tailored the permeability of the polymer shell by controlling the sintering of the particles and with polystyrene particles, a sintering temperature of around 100 °C was required. Using different polymers with lower glass transition temperatures, sintering can occur at much lower temperatures.

Based on the self-assembly method, Yi *et al.*[23] and Ashby *et al.*[24] improved the size distribution of the fabricated colloidosomes. This was achieved by using a droplet break-off technique, where the particle suspension was introduced into a co-flowing, surfactant-laden continuous phase *via* a tapered capillary.

Another novel type of colloidosome was introduced by Cayre *et al.*,[25] Noble *et al.*[26] and Duan *et al.*,[27] who applied a gel trapping technique. Instead of a liquid-core, gelling the aqueous sub-phase and formation of a particle monolayer at the interface results in colloidosomes with a solid-like core. The advantages of this include better support for the shell as well as extra stiffness and structural integrity for the colloidosomes to survive their transfer into an aqueous phase.

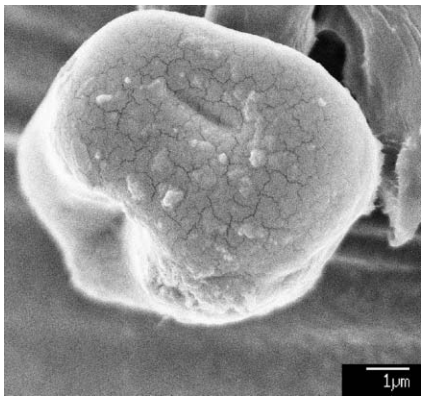

Fig. 3 SEM image of a buckled water-core colloidosome.

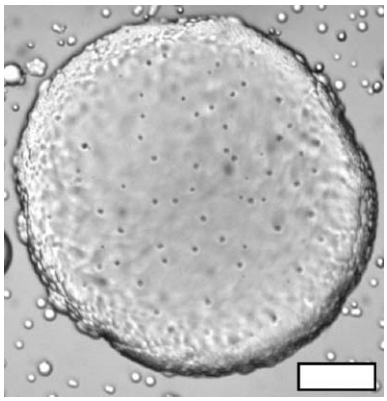

Fig. 4 Optical micrograph of a water-core colloidosome with titania incorporated (white bar = 50 μm).

The gel core also provides an additional level of encapsulation on top of the particle monolayer.

Currently, Yow and Routh are encapsulating aqueous cores with polymer shells using sunflower oil as the external phase and hexadecyltrimethylammonium bromide (CTAB) as a stabiliser. The choice of organic phase is insignificant and merely dictated by the user's preference. By ensuring marginal colloidosome stability during the shell sintering stage, colloidosomes are formed, as shown in Fig. 3, which shows a buckling in the shell. This is believed to be caused by the osmotic pressure from the external aqueous phase, which contains 1 vol% surfactant.

The self-assembly formation of aqueous core microcapsules is the greatest attraction of colloidosome technology, especially for biocompatible encapsulations. With an extensive choice in colloidal particle morphology and potential release mechanisms, the colloidosomes can be tuned to have the desired mechanical, optical, electrical and magnetic properties. In addition, deposition with inorganic, metal, or metal oxide components in the shell allows reactants to undergo transformations in the shell before encountering the encapsulated active. An example of this is shown in Fig. 4, which shows an optical micrograph of a water-core colloidosome with titania dispersed in the shell.

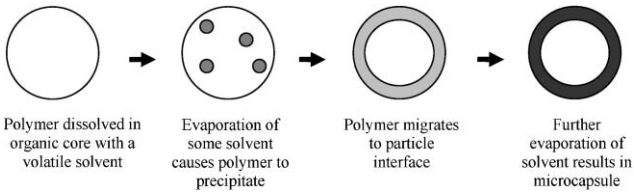

Fig. 6 Schematic of steps involved in solvent extraction and evaporation fabrication (Adapted from Loxley and Vincent[31]).

Polymer precipitation by phase separation

Formation of hollow microcapsules by phase separation and precipitation of a shell-forming polymer has been described in depth by various patents and publications. There are two approaches that dominate this formation: (i) polymerization induced phase separation and (ii) solvent extraction and evaporation.

The concept of polymerization induced phase separation uses an emulsion droplet containing a dissolved monomer. After initiation, as polymerisation proceeds, the growing polymer chains become immiscible with the dispersed phase. The polymer phase separates leading to deposition at the interface and shell formation. It is common for this to occur with oil cores in an aqueous continuous phase, as shown in various publications, including Kasai *et al.*,[28] Berg *et al.*,[29] and Tiarks *et al.*[30] The fabrication method is shown in Fig. 5.

A second method, solvent extraction and evaporation, also predominantly uses oil-in-water emulsions. The oil phase consists of a mixture of the shell-forming polymer, a volatile good solvent and a non-volatile non-solvent. As the good solvent evaporates, the polymer phase separates as small droplets of polymer-rich liquid within the emulsion droplets. Provided the right wetting conditions are achieved, these droplets will migrate to the interface and engulf the original droplet. Further solvent removal encourages more polymer precipitation into the shell and forms the core-shell microcapsules. This fabrication method is sketched in Fig. 6.

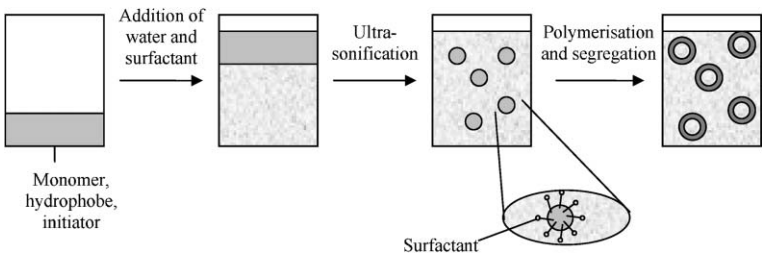

Fig. 5 Polymerisation induced phase separation fabrication overview (adapted from Tiarks *et al.*[30]).

The recent work on solvent extraction and evaporation has been performed by Loxley and Vincent,[31] Romero-Cano and Vincent[10] and Dowding *et al.*[32,33] In addition there are a few patents on this methodology, established by Baum *et al.*[34] and Mathiowitz and Langer.[35]

A new alternative to induce phase separation has recently been developed by Shulkin and Stöver,[13] who utilise light to stimulate the phase separation process. The success of this lies in the photo-responsive polymer used, which can isomerise between its *trans* and *cis* forms to alter its solubility in the core oil and thereby form a stable, permanent shell.

The phase separation techniques outlined above are mainly suitable to encapsulate oil cores. Although conceptually analogous, the necessary modifications to enable easy encapsulation of aqueous cores are still an active research topic. Currently, there are two established, though complicated methods.

The first was introduced by Atkin *et al.*,[18] who applied the solvent extraction and evaporation technique. The drawback in this is the high concentration of acetone needed as the volatile good solvent in the aqueous phase. This results in an acetone-in-oil emulsion instead of water-in-oil. To dissolve the shell-forming polymer, a minimum mass ratio of acetone to water of 12 : 1 is needed. As the acetone evaporates, the overall mass of the aqueous phase is greatly reduced, resulting in much smaller microcapsules. This is more clearly illustrated in Fig. 7. Despite this, the solvent evaporation approach has successfully produced aqueous core microcapsules.[18]

The second approach was proposed by Zydowicz *et al.*[36] and Lorenceau *et al.*,[37] who utilised a double emulsion (water-in-oil-in-water) solvent evaporation technique. Initially, a small volume of aqueous phase is emulsified within a polymer–solvent oil phase. A subsequent emulsification of the organic phase in a larger volume of water generates the double emulsion. The volatile solvent is removed as it diffuses into the external aqueous medium and evaporates off. The removal of the solvent precipitates the polymer, thus encapsulating the inner aqueous phase.

Regardless of approaches, the key elements that govern the success of fabrication by phase separation are the efficiency of the forming or preformed polymer to phase separate from its dissolved condition and the smooth spherical formation of the shell. The final morphology of the core–shell systems is determined by the relative surface energies. If the core and external phase have a very large surface energy, then an encapsulated state is favoured. Conversely, if the shell–core surface energy is large, then a separation between phases is observed. The relative surface energies are controlled experimentally by the use of surfactant, and for different systems,

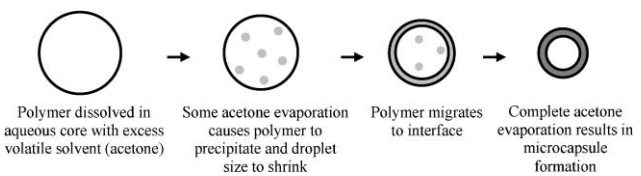

Fig. 7 Schematic of steps for aqueous core microcapsules by solvent extraction and evaporation (adapted from Atkin *et al.*[18]).

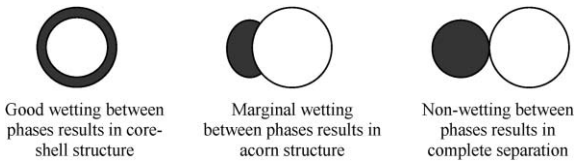

Fig. 8 Possible equilibrium configurations corresponding to three different wetting conditions (adapted from Dowding *et al.*[32]).

each of the morphologies in Fig. 8 has been observed.[31] This idea of monomer/polymer phase separation and effects of different wetting conditions had also been demonstrated by Mock *et al.*[38] in their research on seeded emulsion polymerization to form anisotropic nanoparticles.

Polymer precipitation microcapsules have been widely used in various applications, including protection, oxidation prevention, perfume trapping and controlled release. The main advantages of this fabrication are the reasonably narrow size distributions and controllable shell thickness, with thick shells easily produced to give predictable and tuneable release profiles. However, the drawbacks include less than 100% release of the active ingredient as well as the use of volatile organic solvents which may well harm the encapsulated active. In addition, it is often very difficult to choose the necessary ternary system.[18]

Polycondensation interfacial polymerisation

Microcapsules from this method of preparation can be produced as either oil-in-water or water-in-oil emulsions. The technique involves two monomers that are dissolved in incompatible phases meeting at the interface and reacting to produce a 'primary membrane' almost instantaneously. The reaction rate is then decreased as diffusion of monomers becomes restricted by the polymeric shell. Sufficient time is required to ensure complete wall formation. The process is shown schematically in Fig. 9.

Generally, microcapsules of this form can be fabricated with either nylon or polyurethane as the shell. For nylon microcapsules, aqueous phase diamine and/or triamine will diffuse and meet with the organic phase of terephthaloyldichloride to produce and precipitate the nylon polymer as the microcapsule wall. A common model of this interfacial reaction involves polycondensation of ethylenediamine with terephthaloyldichloride. The structure of the reactants is shown in Fig. 10.

The original work to produce nylon shell capsules, which were a millimetre in size, was achieved by using a syringe pump to push aqueous drops of monomer in basic solution into an organic phase. Rosenthal and Chang[39] produced capsules with

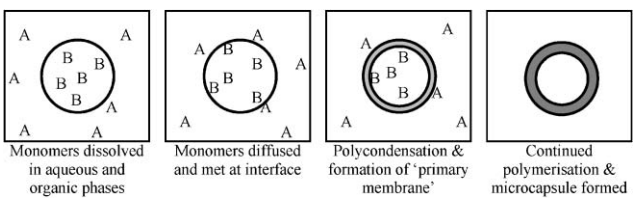

Fig. 9 Schematic of the polycondensation formation of shells around emulsion droplets (adapted from Bouchemal *et al.*[48]).

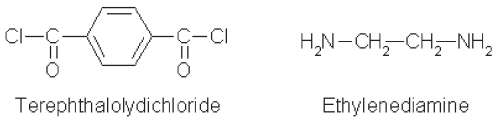

Fig. 10 Reactants for a typical polycondensation reaction.

1,6-hexanediamine in 0.2 M NaOH aqueous solution as the core, with sebacoyl chloride as the organic-based monomer in a cyclohexane–chloroform mixture.

Okahata *et al.*[40–43] produced 2 mm diameter drops with 5 μm thick shells using a very similar method, which involved adding ethylenediamine in 0.8 M NaOH aqueous solution into an organic mixture of chloroform and cyclohexane. The organic-based monomer was terephthaloyl chloride or 1,10-decanedicarbonyl chloride with a crosslinker, trimesoyl chloride, added to produce a strong non-dissolvable shell.

Janssen and te Nijenhuis[44–46] produced droplets of 4 mm diameter but with an organic core through the use of terephthaloyldichloride in dibutylphthalate and diethylenediamine in basic aqueous solution. The authors modelled the growth in shell thickness, and since the transport of monomer through the forming shell was the limiting step, the shell thickness was predicted to grow with time to the power of ½.

For polyurethane microcapsules, the reaction of a diol with a diisocyanate will result in the formation of polyurethane. This reaction is exactly analogous to nylon production. The diol is dissolved in the aqueous phase and the diisocyanate in the organic. Reaction at the oil–water interface produces the encapsulating shell. The reaction scheme is outlined in Fig. 11.

Frere *et al.*[47] made water-core particles using pentane diol in water and emulsifying in toluene containing a di- or multi-functional diisocyanate. The particles produced were 50–400 μm in diameter, although this was controlled by the stirring rate.

Bouchemal *et al.*[48] produced oil-core particles with isophorone diisocyanate dissolved in an acetone α-tocopherol mixture. In each experiment, a different diol (ethylene glycol, 1,4-butanediol and 1,6-hexanediol or different molecular weights of polyethylene glycol) was dissolved in water and the organic phase was introduced whilst stirring. Emulsion droplets were formed with the acetone dissolving in the aqueous continuous phase resulting in the wall growth polymerisation. Bouchemal *et al.* reported the particle size to be between 100 and 500 nm, with the use of higher molecular weight polyethylene glycol resulting in larger particles.

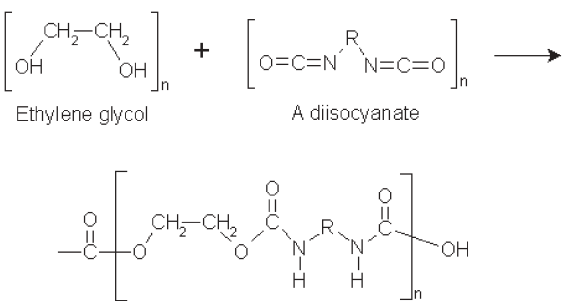

Fig. 11 Polyurethane formation (adapted from Bouchemal *et al.*[48]).

Dobashi *et al.*[49,50] produced poly(urea urethane) shell microcapsules. This was done by dissolving a triisocyanate in an ethyl acetate–dioctyl phthalate organic phase and emulsifying in an aqueous solution containing poly(vinyl alcohol-co-vinyl acetate) stabiliser. In a later publication, the dioctyl phthalate was replaced with phosphoric acid bis-(2,3-dibromopropyl)-2,3-dichloropropyl ester, producing particles of about 200 nm in diameter.

Polycondensation interfacial polymerisation provides an easy control of final shell thicknesses and has an ease of manufacture. Examples of the use of polyurethane microcapsules are in toner particles and pesticide encapsulation. However, the use of monomers in both phases negates the possibility of putting biologically active materials in the core and indeed, as far as the authors are aware, there are no reports of biological encapsulation using this method.

Layer-by-layer polyelectrolyte deposition

Building up alternating layers of polyelectrolytes through electrostatic deposition has been studied extensively with the earliest papers describing deposition onto planar surfaces.[51,52] This methodology was subsequently applied to particulate systems to fabricate capsules of various sizes, ranging from nanometre to micrometre dimensions.[53,54] The production method is depicted schematically in Fig. 12.

The principle behind this technique is in the utilisation of electrostatic attraction and complex formation between oppositely charged polyions to form the polyelectrolyte shell microcapsules. A charged particle is initially placed in a dilute solution of polyelectrolyte of opposite charge. The electrostatic driving force forces the polymer to coat the particle, thus changing its apparent charge. Any excess polyelectrolyte is then removed by cycles of centrifugation and washing. Once cleaned, the deposition is repeated with a polyelectrolyte solution of opposite charge and the process is repeated as many times as desired. Finally, the core is dissolved to obtain a hollow microcapsule. Poly(styrene sulfonate) is typically used as the polyanion, and poly(allylamine hydrochloride) as the polycation.

Various applications of this production method have been investigated. An example involves the use of latex particles, in which core–shell structures were reported and eventual dissolution of the latex resulted in hollow polyelectrolyte

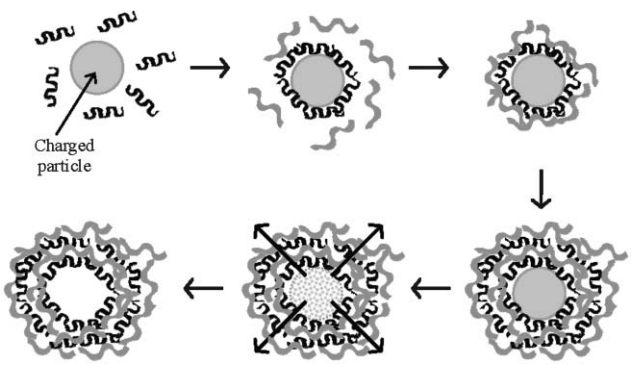

Fig. 12 Schematic on layer-by-layer polyelectrolyte deposition (adapted from Donath *et al.*[54]).

capsules.[55] The encapsulation of an enzyme with this technique had also been reported,[1] in which a solid enzyme crystal was repeatedly coated and then solubilised to form a solution inside the capsule. Other applications include coating of latex particles with semiconductors and metallic layers,[56] functionalisation of particle surfaces[57] and control over interparticle potentials.[58] A review article on this type of particles had been recently published by Antipov and Sukhorukov.[59]

Recently, an alternative production method has been developed, which utilises an *in situ* coupling reaction rather than electrostatic attraction to encourage polyelectrolyte deposition.[60] This technique is known as 'covalent layer-by-layer assembly' and the synthesis is almost identical to the electrostatic assembly. The advantage of this method is to extend layer-by-layer assembly from aqueous (which is the basis for electrostatic assembly) to non-aqueous systems. In addition, the shell has a covalent nature and therefore enhanced stability. This technique, introduced by Zhang *et al.*,[60] utilised *N*-methyl-2-nitro-diphenylamine-4-diazoresin and *m*-methylphenolformaldehyde resin as the alternating polymers.

The layer-by-layer polyelectrolyte deposition approach allows a user-specified shell thickness and avoids the use of harsh solvents. The polyelectrolyte shell maintains its shape and a hollow sphere morphology has been demonstrated successfully after the removal of the template, though this stability, especially in the long run, is critically dependent on the environment surrounding the particles. The successful encapsulation of an enzyme, with continued biological activity, demonstrates the possibility of biocompatibility with such hollow particles.[1] The downside of this technique is the long time involved with the multiple deposition steps as well as the tedious particle cleaning required after each deposition to remove the excess non-adsorbed polyelectrolyte. Another issue is the high tendency for polyelectrolyte-induced particle flocculation, resulting in the requirement to work at very low particle concentrations, thus affecting the overall production rate.

Polymer growth by surface polymerisation

An alternative method of placing a polymer shell around a colloidal template is to use surface polymerisation. This begins with an initial modification of the template surface and their use as seeds for polymerisation. Subsequent polymer cross-linking then creates the core–shell structure. This system can be made hollow by removing the core through chemical etching. A sketch of the fabrication method is presented in Fig. 13.

This encapsulation method had been demonstrated by Zha *et al.*,[14] who grew poly(*N*-isopropylacrylamide) (PNIPAM) chains from silica particles with subsequent dissolution of the silica by hydrofluoric acid etching. The benefit of these particles, as reported by Zha *et al.*,[14] was the temperature responsiveness of the shell, with PNIPAM showing a temperature induced swelling below 32 °C.

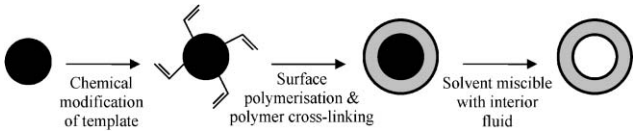

Fig. 13 Schematic on polymer growth by surface polymerisation (adapted from Zha *et al.*[14]).

As a method of placing polymer chains from a solid surface, direct growth is the obvious choice. However, for the attainment of liquid cores and hence, a wide range of encapsulations, this method is not feasible.

Copolymer vesicles

Amphiphilic block copolymers are able to self-assemble to form a thin molecular membrane, enclosing an inner core. This arrangement has been termed copolymer vesicles. The idea was developed from liposomes, to give more stable, robust carriers.[61,62] Various factors govern the vesicle formation: the free energy contribution by the chains including their preferred arrangement in terms of order and crystallinity,[63] the environment choice for the polymer *i.e.* nature of solvent, additives and temperature,[64] however, the most crucial factor is the composition of the block copolymer. The relative size of the hydrophobic to hydrophilic moieties determines whether the bilayer membrane will spontaneously form a vesicle or a planar lamellar structure.[63–66]

Generally, copolymer vesicles are nanometres in size, as reported by Adams *et al.*,[67] Soo and Eisenberg,[64] Ding and Liu,[68] Holder *et al.*,[69] Meier[5] and Nardin *et al.*[70] However, since this article is concentrating on microcapsules, the following will discuss micron-sized copolymer vesicles, known as polymersomes. This term was coined by Discher *et al.* in 1999.[71] In this paper, Discher *et al.* introduced the formation of polymersomes by electroformation. This method used an alternating electric field to generate the vesicles from the polymer film-coated electrodes. The assembly was originally submerged in a sucrose solution and the formed vesicles were then dissociated by lowering the field frequency.

Alternatively, polymersomes can also be made by rehydration.[61] In this technique, water, or a solution of sucrose, was added to a dried lamellar polymer film, a few microns in thickness. Rehydration induced the lamellar copolymer to buckle and thus form the vesicles. Other structures like micelles and/or wormlike micelles were also formed simultaneously through this method. Apart from this, polymersomes can also be made by direct dissolution in water.[72] In this approach, the copolymer was initially dissolved in an organic solvent, which was then added dropwise into a stirred aqueous phase to form the vesicles.

Despite the simple synthesis methods, the microcapsules formed are typically polydisperse and coexist with other ordered structures. Therefore, Utada and co-workers improved on the polymersome formation by using a double emulsion solvent evaporation technique, coupled with microfluidics.[37,73,74] The key to this technique lay in the use of a microcapillary device to generate the water/oil/water double emulsion, in which the inner and outer fluids were always kept separate. The copolymers were initially dissolved in the organic phase. As the emulsion droplets formed, the copolymers migrated to the concentric interfaces and self-assembled.

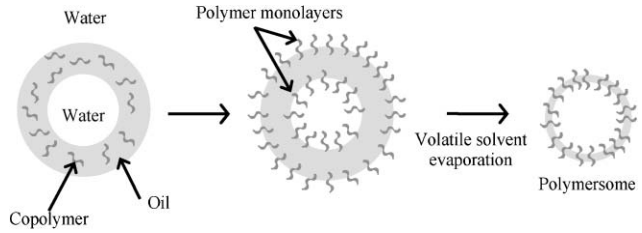

Fig. 14 Schematic for formation of polymersomes by double emulsion solvent evaporation technique with microfluidics (adapted from Hayward *et al.*[74]).

Gradually, all the volatile solvent evaporated, and thus formed the polymersomes, depicted in Fig. 14.

The attractiveness of polymersomes for encapsulation lies in the availability of biodegradable copolymers, especially for use in biomedical applications.[62,72,75] These microcapsules are generally more robust than liposomes, and this can be further enhanced by cross-linking the polymer network.[65] Another appeal of the polymersomes is in their formation within microcapillary devices. This apparatus enables formation of uniform vesicles with high encapsulation efficiencies as well as ease of control over particle size and architecture, including multi-inner-compartment structures.[73] The main downside is the number of vesicles formed, as this is limited by the droplet formation frequency of the device.

3 Responsive shells

A large effort has been put into the making of microcapsules with responsive shells to allow release of active ingredients in response to an external stimulus. Chu *et al.*[76,77] reported capsules synthesised by the polycondensation interfacial polymerisation method outlined above, with poly(*N*-isopropylacrylamide) plasma polymerised into the pores. The subsequent particles showed a temperature mediated release profile.

Sauer *et al.*[11,78] reported pH-responsive particles made *via* a different route. Surfactant vesicles were prepared in an aqueous solution and hydrophobic monomers were introduced to swell the vesicles with polymerisation started by UV irradiation. Subsequent removal of the surfactant led to polymer capsules in the size range of a few hundred nanometres. The use of poly(acrylic acid) shells resulted in a pH-mediated swelling around pH 5 and thus, a pH-mediated release from the capsules was achieved.

A new advancement is the self-rupturing microcapsule, as introduced by De Geest *et al.*[79] These pH-responsive microcapsules are made using the layer-by-layer polyelectrolyte deposition method. The rupture time of the microcapsules is governed by the degradation kinetics of the entrapped microgel, dextran-hydroxyethyl methacrylate (dex-HEMA). This in turn controls the swelling pressure within the microcapsules as a function of time. Above a certain inner swelling pressure, the capsule ruptures releasing the encapsulated ingredient. The advantage of this microcapsule is that it allows pulsed delivery of the ingredient, resulting in non-uniform release profiles, as is often desired in medicinal application of hormones and vaccines.

4. Concluding remarks

The methods outlined above are all capable of creating microcapsules with sizes ranging from sub-micrometre up to a few hundreds of microns. The shell thickness is the major factor controlling release, offering a way of manipulation on the dissolution rates and fracture stresses that govern the release of the active ingredient. The production of organic core particles are the most commonly reported, however for biocompatible systems, it is imperative to formulate aqueous core capsules without the use of harsh chemicals.

The encapsulation of an enzyme has been reported using the layer-by-layer polyelectrolyte deposition approach with the biological activity retained. The only other method that seems capable of also achieving this is colloidosomes. Whilst, the other methods outlined all show ingenious ways of producing hollow particles, the self-assembly approach without recourse to denaturing environments is a huge advantage of the layer-by-layer polyelectrolyte deposition, copolymer vesicle and colloidosome methods.

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