Microencapsulation: Methods and Pharmaceutical Applications

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INTRODUCTION

Microencapsulation is the process of preparing micron-sized particles consisting of one or more core materials within single or multiple shell materials. The concept of microencapsulation dates back at least to the 1930s, when carbonless copy paper became the first commercial product to emerge as a result of microencapsulation technology (1). Since then this technology has developed rapidly, leading to a variety of products in pharmaceutical, medical, agricultural, food, manufacturing, and cosmetics industries. Microencapsulation techniques are particularly prevalent in the development and production of drug delivery systems within the pharmaceutical field. Representative and potential applications and benefits of microencapsulation in pharmaceutical industry include:

- Reduction of adverse effect and increase of therapeutic efficacy by targeting the intended site
- Control of drug release from encapsulated microparticles
- Enhancement of stability of drugs by forming a barrier between drug and surrounding environment
- Enhancement of solubility of poorly soluble drugs by particle size reduction
- Masking of taste and odor of certain drugs (2).

Microencapsulated particles have become indispensable in controlled drug release systems. Biocompatible microparticles with modified drug release profiles are particularly useful for the development of parenteral formulations. Examples of useful types of modified release profiles include:

- *Sustained release*: Encapsulation of drugs within one or more shell materials controls the rate at which drugs diffuse out of the microparticle into the surrounding environment. In addition, some microparticles release drugs by an erosion mechanism, whereby the rate and extent of drug release is directly related to the rate and extent of shell material degradation. Consequently, drugs are released from the microparticles continuously over a period of time. The duration of drug release can generally be controlled by defining a set of microencapsulation process parameters. The major advantage of this approach is the ability to maintain drug concentrations in the blood within the therapeutic window for an extended period of time. This has important implications in the improvement of patient compliance, which generally benefits from reduced number of necessary administrations.
- *Signal-Responsive Release*: Drug release from microparticles in response to internal or external stimuli is a sophisticated way to modify the release profiles of conventional formulations. In this case, microparticles release little or no drug until a signal is detected that modifies the release rate. Significant difficulties have been encountered in attempts to couple drug release to internal stimuli such as local chemical signals or biological needs. However, release triggered by external stimuli such as magnetic field has been studied extensively with promising results. In addition, magnetic field can direct the local accumulation of microparticles. Signal-responsive release can potentially reduce toxic side effects associated with systemic administration of parenteral formulations.
- *Pulsatile Release*: Pulsed systems involve the release of drugs in one or more pulses over a controlled period of time. Usually, these systems are produced by engineering a single or multiple cycles of time delay in the microparticle degradation mechanism. The concept of pulsatile delivery is still in its infancy but promises great potential, especially for the delivery of multiple-challenge antigens and peptide hormones. Delivery of antibiotics in divided pulses prevents the formation of antibiotic-resistant microbacterial strains. Patient compliance can be enhanced by eliminating the need for subsequent boost injections following an initial injection, since pulsatile systems can be made to mimic the drug delivering effect of the process (3).

As new materials continue to be discovered and technology advances, the science of microencapsulation and its applications will grow and expand to encompass a wider range of processes and products. However, to date no single encapsulation process has been developed that is capable of producing the full range of encapsulation products. It may be simply impossible to develop one microencapsulation method that can be used for widely different applications, since the nature of the drug and microparticles will vary significantly depending on the applications. This chapter is designed to provide an up-to-date overview of

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the existing microencapsulation methods with emphasis on processes that have achieved significant pharmaceutical use and to discuss the various current applications of microencapsulation, including potential applications that are yet to be commercialized.

TERMINOLOGY

A vast number of articles and reviews have been devoted to the subject of microparticulate systems. In these texts the terms 'microparticle', 'microsphere', 'microcapsule' and sometimes even 'nanoparticle' are used interchangeably. There is no universally accepted definition of 'microparticle' or 'nanoparticle' because it is difficult to use any one parameter, such as diameter, for such a definition. For simplicity, a 'microparticle' is defined in this chapter, as a particle with an equivalent diameter of around 1 μm and higher. The concept of equivalent diameter was developed for the size determination of non-spherical objects and is well-defined by the IUPAC (4). The term 'microcapsule' originally refers to microparticles that consist of one or more core materials surrounded by a distinct shell or wall, but it has evolved to include microparticles in which the core materials are embedded randomly or homogeneously dispersed within a matrix (shell). In some texts, spherical microparticles in which the core material is dispersed evenly throughout the shell material are also known as 'microspheres.' A variety of materials have been used in microencapsulation, ranging from drugs, agrochemicals, enzymes and fragrances for the core and polymers, fats and waxes for the shell. In consideration of the scope of this chapter, the discussion will be limited primarily to encapsulation using synthetic or natural polymers.

METHODS OF MICROENCAPSULATION

Currently, there are many methods of microencapsulation. We will examine the representative techniques with emphasis on processes that have produced commercially significant products and identify important parameters that affect the quality of the microparticulate systems produced.

Coacervation

The process of coacervation is the first reported microencapsulation method to be adapted for the industrial production of microparticles (1). The first significant commercial product that utilizes coacervation was carbonless copy paper. Coacervation involves the partial desolvation of a homogeneous polymer solution into a polymer-rich phase (coacervate) and a polymer-poor dilute liquid phase (coacervation medium) (5). Two types of coacervation have been identified, namely simple and complex coacervation. The mechanisms of microparticle formation for these two processes are similar with the exception of the method in which phase separation is carried out. Simple coacervation requires a change in the temperature of the polymer solution (6) or the addition of a desolvation agent, usually a water-miscible non-solvent such as ethanol, acetone, dioxane, isopropanol or propanol (7), or an inorganic salt such as sodium sulfate (8). On the other hand, complex coacervation involves inducing polymer–polymer interaction between two oppositely charged polymers, such that electrostatic interaction between two oppositely charged polymers produces phase separation. In general, for both simple and complex coacervation, formation of immiscible phases is followed by polymer deposition on the core material(s). The deposited polymer can be stabilized by cross-linking, desolvation or temperature change (9).

The successful encapsulation of drugs by coacervation is dependent upon several process parameters. The ability of a coacervating agent to spread and engulf dispersed drugs is highly affected by the types of coacervate used and its viscosity (10). Complex coacervation involves electrostatic interactions, and thus, the pH of the medium must be carefully controlled to maintain the charges on the polymeric species. For example, in a gelatin–gum arabic system, the pH should be adjusted to below the isoelectric point of gelatin such that the positively charged gelatin is attracted to the negatively charged gum Arabic (11). In the same study, it was shown that the acidifying rate of the medium affects the microparticle size distribution (11). Another factor is the concentration of surfactants used in the process. Several studies have demonstrated the effect of various concentrations of surfactant on particle size distribution (12), coacervation yield (13) and drug-loading (14).

Interfacial and In Situ Polymerization

Interfacial polymerization is a microencapsulation technology routinely used to produce pesticides and herbicides. In this process, a capsule or shell is formed at the interface between the core material and shell material through polymerization of reactive monomers. This technique can be used to encapsulate both water-miscible and water-immiscible core materials. A water-miscible core material is dissolved in an aqueous solution to which a polymerizing reactant is added. When the aqueous mixture is dispersed in an organic phase containing a coreactant, rapid polymerizing occurs at the interface to produce a capsule shell surrounding the core material. For water-immiscible core materials, the reaction sequence is reversed. The organic phase now contains the core material along with a multifunctional monomer. The organic phase is dispersed into an aqueous phase and a coreactant is added, resulting in polymerization at the interface. Microparticles formed by interfacial polymerization often have a continuous core–shell structure with a spherical shape.

In situ polymerization is closely related to interfacial polymerization in that shell formation occurs via polymerization reactions within the encapsulation mixture. However, a major difference between these two methods is that no reactive agents are added to the phase containing core materials in the *in situ* polymerization. At the interface between dispersed core materials and the continuous phase, polymerization occurs exclusively on the side facing the continuous phase. As the polymer grows, it deposits onto the surface of the core material, where cross-linking reactions may occur alongside polymer chain growth, eventually forming a solid capsule shell. *In situ* polymerization

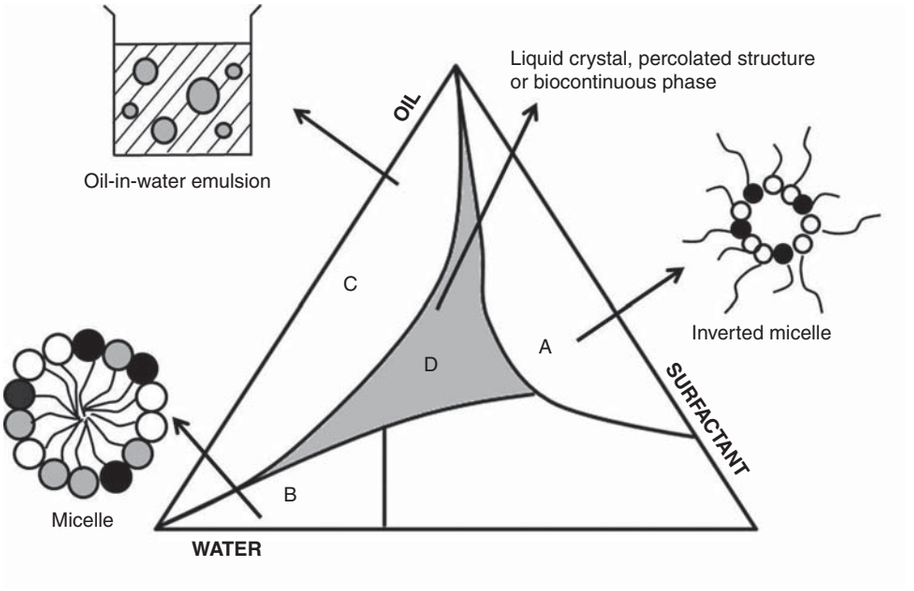

Figure 1 Hypothetical phase diagram of emulsion system composed of water, oil and surfactant. The different regions of the phase diagram (**A**, **B**, **C**, and **D**) are presented as well as the characteristic structures formed from these regions.

has been used extensively in the production of microcapsules loaded with carbonless paper inks or perfume for scented strips (15). In the cosmetics industry, this technique is used to produce microcapsules containing mineral oils.

In the discussion of processing and formulation parameters that affect interfacial and *in situ* polymerization, two common processes can be isolated and discussed separately. First is an emulsification step which determines the microparticle size and size distribution, and the second is a capsule formation step. Parameters that affect emulsification will be discussed in more detail in the section devoted to emulsions. Several important processing variables govern the formation of capsules. The thickness of the capsule wall is dependent upon the wall growing time (i.e., reaction time) (16), as well as the chemical nature and concentration of the monomers (17). The thickness of the capsule wall in turn affects the rupture resistance of the capsule wall. The ratio of monomer to cross-linking agent influences the integrity and morphology of the capsule shell (18). Other parameters such as pH, stirring rate and temperature, also play a role in determining the success of interfacial and *in situ* polymerization.

Emulsion

A common method to prepare microparticles is the emulsion technique. An emulsion is a mixture of two or more immiscible liquids. Pharmaceutically relevant liquids usually include some type of volatile organic solvent as the dispersed phase and water containing appropriate tensioactive substance as the continuous phase (Fig. 1). For example, hydrophobic drugs can be dissolved along with the wall-forming polymer in a common organic solvent, such as methylene chloride or dichloromethane, and the entire mixture emulsified in an aqueous solution containing a polymeric surfactant such as poly(vinyl alcohol). This type of oil-in-water (O/W) emulsion is widely used for encapsulation of lipophilic active moieties like steroidal hormones (19) and neuroleptics (20). The procedure can be adapted for encapsulation of hydrophilic drugs, where the drug is incorporated into an aqueous dispersed phase and poured into an organic continuous phase containing wall-forming polymer (water-in-oil, W/O). This primary emulsion is then further emulsified in an external aqueous phase, leading to a type of double emulsion known as water-in-oil-in-water (W/O/W) emulsion. Yet another class of emulsions consists of oil-in-oil (O/O) emulsion and multiple emulsions involving O/O procedures (W/O/O and W/O/O/O). W/O/O and W/O/O/O processes are carried out with the primary purpose of protecting highly water-soluble active agents from partitioning into the oil-water interface, causing drug loss and low encapsulation efficiencies. For all types of emulsions, the emulsification procedure is followed by solvent elimination step in complement with solidification step. Depending on the method of solidification, emulsion can be further classified as solvent evaporation, solvent extraction and cross-linking method.

In the solvent-evaporation method, solvent is eliminated in two stages: first the solvent diffuses through the dispersed phase into the continuous phase, and second the solvent is eliminated at the continuous phase–air interface. To facilitate the evaporation of solvent from the continuous phase–air interface, an appropriate amount of heat may be applied to the system. Theoretically, if the solvent can be extracted completely from the microparticle into the continuous phase, then the solvent evaporation step is no longer necessary. In practice, this is the concept behind the solvent extraction method. Using a sufficiently large volume ratio of continuous phase to dispersed phase or by choosing a cosolvent in the dispersed phase that has a great affinity to the continuous phase, the solvent can be extracted

from the microparticle to completion. The third type of emulsion method is the cross-linking method, which takes advantage of the ability of certain naturally available hydrophilic polymers such as gelatin, albumin, starch, dextran, and chitosan to cross-link and solidify. The cross-linking reactions may take place upon heating (21) or the addition of counter polyions (22) and cross-linking agents (23). It is crucial to take into consideration of the toxicity of added reagents when formulating pharmaceutically relevant microparticles using this method.

A vast number of studies have been conducted on the parameters that influence emulsion. Here, we will briefly examine some of the most important ones. The characteristics of microparticles produced by emulsion may be affected by physical parameters(such as the configuration of the apparatus, stirring rate, volume ratio of the dispersed to continuous phase, and weight ratio of encapsulated core material to shell material),physicochemical parameters (such as interfacial tension, viscosities and densities of the dispersed and continuous phases), and chemical parameters (such as the types of polymer, drug, surfactant and solvent used in the emulsion reactor). The optimization of these parameters is material-specific, i.e., for different drug–polymer systems, the values of the parameters differ. Furthermore, the set of parameters producing the most significant impact on microparticle characteristics varies with the system of drug–polymer under investigation. For the well-characterized poly(lactide-co-glycolide) (PLGA) system it is generally accepted that mean particle size increases with increasing polymer concentration (24,25) and is independent of the ratio of lactide to glycolide units. The ideal weight percentage of drug in polymer is in the range of 20–40%. Higher theoretical drug loading generally leads to lower encapsulation efficiency of drugs in PLGA microparticle (26). Increasing the volume of continuous phase relative to the dispersed phase is expected to reduce the PLGA matrix density in the microparticle, resulting in increased burst release (27). However, if the volume ratio is increased sufficiently high, a decrease in burst release is observed (28).

Supercritical Fluid

Supercritical fluids offer a wider scope of choices as solubilizing agents for core and/or shell materials. The ability of supercritical fluids to solvate core and shell materials can be altered by varying temperature and pressure conditions, the two key parameters in this particular microencapsulation technique. In addition to solvating the active principles, the use of supercritical fluids as extractants are also well documented (29). Therefore, if the starting solution is appropriately prepared, the final microencapsulated product can be obtained in one step that consists of two main processes: solvation of active principles by supercritical fluid in the rapid expansion of supercritical solutions (RESS) process (30) and precipitation of compounds by the supercritical fluid in the supercritical anti-solvent crystallization (SAS) process (31).

Spray Drying

Spray drying is a relatively low cost, commercially viable method of microencapsulation. Current industrial applications of spray drying range from the encapsulation of flavors and fragrances by the food industry to paint pigments in manufacturing. During this process, the core material is first emulsified or dispersed into a concentrated solution of the shell material. The mixture is then atomized into a heated chamber containing carrier gas where the solvent is rapidly removed to produce dry microparticles (Fig. 2). A major advantage of spray drying is the ability to mass produce microparticles with relative ease and low cost. However, one major limitation is the restricted use of many solvents other than water due to flammability issues. This severely limits the types of shell materials to those soluble or at least dispersible in water. Currently, other solvent options such an ethanol–water cosolvent system (32) and methylene chloride (33) are being explored. Another disadvantage of spray drying is the limited control over the geometries of the produced microparticles and the tendency for the microparticles to form aggregates.

The viscosity and particle size distribution of the primary emulsion have significant impact on the morphology and size distribution of subsequent spray drying process. For example, if the viscosity is too high, elongated and large droplets may form (34). The concentration of wall-forming materials in the solution has a direct impact on the microencapsulation efficiency of core materials (35). During spray drying, a number of processing parameters must be optimized in order to produce high quality microparticles. These parameters include feed temperature, air inlet and outlet temperatures (36), as well as the rate of emulsion mixture being delivered to the atomizer and rate of air flow (37). Optimization of these and many other factors that affect spray drying microencapsulation are mainly carried out by trial and error experimentation.

Spray Coating

Spray coating is used extensively in encapsulating solid or porous particles. In spray coating processes, particles are rotated and moved around in a designed pattern so that a liquid coating formulation can be sprayed evenly onto the surfaces of the individual particles. The coating formulation is allowed to dry by solvent evaporation or cooling. Usually, the coating cycle may be repeated until a desired capsule thickness is achieved. Depending upon the method by which the particles are rotated and mixed, spray coating can be broadly classified as fluidized bed coating and pan coating. The former is widely used in microencapsulation, whereas the latter is more often used to coat the surface of tablets. Our discussion here will be limited to fluidized bed coating only.

Fluidized bed coaters function by suspending the solid microparticles in a moving gas stream. Three types of fluidized bed coaters are available, each differ in the position of the nozzles that apply the liquid coating formulation: top spray, tangential spray and bottom spray (Fig. 3). In a top spray coater, the coating solution is sprayed from the top part of the unit onto the fluidized bed. Microparticles are moved

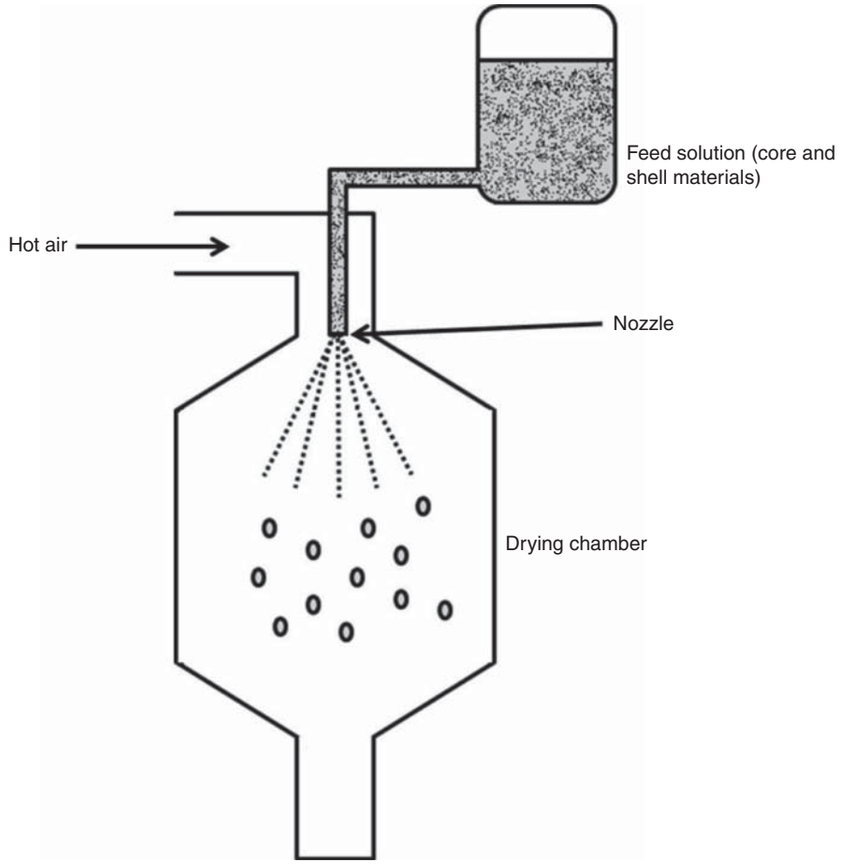

Figure 2 Schematic of a spray drying unit.

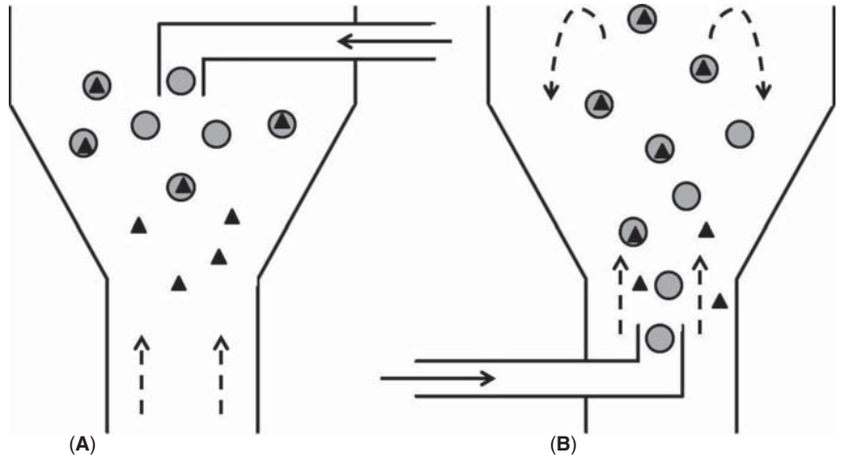

Figure 3 Schematic of top spray unit (**A**) and bottom spray unit (**B**). Solid arrows: direction of shell formulation; dashed arrows: gas stream; triangle: core material; circle: shell material droplet.

by gas stream upward until they meet droplets of coating formulation. If the coating solution contains a volatile solvent, the lapse in time between the moment the droplet leaves the nozzle and when it encounters the microparticle will result in the increase of solid content in the coating formulation droplet, causing a decrease in the droplet's ability to spread on the particle surface. Subsequently,microparticles coated by this method tend to have porous coatings and a certain extent of internal void volume. Tangential spray and bottom spray (Wurster spray) units are capable of producing a more continuous coating. In these two types of fluidized bed coaters, the sprayed droplets move in the same direction as the gas stream that carries the microparticles. The coating formulation moves a shorter distance before impacting on the surface of microparticles, thereby minimizing premature solvent evaporation. Once the microparticles have been

coated, they are carried by the gas stream into the upper section of the spray coating unit, allowing the coating to solidify by solvent evaporation or cooling. The microparticles fall and settle, and another cycle begins. This process is repeated until the desired coating thickness is achieved. Currently, the drying progress is also monitored by process analytical technologies (PAT), such as near infra-red (NIR) spectrometry.

The quality of encapsulation using spray coating methods is perhaps more dependent on physical parameters than any of the encapsulation methods mentioned previously. Within the same type of spray coating apparatus, factors such as rate of gas flow, nozzle-to-bed distance, number of nozzles used, rate of spraying and temperature all contribute to the quality of coating. For instance, if the nozzle-to-bed distance is too far, premature solvent evaporation may occur to the extent that some surfaces of the microparticles are not evenly coated. In addition to physical parameters, physicochemical factors such as the viscosity of the coating formulation and density of the core material also affect the quality of spray coating.

Centrifugal Extrusion

Centrifugal extrusion process requires two immiscible liquids that are pumped into a spinning two-fluid nozzle (Fig. 4). The core liquid is fed into the center fluid channel whereas the shell liquid is fed into the peripheral fluid channel. When the two-liquid column emerges from the nozzle, it spontaneously breaks up into a stream of small droplets with liquid cores surrounded by liquid shells. The shell material can solidify by rapid cooling as the droplets fall away from the nozzle, or alternatively, the droplets may fall into a gelling bath where the aqueous shell is converted to a gel-like capsule. The method of solidification depends on the properties of the polymer used as shell material.

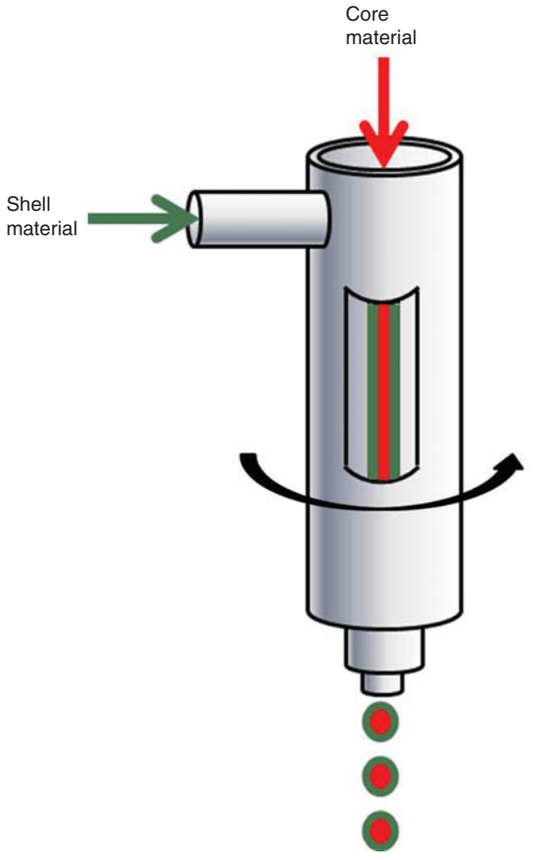

Figure 4 Schematic of centrifugal extrusion apparatus used to produce microparticles.

Rotational Suspension Separation

This microencapsulation method is a relatively new technology that is a fast, low-cost way to produce large quantities of encapsulated microparticles. Core material is dispersed in a liquid wall formulation and the mixture is fed onto a rotating disk. Individual microparticles with surface layers of wall material are flung off the rotating disk and cooled rapidly to solidify the coating layer (Fig. 5). Microencapsulation by this method can take between a few seconds to several minutes. To obtain optimal results, it is suggested that the core materials are spherical in shape before undergoing encapsulation. This may require extra processing steps such as granulation, which may pose restrictions on the type of core materials that can be used in this process. In addition, this technique requires wall materials that can solidify rapidly. Other parameters that need to be taken into consideration include viscosity of the coating formulation and the rotational speed of the disk.

Summary of Microencapsulation Methods

Most microparticles with industrial applications are produced by methods outlined in the above sections. Currently, progress is being made in the commercialization of an increasing number of microparticle-based products as well as the technology of microencapsulation itself. However, it is important to note that to date, no single microencapsulation process is able to produce the full range of products required by the consumer market. The encapsulation of pharmaceutical drugs is a particularly good demonstration of this point. When selecting encapsulation methods for a certain drug particles, it is crucial to consider the physicochemical properties of the drug. These properties serve as starting points for any encapsulation technology development. Although many studies are underway in finding alternative solvents to water, presently aqueous-based solutions remain the most widely used systems in drug encapsulation. Logically, then aqueous solubility effects of drug particles must be given careful thought when attempting to microencapsulate.

PHARMACEUTICAL APPLICATIONS

In the following sections, we will examine some of the major pharmaceutical applications of microencapsulation technology. Each section addresses a representative issue encountered in the microencapsulation arena. Strategies to overcome these challenges are an ongoing interdisciplinary

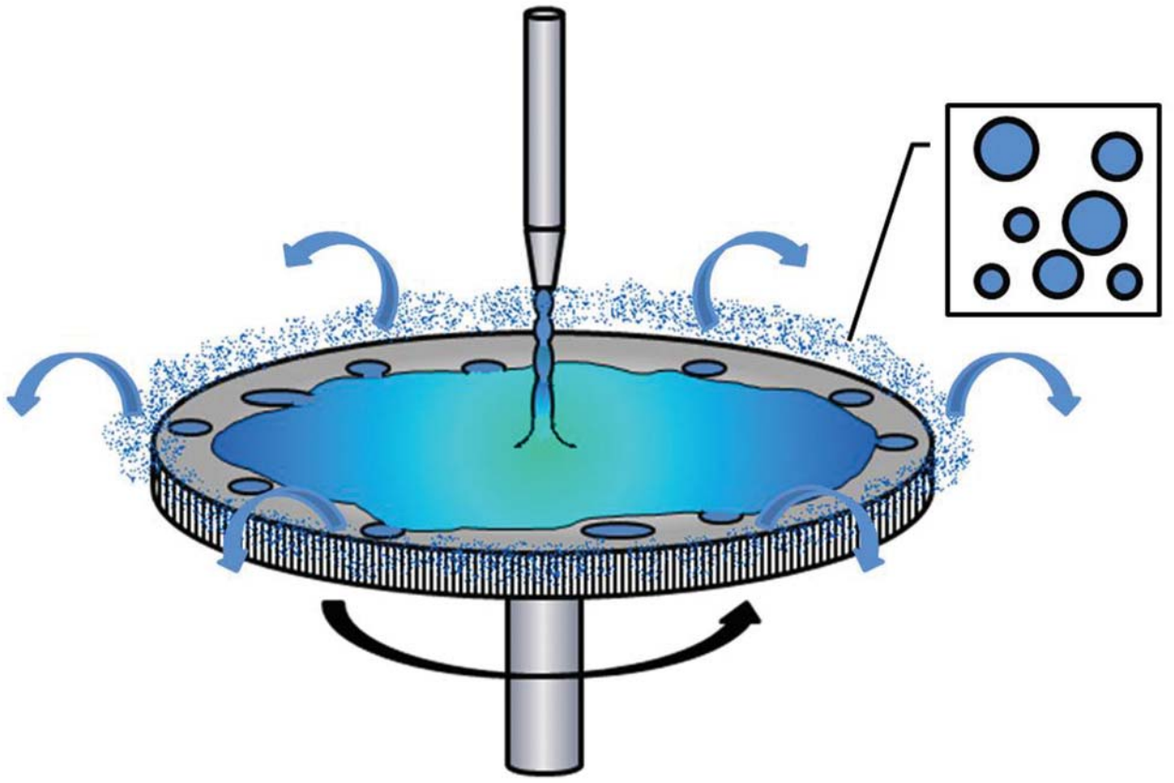

Figure 5 Schematic of microencapsulation by rotational suspension separation.

effort between the pharmaceutical, biomedical and chemical fields. We will also briefly present some current and potential clinical applications of microencapsulation technology within the pharmaceutical industry.

Drug Table Release

The controlled release of drugs from a polymeric microparticulate system is perhaps the most widely investigated application for microencapsulation techniques. To achieve effective control of pathological state, it is desirable to maintain the concentration of released drugs within the therapeutic window for a predetermined period of time with minimum fluctuations. For diseases such as cancer that require long duration of action and patient compliance is greatly enhanced if the formulation has a sustained-release profile such that frequent dosing is obviated. A typical microparticulate release profile shows three distinct stages: an initial burst release, a lag period followed by erosion-based release. In general, the release profile is controlled by the rate of diffusion, erosion, osmotic-mediated events, or a combination of these mechanisms. These parameters are in turn dependent upon the structural features of the microparticle, the distribution of drugs within the polymeric matrix, and the degradation kinetics of the polymers. By manipulating these parameters it is possible to achieve the desired release profile for controlled drug delivery.

Biodegradable Polymers

Two classes of polymers are often used for controlled-release purposes: polyanhydrides and polyesters. Polyanhydrides are a class of polymers composed of hydrolytically labile anhydride linkages. The attractiveness of polyanhydrides lies in the fact that these molecules can be easily modified by vinyl moieties or imides to create cross-linkable systems (38). Especially appealing is the ability to tailor-release rates to the degree of cross-linking density. Studies have shown that mass loss of polyanhydrides follows a surface degradation mechanism (39), which is highly significant since drug release would be exclusively controlled by surface erosion processes. The second class of biodegradable polymers often used in microencapsulation is polyesters. Polyesters such as poly(ε-caprolactone) (PCL), poly(lactic acid) (PLA) and poly(lactide-co-glycolide) (PLGA) have been used in controlled-release formulations that were approved by FDA. Among these polymers PLGA is one of the most studied diblock copolymers for microencapsulation. PLGA microparticles are usually synthesized by emulsion methods (including solvent evaporation (40), solvent extraction (41) and cross-linking (26)) and interfacial polymerization techniques. Unlike polyanhydrides, PLGA undergoes bulk erosion, where drug contents are released by both diffusion and erosion processes. The drug release kinetics are influenced by the several characteristics of the PLGA polymer. Well-recognized factors include copolymer composition, molecular

weight, crystallinity, and drug-specific interactions with the polymer. The influence of these and other parameters has been extensively reviewed in literature (42). In addition to polyanhydrides and polyesters, copolymers of polyanhydrides and polyesters have also been investigated for their ability to achieve better controlled release of drugs from microparticles (43).

Burst Release

Initial burst release is one of the major concerns in controlled release of drugs. A high initial burst release is undesirable unless the formulation is designed for vaccines or antibiotic delivery. High initial burst release is usually observed in microparticulate systems containing hydrophilic drugs, though some relatively hydrophobic drugs such as risperidone have also been known to demonstrate initial burst release phenomenon. In general, burst release from microparticles is attributed to two causes: (1) dissolution of surface-associated drugs and (2) an increased concentration of drugs near the surface of the microparticle due to convective solvent flow during processing. However, studies have shown that burst release also occurs for formulations where the drug was exclusively present inside microparticles (44) and particles containing homogeneous distribution of drugs (45). Therefore, burst release is not only a surface phenomenon.

The initial burst release can be regulated by physical barriers within microparticles limiting the diffusivity of drug molecules, the polymeric matrix density, and the porosity of the microparticle. Physical barriers include coating a blank layer of shell material on the surface of the microparticles or preparing double-walled microparticles using phase separation of the constituent polymers. There are a number of disadvantages associated with these preparation methods. Coating a blank layer on the surface of the microparticles causes an increase in particle size that could potentially affect the absorption and distribution of the microparticles. In addition, coating reduces the production efficiency and raises the cost of production. The polymer phase separation approach also has its weaknesses, mainly that the phase separation process is minimally controlled, which leads to batch-to-batch variations in wall composition (46). On the other hand, the matrix density and microparticle porosity are relatively easier to manipulate using a set of formulation and processing parameters. Consider the classic example of an oil-in-water emulsion. Because the bulk of dispersed phase contains organic solvent, removal of the solvent during evaporation or extraction procedures will lead to decreasing microparticle volume before polymer gelation and vitrification (47). The extent to which the microparticle shrinks prior to hardening determines the matrix density. In general, the faster the solvent removal rate, the lower the matrix density. The exception is when the solvent removal is so rapid that localized polymer hardening takes place, such that a dense exterior shell forms. In this case the burst release may be reduced (28). Other factors in the emulsion process besides the solvent removal rate also contribute to the processing-microparticle structure relationship as it pertains to burst release. For example, within a certain range, increase in the volume ratio of continuous phase compared to the organic dispersed phase is expected to reduce polymer matrix density and therefore increase burst release. However, when the volume ratio is increased out of this range, the formation of a hardened high density polymer shell is expected to occur such that burst release is reduced. For another example, addition of plasticizing surfactants to the processing medium and/or increasing the processing temperature to above the T_g of the polymer led to enhanced polymer mobility at the surface of the microparticle, which facilitates pore closure and decreases surface porosity. Both of these outcomes have been shown to lead to lower burst release (48).

Drug Properties

So far we have examined formulation efforts on polymeric wall materials to control burst release. Equally important are drug-specific properties that must not be overlooked in formulation efforts to limit burst release. These drug-specific factors include drug molecular weight, drug solubility in solvents and drug partition coefficient between polymer and processing medium environment. Drug molecular weight determines the extent to which matrix density and porosity impact initial release: generally speaking, the effect of matrix density is more dominant for small, low M_w compounds whereas porosity is more dominant for high M_w drug molecules. The solubility of drug in organic solvent influences the distribution of drug molecules within the microparticle. Hydrophobically active moieties are typically soluble in organic solvents commonly used for microencapsulation and usually form molecular dispersions within the polymeric matrix. However, it is worthwhile to note that a drug may be encapsulated as a molecular dispersion in a polymer but has little affinity for the polymer, leading to heterogeneous drug distribution over time. On the other hand, large hydrophilic drug molecules such as peptides or nucleotides demonstrate limited solubility in organic solvents such that drug molecules are likely to reside on microparticle surface. In this case, the partition coefficient of the drug becomes a dominating factor. The partition coefficient is essentially a comparison of the affinity of the drug molecules for the polymer and for the continuous phase. When the drug has higher affinity for the continuous phase compared to the polymer, drug molecules may diffuse out of the encapsulating wall material into the surrounding processing medium, causing a low encapsulation efficiency as well as heterogeneous drug distribution in the polymer matrix. Possible formulation efforts include finding alternative polymeric forms that are more compatible with the drug and varying process parameters outlined previously. For example, adding a small amount of glycerol into the dispersed phase enhanced the internalization of the active moiety insulin and reduced burst release from 40% to 10% (49). In another example, modifications to the encapsulating polymer such that hydrophilicity increases drug internalization and decreases initial release (50).

Drug Stability

Interest in biomacromolecules has been growing within the pharmaceutical field as the industry continues its search for novel drug compounds. Unfortunately, these biomacromolecules are difficult to encapsulate without some loss of bioactivity. In particular proteins are notorious for their physical and chemical instability. The stability of drugs is crucial for obvious reasons: (1) instability changes the function and pharmacokinetics of the drug and (2) instability may produce by products that can cause toxicity or immunogenicity issues. Besides biomacromolecules, traditional small molecular drugs also experience instability issues, with the issues most prominent during storage. Currently, microencapsulation methods are being developed that address these problems.

Causes of Instability

In general, two broad categories of causes have been identified that are detrimental to the stability of biomacromolecules such as proteins, peptides and nucleic acids: instability due to processing conditions or instability due to polymeric degradation and polymeric interactions (Table 1). Water-in-oil-in-water (W/O/W) encapsulation methods are the most commonly employed way of encapsulating these hydrophilic biomacromolecules using emulation methods. However, it is found that these biomacromolecules are often denatured at the water–oil (organic solvent) interface. For example, in a study involving vortex mixing of the protein carbonic anhydrase in aqueous solution with the organic solvent methylene chloride, protein adsorption, denaturation, and aggregation were observed at the interface (51). Exposure of hydrophilic biomacromolecules to organic solvent causes conformational changes because of the highly hydrophobic environment. Microencapsulation methods that require some stress conditions such as shearing or thermal stress could affect the structural and therefore functional integrity of the biomacromolecules.

Table 1 Sources of instability for encapsulated protein/peptide drugs and stabilizing strategies

	Source of instability	Stabilizing strategy
Instability due to processing conditions	Exposure to oil–water interface	Use protective excipients or non-aqueous techniques
	Exposure to hydrophobic compounds	Decrease hydrophobicity by covalent modifications or use more hydrophilic solvents
	Shear and thermal stress	Employ non-shearing and non-heating techniques
Instability due to polymer degradation	Hydrolysis of polymer produces acid microenvironment	Add pH modifiers, increase permeability of polymer matrix or alter polymer degradation rate
Instability due to protein–polymer interaction	Acid-catalyzed deamidation and chain cleavage	Add pH modifiers, use techniques that do not allow protein–polymer contact
	Acylation	PEGylation of protein/peptide, acetylation of N-terminus of protein/peptide

To add further complexity, biomacromolecule instability can also be caused by polymer degradation and drug–polymer interactions. Studies in this field have advanced from initial concern of polymer degradation alone to the recognition that biomacromolecules such as proteins can interact with the polymer through chemical reaction as well as physical adsorption to the solid polymer surface. For example, the most commonly used polymer PLGA undergoes hydrolysis upon exposure to aqueous environment to produce primary alcohol and carboxylic acid subunits. The microclimate within PLGA microparticles changes with the increasing concentration of free carboxylic end groups as the polymer degrades, with lower pH values measured in the core of the particle by multiple studies (52,53). This transition to a more acidic environment has a profound effect on the stability of encapsulated proteins and peptides, since acid-catalyzed reactions such as deamidation and chain cleavage could take place. In addition, recent studies have reported that encapsulated biomacromolecules can also directly react with the polymeric material. For instance, the incorporated protein or peptide can react with PLGA through the nucleophilic attack of a primary amine on the carboxyl carbon in PLGA ester bond (54). These reactions contribute to the instability of encapsulated biomacromolecules within polymeric microparticles. Biomacromolecules dissolved in aqueous solution are also prone to adsorb to the solid surface of the microparticles.

Small molecular drugs also encounter stability issues especially during storage of the microparticles. It is often overlooked that the polymers used for encapsulation are often amorphous, and undergoes structural relaxation over time. The change in polymeric structure leads to solid state variations that affect drug efficacy. For instance, the anti-inflammatory drug triamcinolone encapsulated in PLGA systems has been shown to vary from one polymorphic form to another during long term storage (55). Some drugs with poor affinity for the encapsulating polymer tend to crystallize out over time, resulting in undesirable release profiles.

Controlling Drug Stability

Abundant recent literature has been devoted to formulation modifications as ways to improve stability of biomacromolecules. These formulation modifications can be broadly classified as pH modifiers and covalently-linked modifiers.

The most commonly used pH modifiers for PLGA systems are weakly basic salts such as calcium carbonate (56,57), magnesium hydroxide (57,58) and zinc carbonate (58). These salts are encapsulated within the polymeric matrix along with the active moiety and buffer against pH change as monomers accumulate. It should be noted that highly dissociative hydroxide salts can also reduce the stability of encapsulated proteins and peptides by creating a basic environment conducive to base-catalyzed peptide degradation (59). Covalently-linked modifiers function by preventing polymer-core material interactions. A possible modifier is poly(ethylene glycol), which can be covalently attached to a peptide drug to prevent nucleophilic reactions between peptide and polymer (60). The PEGylation did not affect the bioactivity of the peptide (61).

In addition to formulation modifications, processing modifications are also investigated for control of biomacromolecule stability. Since the water–oil interface was known to destabilize proteins and peptides, the logical step is to develop methods that prevent protein or peptide contact at the aqueous solution–organic solvent interface. A recent development is a method known as solid-in-oil-in-hydrophilic-oil-in-ethanol (S/O/hO/E) (62), where preformulated solid protein particles are added to a hydrophilic non-aqueous 'oil' phase containing hydrophobic solution of polymer dispersion. The whole mixture is transferred into a cold ethanol bath to extract remaining solvent. This approach has been shown to retain the bioactivity of over 90% of the encapsulated proteins. In another method, protein molecules are first encapsulated in dextran glass particles and then dispersed in polymeric (PLGA) microspheres (63). This technique avoids protein contact with oil/water interface and the hydrophobic PLGA.

Drug Targeting

The ability to target drugs and therapeutics to specific sites has been one of the most sought-after goals in the pharmaceutical field. There are several major issues associated with systemic drug administrations. The therapeutic agents are evenly distributed throughout the body, such that there is a lack of accumulation at the pathological site where the active moieties are needed the most. Due to the limited drug specificity, higher total doses are required to achieve the necessary concentration at the pathological site. Consequently, there is increased risk of non-specific toxicity and other adverse side effects. These problems are particularly prominent for highly potent drugs such as anti-cancer agents. Currently, most research within the targeted drug delivery field focuses on nanoparticles instead of microparticles. However, there are a few instances of using polymeric microparticles as targeting entities. In one approach, a drug is combined with microparticles using microorganism-specific enzyme substrates such that the active form of the drug will only be released in the presence of enzymes specific to the target virus or microorganism. In uninfected macrophages, the drug will remain bound to the microparticle (64).

Clinical Applications

Several microparticle-based pharmaceutical products are currently on the market (Table 2) and several more are in clinical trials (Table 3). A variety of drugs from different therapeutic classes has been encapsulated in microparticles and is currently being closely examined for clinical applications, particularly through parenteral administrations. These drugs include chemotherapeutic agents such as paclitaxel (65), docetaxel (66), doxorubicin (67), vascular endothelial growth factor siRNA (68), 5-fluorouracil (69).and tamoxifen (70); analgesics such as morphine (71), nalbuphine (72) and

Table 2 List of microparticulate products currently approved for use (82,83)

Drug	Approval year	Polymer used	Disease treated
Buserelin acetate[a]	1988	Poly(D,L-lactide-co-glycolide)	Endometriosis, uterine myoma
Goserelin acetate	1989	Poly(lactic acid)	Breast and prostate cancer
Leuprolide acetate	1997	Poly(D,L-lactide-co-glycolide)	Prostate cancer
Octreotide acetate	1998	Poly(D,L-lactide-co-glycolide)	Acromegaly
Somatotropin (rDNA origin)	1999	Poly(D,L-lactide-co-glycolide)	Growth hormone deficiencies, growth failures
Triptorelin and derivative (acetate[a], pamoate, embonate[a])	2000 (acetate), 2000 (pamoate), 2005 (embonate) 2010for 6-month dose (pamoate)	Poly(D,L-lactide-co-glycolide)	Prostate cancer, endometriosis, uterine fibroids
Minocycline HCl	2001	Poly(D,L-lactide-co-glycolide)	Peridontal disease
Risperidone	2003	Poly(D,L-lactide-co-glycolide)	Schizophrenia
Estradiol benzoate	2003	Poly(lactic acid)	Cattle growth supplement
Bromocriptine	2005	Poly(D,L-lactide-co-glycolide)	Hyperprolactinemia, Parkinson disease
Naltrexone	2006	Poly(D,L-lactide-co-glycolide)	Alcohol dependence
Lanreotide acetate	2007	Poly(D,L-lactide-co-glycolide)	Acromegaly

[a]Not approved for use in the U.S.

Table 3 Examples of microparticulate products in recent clinical trials (84)

Condition	Intervention	Polymer used	Status	Sponsor
HIV infections	Microparticulate formulation of HIV-1 peptide vaccine	Poly(D,L-lactide-co-glycolide)	Phase II	National Institute of Allergy and Infectious Diseases
HIV infections	Microencapsulated DNA plasmid vaccine	Poly(D,L-lactide-co-glycolide)	Phase II	National Institute of Allergy and Infectious Diseases
Seasonal allergic rhinitis	Chitin microparticles by nasal route	Chitin	Phase III	CMP Therapeutics Ltd.
Schizophrenia	Microencapsulated iloperidone	Poly(D,L-lactide-co-glycolide)	Phase I Phase II	Novartis

fentanyl (73); non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (74) and diclofenac (75); hormones such as growth hormones (76), and sex hormones (77); and antibiotics such as amphotericin (78). More recent developments include the use of polymeric microspheres for the delivery of DNA vaccines (79). Initially PLGA was used as the encapsulating polymer with some success; however, the drug stability issues within the polymeric matrix quickly became a concern and other polymers such as poly(ortho esters) (80) and poly-β-amino esters (81) were investigated.

CONCLUSIONS

Microencapsulation has become one of the most widely investigated fields in the pharmaceutical arena. A variety of microencapsulation methods are currently available and novel techniques are continuously being discovered and developed. Although several microencapsulated products are commercially available, there still exists a wide gap between the practical applications and full potential of this technology. Bridging this gap depends on a deeper understanding of the mechanisms involved in microencapsulation processes as well as better assessment of drug and polymer specific properties. Major issues that need to be addressed include how to control drug release to achieve desired release profile, how to maintain the stability and activity of the encapsulated drug (especially biomacromolecules), and how to effectively direct microparticles to target pathological site. Additionally more emphasis should be put on the transfer of bench-scale processes to manufacturing scale. Overcoming these challenges will advance microencapsulation technology to a new level that will allow increasingly more sophisticated pharmaceutical drug systems to be realized.

CHAPTERS OF FURTHER INTEREST

Drug Delivery: Controlled Release, p.
Emulsions and Microemulsions, p.
Microsphere Technology and Applications, p.
Nanofabrication for Drug Delivery, p.
Polymeric Delivery Systems for Poorly Soluble Drugs, p.

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