

Manufacture of microcapsules



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Abstract

The following report is a summary of literature reviewed for the manufacture of microcapsules. More specifically the main focus of the review is the preparation of polyelectrolyte microcapsules by the Layer-by-Layer method of manufacture. This method involves the consecutive coating of by oppositely charged polyelectrolyte species onto a core template, which is then dissolved to give a hollow microcapsule. This method provides microcapsules with complex architecture, which can then be used in a variety of applications. The material reviewed includes templates, polyelectrolytes and core dissolution methods that can be used for preparation of such microcapsules. Methods of filling the core with certain materials are also discussed, as are mechanisms for release of the encapsulated material. There are also various detection methods available, which have also been reviewed – some of which requiring modification of the polyelectrolyte wall during synthesis to ensure detection and characterisation can be carried out accurately. Finally the preparation and application of anisotropic (or ‘Janus’) microcapsules is discussed, with the relative lack of literature relating to this topic providing an interesting area for possible further research.

Introduction

Encapsulation is a technique that has been used to great effect throughout history in order to protect materials (solid, liquid or gasses) from a surrounding environment. The majority of examples relate to the macroscopic world, including examples such as the storage of food, drink, volatile liquids and chemicals in various containers to prevent reactions with

the surrounding air occurring. Nature itself provides many examples of encapsulation such as eggs, seeds and fruits, all of which have different properties such as permeability and composition based on the intended purpose of the enclosed material. Another particularly good example of encapsulation in nature is demonstrated in the composition of cells. Each cell has a flexible biolipid membrane enclosing the cell material, which acts as a permeable barrier capable of controlling what enters and leaves the cell.[1] The reality is that there are an infinite number of examples of encapsulation on a macroscopic scale.[2]

The principle of microencapsulation links to the same principle of protecting a material from the environment in which it is surrounded, however it relates to particles with diameters on a μm scale.

Microcapsules are used in a wide variety of applications including pharmaceuticals, cosmetics, agricultural industry, food technologies and textiles industry. Microcapsules have also been used for over 50 years in the printing industry, with an early application being sheets containing ink filled microcapsules which would rupture when pressure was applied to them and hence acting as a replacement for carbon copy paper.[3] A better known application of microcapsules can be found in the production of many pharmaceutical products for targeted drug delivery. In this example the core material of the microcapsule is a specific drug which can be released over a certain period of time via diffusion, by a pressure change causing the capsule to rupture or by combination of the microcapsule wall with the target cell wall.[4] The method of drug delivery is dependent on the design of the shell of the microcapsule which can be tailored to the required application, <https://assignbuster.com/manufacture-of-microcapsules/>

with certain properties being easier to achieve than others. A relatively easy and commonly used method of preventing release of drugs into the stomach and oral cavities is the use of gelatine capsules that are resilient to low pH. This property allows them to be digested further in the GI tract and the drug released at a specific point/time. The difficulty comes when designing a microcapsule for sustained drug release over a designated time period, which requires slow decomposition of the shell of the capsule in order to be achieved. A recent area of interest is the triggered release of drugs from microcapsules, which allows the release of drugs at an exact point e. g. when in contact with a cancerous cell or tissue. This technology is still relatively experimental with most triggered release mechanisms requiring a triggering system such as ultrasound[5], external magnetic fields and laser irradiation (discussed in further detail later in this review). Other approaches use self assembling vesicles and liposomes that form capsules under specific conditions. Another approach to achieving targeted delivery is the use of polyelectrolyte capsules which are formed by the alternate deposition of oppositely charged electrolytes around a core material such as polystyrene (PS). The core can be dissolved once the shell has been formed allowing the hollow microcapsule core to be loaded with a material for the designated purpose. This layer-by-layer (LbL) technique of forming polyelectrolyte capsules was first published nearly 20 years ago,[6] will be the primary focus of this literature review which will also discuss the progressions made in the field of microencapsulation as well as different types of microcapsules, methods of manufacture, stability, application and detection of such microcapsules.

It should be mentioned that there are other methods than the LbL technique, which can be used to create microcapsules without utilising polyelectrolytes. An example of an alternative method is the heterocoagulation of 'large' cationic microbeads (used as the core material), with small anionic polymer beads. The small anionic particles surround the core material and after an annealing process is applied, form a dielectric shell around the core material. This can then be dissolved if required to complete the synthesis of a hollow microcapsule.[7]

Polyelectrolyte Microcapsule Manufacture

Basic Principles

As previously stated, the LbL technique of creating microcapsules from colloidal particles has been published for around 20 years. The principle behind this method is the consecutive deposition of oppositely charged aqueous polyelectrolytes. This means that after initial deposition onto the core template, electrostatic interaction causes a layer of polyelectrolytes to form around the template as the oppositely charged species bond to the corresponding polyanion/cation. Once the polyelectrolyte shell has been formed to the required specification and the excess material removed if necessary, the core can then be dissolved by using an appropriate solution (commonly an acid) depending on the initial core template. When compared to liposomes and other hollow core particles, microcapsules created by this particular method offer much greater permeability, stability and selectivity. This technique was initially used to create polyelectrolyte layers on planar surfaces,[8] however by using a spherical template such as a colloidal particle it is relatively easy to apply the method to this application. Figure 2 gives a schematic diagram of the LbL method.

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There are two approaches which can be used to apply this method, the first being where the correct amounts of polyelectrolyte material required to form a layer are added at each step, or the second in which the polyelectrolytes are added in excess. Both methods have advantages and disadvantages, the advantage of the first method is that the process is relatively quick since the polyelectrolytes adsorb onto the surface quickly and no washing or filtration is required in between cycles. A further advantage comes from the fact that there is no loss of polyelectrolytes during washing cycles as exact amounts are used for the synthesis. The disadvantages of this method are that it can be difficult to use exactly the correct amount of polyelectrolytes necessary to form a saturated shell and not to add the polyelectrolytes in excess, which can lead to the formation of polyelectrolyte complexes and aggregates in solution. This issue is extremely difficult to overcome and as a result the use of polyelectrolytes in excess is often chosen in favour of this method. A further disadvantage is that as a consequence of this method it is often common to lose the controlled layered structure.[10] Despite the excess polyelectrolyte method being more favourable there are still several disadvantages associated with using this method. One example being that since an excess of material is used there is a need for filtration/centrifugation and washing after each step in order to prevent a complex solution of polyelectrolytes forming, which can often mean the process is very time consuming. Removal of excess material by centrifugation can also add further complications as it can often lead to loss of material, cause resuspension issues as well as making it difficult for small and low density particles to successfully settle.

Polyelectrolytes and Templates Used

The polyelectrolytes used in the synthesis of the microcapsules will depend upon its intended application. Certain polyelectrolytes will give different properties to the microcapsule wall such as permeability, stability, pH resistance etc. compared to others.

In order for formation of a microcapsule wall, the material chosen must have sufficient charged groups along the length of the unit. Polyelectrolytes should ideally be chosen where at least 50% of the monomer units comprising them carry a functional charge.[11] Commonly used polyelectrolytes used for both microcapsules and on planar surfaces are Poly(styrene sulfonate) (PSS), Poly(allylamine) (PAH) and Poly(diallyldimethylammonium) chloride (PDA or PDADMAC).[12] While PAS and PAH are the most commonly used and studied polyelectrolytes in this field, there have been other types of polyelectrolytes used such as polyacrylic acid (PAA), Dextran sulfate, Nafion[13] and poly(ethyleneimine) in applications such as delivery of ibuprofen and other drugs.[14] Table 1 illustrates some commonly used polyelectrolytes.[15]

The choice of polyelectrolyte is obviously extremely important when designing a microcapsule, however before this selection is made it is necessary to choose a core material that will be used as a template for the microcapsule to be built around. The core template itself must remain stable during the LbL polyelectrolyte deposition process and must be able to be fully dissolved without affecting the structure or stability of the multilayer shell. For obvious reasons it is also preferential to have a template with spherical geometry.

The most commonly used template in LbL microcapsule synthesis is melamine-formaldehyde (MF)[16]. The reasons for this are that MF templates remain stable at pH values above 5, hence allowing polyelectrolyte deposition to be carried out at a favourable pH of 7, also MF is readily dissolved in 0.1M hydrochloric acid. [17] One drawback of this however is that on dissolution of the MF core, the protonated oligomers produced cannot diffuse out as readily as would be desired. The size of the oligomers produced is directly linked to the molecular weight of the MF used in the synthesis, which can often differ quite significantly in a batch. This causes the capsules to swell, generating an increased osmotic pressure inside the capsule which in turn creates stress on the polyelectrolyte wall. If the capsule has many layers of polyelectrolyte (> 12) then the capsule is often not able to shrink back in size as the oligomers diffuse out, which can then lead to rupture of the capsule wall. 15 Another drawback is that the MF core can often leave residues inside the microcapsule as a result of the strong interaction between MF and the inner PSS layer of polyelectrolyte. In the event of this occurrence, up to 50% of the mass of the microcapsule can be attributed to these residues. MF templates are also very expensive compared to other more readily available materials.

Other templates used include polystyrene, latex, silica, calcium carbonate (CaCO_3)[18], manganese carbonate (MnCO_3)[16], metal nanoparticles as well as organic and inorganic crystals. No single core template gives the exact requirements, for example polystyrene cores are dissolved with THF[19], which can lead to high mechanical stress on the capsule and leave residues after dissolution, whereas silica particles tend to aggregate when dissolved.

Despite these drawbacks until new alternatives are found then it is necessary to use these templates in such a way that will give the maximum yield of microcapsules possible.

Once the core has been dissolved it is still possible to change certain properties of the microcapsule. For example it is possible to change the permeability by the addition of further polyelectrolyte layers if required.[20]

Due to the high applicability of microcapsules to the pharmaceutical industry there is an ever-increasing interest in the development of using polyelectrolytes that are naturally occurring species. An example of such polyelectrolyte is chitosan which is a naturally occurring linear polysaccharide. Chitosan is also biodegradable and non-toxic, which means that it is well suited to a pharmaceutical application. The LbL synthesis of chitosan microcapsules requires a slightly different synthetic method compared to a microcapsule made of polyelectrolytes such as PSS and PAH. Zhang et al. have demonstrated that it is possible to use the LbL method with chitosan and poly-(acrylic acid) (PAA) along with a silica template to form a polyelectrolyte shell, which can then be converted into a single component chitosan shell if required. This is achieved by selectively cross-linking the chitosan in the microcapsule wall, removing the PAA component before dissolution of the core template. This method is demonstrated in Figure 3.[21]

Modification of Polyelectrolyte Wall

It is possible to alter the properties of the polyelectrolyte wall of the microcapsule in order to introduce elements of functionality. One such

alteration is the addition of a dye or fluorescent labelled material during the LbL synthesis of the microcapsule. This particular example can be used as a method of detection and will be discussed in further detail later in this review.

Use of Magnetic Particles

Another useful modification of the polyelectrolyte wall is the incorporation of magnetic particles during synthesis of the microcapsule. This allows control of the positioning of the microcapsules when placed in a magnetic field. This is a particularly interesting approach that could be potentially applied to many medical applications such as targeted drug delivery systems. This in practice would involve utilising the magnetic particles present in the shell to concentrate the microcapsules in the desired position, followed by the use of laser irradiation to change the permeability of the shell wall i. e. releasing the drug or other material stored within the core (Illustrated in Figure 4). In addition to this, the use of magnetic particles actually makes the microcapsule wall sensitive to laser radiation, hence making the effectiveness of this combination of techniques possible.[26]

Gorin et al. have demonstrated that it is possible to create functionalised microcapsules that are sensitive to laser radiation by the incorporation of magnetic and gold nanoparticles into the polyelectrolyte shell. This method involves the use of a CaCO₃ core template along with poly(L-arginine) (PArg) and Dextran sulfate as polyelectrolytes in LbL deposition. Once completed, magnetic nanoparticles can then be added to the polyelectrolyte wall by immersion of the microcapsule into diluted water suspensions of the nanoparticles in a ratio of 1: 50. Gold nanoparticles can also be added by

immersion of the microcapsules in an undiluted solution.[27] While the results from these experiments show success in this application, there are also several drawbacks associated such as the tendency for the magnetic nanoparticles to accumulate and not be distributed homogeneously throughout the polyelectrolyte shell. This means that further research is required in order to make efficient use of magnetic particles in microcapsules.

Another approach to using magnetic nanoparticles with microcapsules is the addition of magnetic particles to the core of the microcapsule in order for it to be manipulated by a magnetic field. This can be achieved by complexation of a PAH with an inorganic salt with magnetic properties, i. e. $ZnFe_2O_4$, $MnFe_2O_4$ etc. before depositing the complexes into the hollow core of a polyelectrolyte microcapsule. By altering the pH of the system it is possible to achieve precipitation of the magnetic particles inside the core of the microcapsule.[28] The method of encapsulating a polyelectrolyte such as PAH is discussed in further detail later in this report.

A different method to incorporate magnetic particles with microcapsules is to coat the core template with magnetic particles prior to LbL synthesis. This can be achieved incubating MF particles together with magnetite particles (Fe_3O_4) in order to give them a magnetic coating, which then leaves a magnetic coating only on the innermost polyelectrolyte layer once the core has been dissolved. Figure 5 shows a Transmission Electron Microscope (TEM) image of a microcapsule synthesised by this method. [29]

The use of an alternating magnetic field can also be applied to initiate a triggered release mechanism.

Filling of Microcapsules

The filling of the hollow core provides the next challenge in the manufacture of a useful microcapsule. The most straightforward method is to use a core template made of the material that will ultimately be used in the final microcapsule. This prevents several challenges, as previously mentioned the selection of the core restricts the polyelectrolytes that can be used and visa versa. A common problem that arises when filling microcapsules with low molecular weight species is a tendency for the material not to precipitate in the core of the microcapsule, but instead precipitate either onto the polyelectrolyte walls or in the solution that is being used.

One method used in order to fill the core is similar to a method previously discussed for magnetic particles, and involves the addition of the desired resultant core material e. g. a polymer, onto the core template prior to synthesis. Igor et al. have shown that it is possible to prepare microcapsules in this way by the initial complexation of a polymer with multivalent ions such as Y^{3+} , which are then deposited onto the core template. Conventional LbL synthesis is then carried out to form the microcapsule. Due to the low stability of the polymer/metal ion complexes these readily break down after the core has been dissolved. This then leaves the polymer in the core of the microcapsule which is not capable of diffusing out. The scheme for this synthesis is shown in Figure 6.[30]

A drawback with this technique is that due to the relative large size of the metal ions used for complexation, they are often too large to diffuse out of the microcapsule, meaning that they too become trapped within the core. This can have different implications depending on the intended use for the microcapsule itself.

Another method of filling microcapsules is known as the ‘ship in a bottle technique’.[31] This involves the synthesis of copolymers inside the microcapsule from monomers deposited into the core. Dahne et al have demonstrated a practical way to achieve the polymerisation of sodium styrene sulfonate (SS) into PSS. The first step in this process is to synthesise a conventional polyelectrolyte microcapsule using PSS and PAH polyelectrolytes together with a MF core template, which should then be dissolved using 0.1M HCl. The polyelectrolytes are then incubated in solution together with the monomer units. These monomer units (plus a required initiator – such as potassium peroxodisulfate) diffuse through the polyelectrolyte wall and into the core, which when heated begin polymerising. Subsequent washing cycles allows the polymer-filled microcapsules to be isolated from the matrix. There are several issues associated with using this method, one of those being that due to surface charge existing on the microcapsule wall it is common for the initiator to be unequally distributed, meaning that it is common to observe polymers being synthesised onto the capsule wall or within the wall itself. This means that the overall properties of the microcapsule are altered which then has implications when attempting to use it for its intended application and can often lead to rupturing of the polyelectrolyte wall.

A further method that can be used to encapsulate small amounts of material is changing the conditions around the microcapsule, for example the pH, in order to alter the permittivity of the polyelectrolyte wall. It is also possible to encapsulate enzymes in microcapsules to create a biologically active species. This usually requires the LbL synthesis to be conducted onto the enzyme (or aggregates of the enzyme) itself, which can often cause certain practical difficulties. Zhao et al. have successfully encapsulated horseradish peroxidase (HRP) into polyelectrolyte microcapsule by first dissolving the HRP enzyme along with CaCl_2 into the CaCO_3 core template. LbL synthesis of the polyelectrolyte layer was then carried out using PAH and PSS, before dissolving the core with EDTA and leaving the enzyme contained within the microcapsule, as illustrated in the scheme shown in Figure 7.

This method of filling the core is not exclusive to enzyme substrates and once the polyelectrolyte core is established this gives a sensitive selectivity to the charge of species that are able to permeate the microcapsule wall. For example if the polyelectrolyte used in the core is negatively charged (such as PSS), then this will selectively allow positively charged species to pass through the capsule wall and will demonstrate repulsion to other negatively charged species, as demonstrated in Figure 8.[32]

The Donnan equilibrium relates to the different chemical compositions between the core of a microcapsule and the solution in which the capsule is immersed.[33] The filling of the core by this electrostatically selective method can be used to shift the equilibrium depending on the species added to solution. An issue arises when attempting to fill the microcapsule with a high molecular weight species that are too large to cross the permeable

polyelectrolyte wall. A technique to temporarily increase the permeability of the microcapsule wall to such molecules is to use an acetone/water mixture (typically around 30%) which leaves the polyelectrolyte shell in an ‘open state’ (Figure 9 B), allowing large molecules to be added to the core. Dilution of the solution with pure water (Figure 9 C) followed by washing then returns the permeability of the capsule wall to its original state (Figure 9 D).[34]

Precipitation can also be used to selectively fill a microcapsule core. This can be achieved by the addition of a polyelectrolyte e. g. PSS to the solution containing the microcapsules with a low salt concentration. The polyelectrolyte cannot penetrate the capsule wall and so the pH inside the core remains constant, whereas the pH in the surrounding solution is altered depending on the dissociation equilibrium. The next step involves addition of the new core material, such as a drug, to the solution. The pH of the solution can then be changed so that pH of hollow cores of the microcapsules have more favourable value, which also relates to the previously mentioned Donnan equilibrium. Once the pH has been adjusted precipitation of the drug into the microcapsule will begin to occur. Once this process is started, material capable of penetrating the microcapsule wall will effectively be ‘sucked’ into the core until the volume is filled completely.[35] The reversal of this process is known as dissolution and can be used as a controlled release mechanism for the microcapsules.

Release Mechanisms

There have been several methods of releasing an encapsulated material discussed already in this review. This section is indented to summarise those methods already mentioned and discussed. The intended release mechanism

should be considered when designing the capsule itself, which obviously links directly to the intended application of the microcapsule. The two types of release mechanisms available are instant release i. e. bursting of the microcapsule, and sustained release over a designated time period.

In the example of microcapsules containing a therapeutic compound or drug, burst release is ideally suited when the compound will be directly absorbed into the target cell i. e. intracellular uptake. However if the drug compound is either toxic in high concentrations or required at a particular sustained level (as is the case for many medical conditions such as schizophrenia[36]), then a sustained release mechanism is best suited to such applications. Burst release can be achieved by using an external triggering mechanism such as application of a magnetic field, laser or light irradiation or pH alteration, depending on the composition of the capsule and the environment that it is in. Sustained release, as previously mentioned is a more challenging mechanism to achieve. This is possible by using a microcapsule wall that either increases in permeability or degrades over a period of time, hence providing constant release of the drug contained in the core. [37] Changing of environmental conditions such as pH may be used to initiate these changes in the microcapsule wall, although this must be done with a high level of sensitivity in order to not trigger a burst release mechanism. Changing ionic strength allows an extra method of achieving sustained release of the core material.

Stability of Microcapsules as a Result of Filling

There have been several possible methods discussed that can be used to fill a microcapsule with a material/species of interest. Once the core has been

filled with the final material such as a drug or polymer unit, this can have an effect on the overall stability of the microcapsule. When the microcapsules are filled with a high concentration of solution then swelling of the capsule will occur, and if the concentration inside the core becomes too high then the polyelectrolyte wall will inevitably rupture. The effect that the concentration in the core has on the stability of the shell has been demonstrated where a PSS/PAH microcapsule is filled with a 0.5M PSS solution and the size of the microcapsule actually reduces by approximately 15% in comparison to the equivalent hollow capsule. In contrast to this, filling the core with a 1M PSS solution via the 'ship in a bottle' method of assembly swell by a factor of nearly 4 compared to their original size (Figure 10b) before rupturing of the microcapsule wall occurs. The swelling is known to be a result of internal osmotic pressure induced by the Na⁺ counterions present inside the capsule. If swollen capsules are treated with a concentrated solution of PDA (2M), then it is possible to reduce the swelling due to the increasing of the osmotic pressure in the surrounding solution (Figure 10c). 31

As previously mentioned, a similar situation can also arise before the microcapsule is filled, as result of the initial core template being dissolved. For example when an MF core is dissolved the resultant oligomers often become trapped and cause the microcapsule to swell and in some cases rupture if the concentration is above a critical level.

Presence of polyelectrolyte in the solution containing the microcapsules can also have an effect on the stability of the capsule itself. For example if a high concentration of PSS is present in the surrounding environment it creates an increased external osmotic pressure since it cannot penetrate the

polyelectrolyte wall. At high concentrations, this mechanical stress on the outer layers of polyelectrolyte can lead to buckling resulting in deformation of the microcapsule (Figure 11). 35

Detection, Measurement and Characterisation of Microcapsules

A commonly used method of detecting microcapsules is the use of fluorescent species that can be added to the microcapsule and then observed using fluorescence microscopy. The use of confocal laser scanning microscopy for the detection of fluorescently labelled species has been investigated in the course of this review[38]. The fluorescent material can either be added directly to the core of the microcapsule, or incorporated into the polyelectrolyte multilayer.

In order to add a fluorescent material to the core of a microcapsule, it is necessary to bond the species to a molecule that will readily permeate the polyelectrolyte shell and be deposited in the core. An example of this method involves the labelling of PAA with fluorescein (giving PAAAF), which can be achieved by covalently bonding aminofluorescein to the PAA component via the formation of amide bonds.[39] Once synthesized, this labelled polyelectrolyte can be captured within CaCO₃ core templates, which can then be used in the synthesis of PAH/PSS microcapsules. After dissolving the core with 0.1M HCl and several washing cycles the PAAAF remains encapsulated in the polyelectrolyte shell. Confocal laser scanning microscopy can then be used to observe and measure the resultant microcapsules (Figure 12).[40] It is also possible to coat the microcapsule with a nano polyelectrolyte film if necessary to prevent leaking of the fluorescent material from the capsule.

In a similar method to this, it is possible to fluorescently label the polyelectrolyte wall of the capsule as opposed to the core. This method of fluorescent labelling gives CLSM images like those shown in Figure 10a.

Another simple method to observe microcapsules is the addition of a dye. This is possible by adding a dye to the bulk solution that the capsules are stored in that is able to permeate the polyelectrolyte wall. Observation can then be made using either CLSM or optical microscopy. ³² In addition to this, dyes also have the added degree of functionality of providing sensitivity of the microcapsules to laser radiation. This makes dyes a useful tool for both detection and targeted release.

Scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy (AFM) are commonly used in the study of polyelectrolyte microcapsules. These techniques provide clear high-resolution images of the microcapsules allowing measurement and further characterisation to be carried out. The choice of technique used is based on the results/images required, for example if high-resolution three dimensional images are required for characterisation the SEM should be chosen. Figure 13 shows the various images obtained from each of the techniques. ⁸

Small-angle neutron scattering (SANS) is a technique that has recently been developed that allows accurate characterisation of multilayer microcapsules. SANS can be used for aqueous, solid or gas phase samples, meaning that no sample pre-treatment such as drying is required prior to microcapsule characterisation. The principles behind this method are rather complex and will not be discussed in depth for the purpose of this review. Experimental

results have shown that SANS it is an extremely useful technique in the determination of the thickness of the polyelectrolyte shell as well as the diameter of the core.[41] The method in itself is similar to small-angle X-ray scattering (SAXS), which can be used as a complimentary technique if structure determination is required.

Anisotropic/Janus Microcapsules

The fabrication of microparticles and microcapsules with varied functionality has been the subject of increasing interest in recent years.[42] A way of achieving these properties is to produce anisotropic microcapsules – commonly referred to as ‘Janus’ microcapsules. The Roman god Janus is commonly depicted as having a head comprised of non identical back to back faces, so for this re