Recent Advances in Microencapsulation Technology

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INTRODUCTION

Microencapsulation technology has been used from 1930s in packaging flavors and vitamins. Since the first commercial product was introduced for the carbonless copying paper,[1] the technology has advanced to a new level. Various microencapsulation techniques are available nowadays, and the microencapsulated products are widely used in pharmaceutical, biomedical, agricultural, food, consumer products, and cosmetic industries. Representative applications of microparticles in the pharmaceutical and biomedical industries include:[2]

- Taste and odor masking.[3]
- Protection of drugs from the environment.[4]
- Particle size reduction for enhancing solubility of the poorly soluble drugs.[5]
- Sustained or controlled drug delivery.[6]
- Cell encapsulation.[7]

The microparticle system has become an indispensable part of the controlled drug delivery fields for the past few decades since it can readily be adapted for various administration methods. In particular, biodegradable polymeric microparticles can provide a number of advantages over conventional parenteral formulations:

- *Sustained delivery*: By encapsulating a drug in a polymer matrix, which limits access of the biological fluid into the drug until the time of degradation, microparticles maintain the blood level of the drug within a therapeutic window for a prolonged period. Toxic side effects can be minimized, and patient compliance can be improved by reducing the frequency of administration.
- *Local delivery*: Subcutaneously or intramuscularly applied microparticles can maintain a therapeutically effective concentration at the site of action for a desirable duration. The local delivery system obviates systemic drug administration for local therapeutic effects and can reduce the related systemic side effects. This system has proven beneficial for delivery of local anesthetics.[8]
- *Pulsatile delivery*: While burst and pulsatile release is not considered desirable for the sustained delivery application, this release pattern proves to be useful for delivery of antibiotics and vaccines. Pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulses can mimic an initial and boost injection, respectively.[9]

With the recent advance of biotechnology and polymer chemistry, the use of microparticle systems will continue to grow for a variety of applications. The objective of this entry is to provide a review of the technical aspects of the microencapsulation techniques that have been widely used in the pharmaceutical industry and recent advances of the technology so that the pharmaceutical scientists can take full advantage of the existing assets of this area in developing new microparticle systems.

TERMINOLOGY

The microencapsulation processes produce small particles ranging in size from 1 to 1000 μm. There are different names for these particles: microparticle, microsphere, microcapsule, and micromatrix. Although they are often used interchangeably, distinctions can be made such that microcapsules are made of one or multiple core substances (solid or liquid) that are surrounded by a distinct capsule wall, whereas micromatrices are polymeric matrices in which the encapsulated substances are homogeneously dispersed. Microparticles or microspheres are general terminologies that involve both.[2] Although micromatrices are also called microspheres depending on the authors,[6] we will follow the former definition in this chapter. In consideration of the scope of this chapter, current discussion is limited to the microparticles that utilize natural or synthetic polymers as an encapsulating material.

MICROENCAPSULATION TECHNIQUES

Existing microencapsulation techniques have been reviewed extensively,[2,6,10–13] and for this reason, here

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we will briefly summarize representative microencapsulation techniques.

Coacervation

The coacervation method is one of the earliest microencapsulation techniques, which has been used for various consumer products. This method is based on separation of a solution of hydrophilic polymer(s) into two phases, which are small droplets of a dense polymer-rich phase and a dilute liquid phase. Coacervation can be divided into simple and complex coacervation depending on the number of polymers that are involved in the formation of microparticles.

Simple coacervation

This process involves only one polymer (e.g., gelatin, polyvinyl alcohol, carboxymethyl cellulose), and the phase separation can be induced by conditions that result in desolvation (or dehydration) of the polymer phase. These conditions include addition of a water-miscible nonsolvent, such as ethanol, acetone, dioxane, isopropanol, or propanol,[14] addition of inorganic salts, such as sodium sulfate,[15] and temperature change.[6]

Complex coacervation

This process involves two hydrophilic polymers of opposite charges.[16] Neutralization of the overall positive charges on one of the polymers by the negative charge on the other is used to bring about separation of the polymer-rich phase (Fig. 1). The best-known example is the gelatin-gum arabic system pioneered by Bungenberg de Jong in the early 1940s.[17] Since electrostatic interactions are involved, the pH of the medium is very important. For example, in the gelatin-gum arabic system, pH should be below the isoelectric point of gelatin so that the gelatin can maintain the positive charge. Once embryonic coacervates form around the dispersed oil or solid phases, these polymer complexes are stabilized by cross-linking using glutaraldehyde.

Commercial products

The first commercial microparticle product based on the complex coacervation method was carbonless copy paper developed by National Cash Register Corp.[1] The back side of the first page is coated with microcapsules in the 3–10 μm size range made of a gelatin-gum arabic shell by the coacervation technique. In the center of the capsules is the oil containing colorless color-forming agent (e.g., crystal violet lactone). The front side of the second page is coated with a developing layer. The pressure imposed on both sheets of paper upon writing induces breakage of the microcapsules and makes the colorless color-forming agent released and react with the developing layer to develop color. The microcapsules have also been used in Scratch-N-Sniff® scent strips and Snap-N-Burst® fragrance samplers.

Emulsion Solidification

Microparticles can be produced from emulsion of two or more immiscible liquids. For example, a solution of

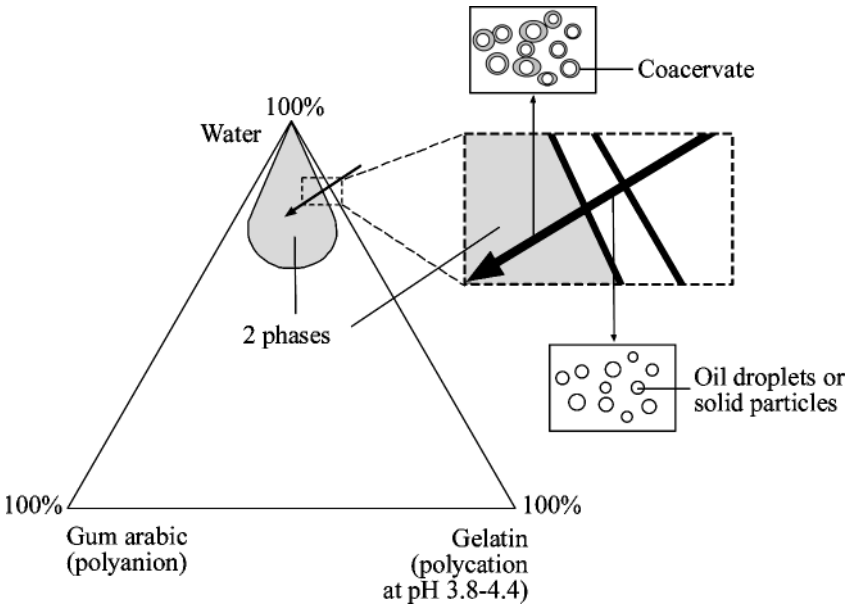

Fig. 1 Phase diagram for complex coacervation.

hydrophobic drug and polymer in an organic solvent (oil phase, dispersed phase) is emulsified in an aqueous solution containing an emulsifying agent (water phase, continuous phase) to produce oil-in-water (o/w) emulsion. The drug containing polymer particles can be solidified as the solvent is removed. Depending on the solubility of drug in water and encapsulating polymer, the emulsion type can be varied from water-in-oil-in-water (w/o/w for encapsulation of water-soluble drug in water-insoluble polymer), water-in-oil-in-oil (w/o/o for encapsulation of water-soluble drug in water-insoluble polymer), or water-in-oil (w/o for encapsulation of water-soluble drug in water-soluble polymer) to solid-in-oil-in-water (s/o/w for encapsulation of water-soluble drug particles in water-insoluble polymer). Depending on the method of solidifying the discontinuous droplets, the emulsion method can be classified as solvent evaporation, solvent extraction, and cross-linking method.

Solvent evaporation

Typically, the polymer is dissolved in a volatile organic solvent such as methylene chloride. Drugs or diagnostic agents, either in soluble form or dispersed as fine solid particles, are added to the polymer solution, and then this mixture is emulsified in an aqueous solution that contains an emulsifying agent such as poly(vinyl alcohol) (PVA). The resulting emulsion is stirred until most of the organic solvent evaporates, leaving solid microparticles that may be washed with water and freeze-dried. To facilitate solvent evaporation, the emulsion is often heated slightly above the boiling point of the solvent. For example, when methylene chloride (boiling point: 39.8°C) is used as an organic solvent, the emulsion is heated to ~40°C.

Solvent extraction

The solvent evaporation method depends on high vapor pressure of the solvent; therefore, this method requires volatile solvents such as methylene chloride. Otherwise, the solidification process takes too long that it results in irregular morphology,[18] high porosity of the microspheres,[19] loss of payload,[20,21] or increased polydispersity of size distribution.[18] In this case, the relatively nonvolatile solvents can be removed by extraction into the continuous phase.[22] This can be done by using a solvent that has significant solubility in the continuous phase,[23] increasing the concentration difference between the dispersed and continuous phase,[18] or adding a third solvent into the continuous phase to facilitate extraction of the solvent.[22]

Cross-linking

A number of hydrophilic polymers from natural origin, such as gelatin, albumin, starch, dextran, hyaluronic acid, and chitosan,[24] can be solidified by a chemical or thermal cross-linking process.[2] A w/o emulsion is prepared by emulsifying the polymer solution in an oil phase (typically vegetable oils or oil–organic solvent mixtures) containing an emulsifying agent such as Span 80. Most proteins are cross-linked using glutaraldehyde, but its toxicity remains a problem for pharmaceutical applications. Heating[25] and adding counter polyions[26] or cross-linking reagents[27] (Fig. 2) are alternative cross-linking methods.

Hot-Melt Microencapsulation

The polymer is first melted and then mixed with solid drug particles or liquid drugs.[28] This mixture is suspended in an immiscible solvent and heated to 5°C above the melting point of the polymer under continuous stirring. The emulsion is then cooled below the melting point until the droplets solidify.

Ionic Gelation/Polyelectrolyte Complexation

Ionic gelation involves cross-linking of polyelectrolytes in the presence of multivalent counter ions. For example, spraying a sodium alginate solution into calcium chloride solution produces rigid gel particles. Ionic gelation is often followed by polyelectrolyte complexation with oppositely charged polyelectrolytes. This complexation forms a membrane of polyelectrolyte complex on the surface of the gel particles, which increases the mechanical strength of the particles. For calcium alginate gel particles, polylysine is often used for this purpose. Other polymer systems that can be used for ionic gelation (polyelectrolyte complexation) are chitosan/triphosphate, carboxymethylcellulose/aluminum (or chitosan), κ-carrageenan/potassium (or chitosan), pectin/calcium, gelan gum/calcium, and polyphosphazene/calcium (or polylysine). This method was developed by Lim and Sun[7] for cell encapsulation; nowadays, it has widely been used for both cell and drug encapsulation.

Interfacial Polymerization

Monomers can be polymerized at the interface of two immiscible substances to form a membrane. An example is a nylon membrane resulting from polymerization of two monomers (typically dichloride and diamine) at the interface. A nonaqueous phase containing surfactant and an aqueous phase containing drugs

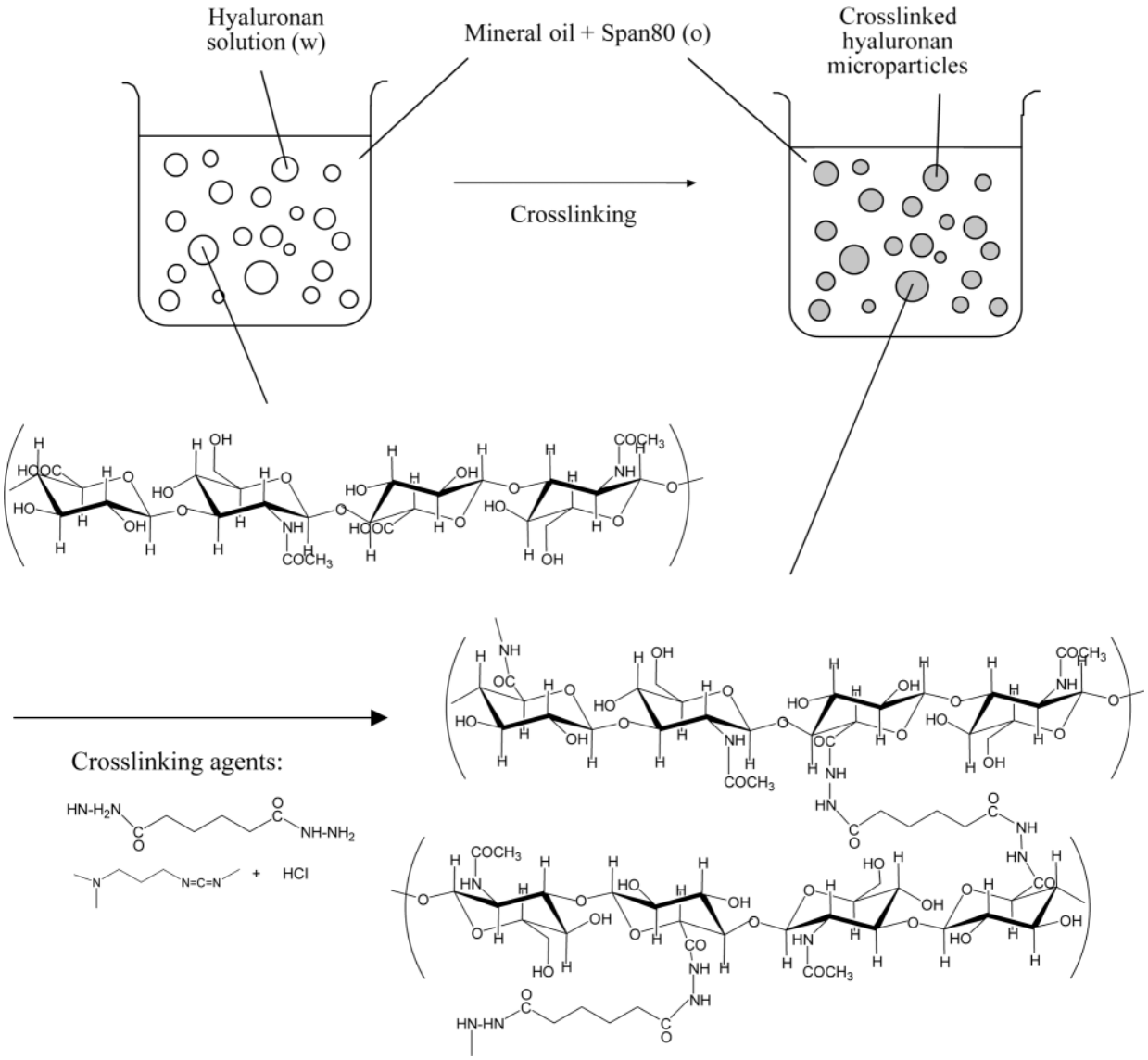

Fig. 2 Microencapsulation based on w/o emulsion and in situ cross-linking. (From Ref.[27].)

and diamine are mixed to form a w/o emulsion. Then additional nonaqueous phase containing acid chloride is added to the emulsion to allow interfacial polymerization. Polymerization can be terminated by adding excess nonaqueous phase.[29]

Spray Drying

Spray drying is a single-step, closed-system process applicable to a wide variety of materials.[2] The drug is dissolved or suspended in a suitable (either aqueous or nonaqueous) solvent containing polymer materials. The solution or suspension is atomized into a drying chamber, and microparticles form as the atomized droplets are dried by heated carrier gas. The result of the spray drying process is heavily dependent on the material properties: The instrument settings, such as inlet temperature, rate of feed flow, spray air flow, and aspirator flow, can together influence the product parameters such as particle size, yield, temperature load, and content of residual solvents. Optimization of these parameters is usually made through trial and error.

Spray Desolvation

Spray desolvation involves spraying a polymer solution onto a desolvating liquid. For example, microparticles can be made by spraying a PVA solution onto an acetone bath. Here, the polymer solvent (water) is extracted into acetone, and PVA precipitates to form solid microparticles.[30] In another example, bovine

serum albumin (BSA) was encapsulated in poly (lactic-co-glycolic acid) (PLGA) by this method. The micronized drug was suspended in a PLGA–acetone solution and atomized ultrasonically into ethanol bath.[31]

A modification of this method is the cryogenic solvent extraction method.[32] Drugs are dissolved or dispersed in the polymer phase consisting of PLGA and methylene chloride. This drug–polymer mixture solution is atomized over a bed of frozen ethanol overlaid with liquid nitrogen. The microdroplets freeze upon contacting the liquid nitrogen, then sink onto the frozen ethanol layer. As temperature increases, the frozen microdroplets begin to sink into the thawing ethanol. Methylene chloride of the polymer phase then thaws and is slowly extracted into ethanol, resulting in hardened microparticles. This process was used to produce a microparticle formulation for human growth hormone (hGH).[33,34] Prior to the encapsulation process, hGH is formulated with zinc to produce insoluble Zn-hGH complex. The encapsulation of this complex contributed to stabilize hGH during the fabrication process and within the microspheres after hydration.[33] An in vivo study of this formulation demonstrated a lower C_{max} and an extended serum level for weeks with a biocompatibility comparable to that of the protein solution.[34] The hGH formulation using this method (ProLease®) was marketed as an injectable suspension for once- or twice-a-month administration (Nutropin Depot®).

Spray Coating

In spray coating, the coating material is sprayed onto solid drug core particles that are rotated in a coating chamber. This method is typically used for coating tables or capsules.

Fluid-bed coating (Air-suspension technique)

There are three commonly used fluid-bed processes: top, tangential, and bottom spray methods. When the granules are coated by the top-spray granulator system, granules usually have a porous surface and an interstitial void space; therefore, the bulk density of produced granules is usually lower than that attainable by other granulation techniques. A rotating-disk method (also called a tangential-spray coating method), which combines centrifugal, high-density mixing, and the efficiency of fluid-bed drying, yields a product that has a higher bulk density but still has some interstitial void space. This method results in particles that are less friable and more spherical in shape. In the Wurster process (bottom spray), the solid core particles are fluidized by air pressure and a solution of wall materials is sprayed on to the particles from the bottom of the fluidization chamber parallel to the air stream. Since the spraying nozzle is immersed in the airflow and sprays the coating materials concurrently into the fluidized particles, the coating solution droplets travel only a short distance before contacting the solid particles. As a result, the film is applied more evenly and the coated film is more homogeneous. The coated particles are lifted on the air stream, which dries the coating as the particles are carried away from the nozzle. The particles rise on the air stream, then settle down, and then begin another cycle. The cycles continue until the desired film thickness is achieved. The Wurster process is particularly well suited for uniform coating of particles with a polymeric membrane in a single operation.

Pan coating

Relatively large particles can be encapsulated by pan coating. Size of solid particles should be greater than 600 μm to achieve effective coating using this method. This is a typical method used to apply sugar coatings on candies. This method employs a rotating drum containing core materials (such as candies), onto which warm sucrose solution is ladled. The rotation distributes the syrup evenly as a thin coat on the cores and increases the surface area of the syrup that aids in evaporation of the water. As the water evaporates, the sugar hardens and coats the cores. For pharmaceutical products, perforated pans are used and the coating solution, usually an aqueous solution, is sprayed onto the tumbling cores.

Supercritical Fluid

The supercritical fluid method is a relatively new method, which can minimize the use of organic solvents and harsh manufacturing conditions taking advantage of two distinctive properties of supercritical fluids (i.e., high compressibility and liquid-like density). This method can be broadly divided into two parts: rapid expansion of supercritical solutions (RESS), which utilizes the supercritical fluid (e.g., carbon dioxide) as a solvent for the polymer,[35] and supercritical antisolvent crystallization (SAS), using the fluid as an antisolvent that causes polymer precipitation.[36] Recent reviews of the supercritical technology for particle production are available in the literature.[37]

Selection of the Microencapsulation Methods

A single microencapsulation method cannot be universally applied for a variety of drugs. In developing a new

Table 1 Selection of microencapsulation methods for drugs with different properties

	Water-soluble drugs	Water-insoluble drugs
Liquid drugs	w/o/w double emulsion[38] w/o/o double emulsion[39] w/o emulsion[27,40] Ionic gelation[41] Spray drying[42]	o/w or o/o emulsion[43,44] Coacervation[1] Spray drying[8]
Solid drugs	Cryogenic solvent extraction method[33,34] s/o/w or s/o/o emulsion[45] Fluid-bed coating[46] Supercritical fluid[36]	Coacervation[47] Fluid-bed coating

microparticle system for a given drug, it is important to understand the physicochemical properties of the drug and find an encapsulation method and polymeric materials that best match the properties. Since water is the most widely used solvent system, solubility of the drug in water often serves a good starting point of the survey. Physical status of the drug can also limit the selection. The microencapsulation methods that have widely been used for drugs of different properties are summarized in Table 1.

ACHIEVEMENTS AND LIMITATIONS

Natural polymers such as proteins, carbohydrates, fats, and waxes constitute an important group of encapsulation materials; however, microparticles for the controlled drug delivery purpose have been prepared using almost invariably water-insoluble synthetic polymers. To date, poly(lactic acid) (PLA) and PLGA have been the most preferred polymers because they have been used in products approved by the U.S. Food and Drug Administration (U.S. FDA), such as surgical sutures and depot formulations, and they have a relatively long history of use for biomedical applications. Poly(lactic acid)- and PLGA-based microparticle systems are commercially available. Lupron Depot® (leuprolide acetate, TAP Pharmaceuticals Inc.) is the first commercial product based on PLA polymers.[48] Since then, various PLGA- or PLA-based products such as Zoladex® Depot (goserelin acetate, AstraZeneca), Sandostatin LAR® Depot (octreotide acetate, Norvatis), and Trelstar™ Depot (triptorelin pamoate, Pfizer) were introduced. Nutropin Depot (human growth hormone, Genentech Inc.) entered the market as the first protein-encapsulated PLGA microparticle product in 1999.

Despite the extensive use of PLGA polymers in the microencapsulation arena, it has been found through decades of research that the PLGA microparticle systems are not universally suited for different applications. One of the limitations in the prevalent PLGA systems is that bulk hydrolysis of the polymer induces acidification of microenvironment of the microparticles, which can be detrimental to various payloads such as proteins[49] and nucleic acids.[50] In addition, their drug release kinetics are not readily tunable and, thus, are inappropriate for specific applications.[51,52]

RECENT ADVANCES IN THE MICROENCAPSULATION TECHNOLOGY

In this section, a few examples of current issues in the microencapsulation technology are summarized. Solutions to these obstacles have been sought through highly interdisciplinary efforts. The latter part of this section introduces some of the recent advances in the microencapsulation technology as well as current applications of the technology.

Drug Stability

Potential sources for drug instability

Stability issues often occur in protein or nucleic acid microencapsulation, which are notoriously sensitive to various chemical and physical stresses.[45,53,54] The instability issue brings about two major problems: 1) incomplete and little release of the functional drugs and 2) immunogenicity or toxicity concern for the degraded or aggregated drugs.[54] Although the main sources of the instability may vary depending on the type of drugs, the following are the ones often attributed as potential causes.

The double-emulsion solvent removal method is the most widely used technique for encapsulation of most water-soluble drugs, including proteins, peptides, and nucleic acids. On the other hand, it is often found that these drugs are damaged at water/organic solvent (w/o) interfaces.[55,56] For example, when an aqueous solution of carbonic anhydrase was subjected to vortex

Table 2 Common inactivation sources of encapsulated proteins and the stabilization strategies

Inactivation source	Stabilization strategy
Exposure to w/o interfaces	Reducing or avoiding denaturation at w/o interfaces by including protective excipients;[56,64] employing anhydrous microencapsulation processes.[45]
Exposure to the hydrophobic organic solvent	Using more hydrophilic solvents such as ethyl acetate[18] and methyl ethyl ketone.[65]
Physical stresses during preparation	Reducing physical stresses by eliminating the emulsification step and employing low temperature processes.[33,34]
Acidification of the microenvironment	Counteracting acidification by coencapsulating antacid excipients;[49] increasing permeability of the polymer matrix;[66] modifying degradation characteristics of the polymer.[66,67]
Interaction between protein and polymer	Preventing adsorption by modifying hydrophilicity of the polymer surface;[68] pre-entrapment of protein in the hydrophilic core;[69] including adsorption competitors.[70]

(From Ref.[63].)

mixing in the presence of methylene chloride,[56] about 40% of carbonic anhydrase was recovered at the interface after centrifugation of the emulsion. Direct exposure to the organic solvent can also induce denaturation of the protein drugs. Proteins that are dissolved or suspended in organic solvents face highly hydrophobic environments, in which their functional configurations are easily disrupted. Shear stresses produced by the emulsion methods are also unfavorable conditions. Especially when it is coupled with another unfavorable condition, the shear rate facilitates aggregation of the protein drugs.[55]

It has also been noticed that the sensitive drugs can be denatured or degraded during the long-term release period.[53] There are different proofs that suggest microparticles made of PLGA polymers generate acidic microenvironments throughout the release period.[49,57] Acidic pH can cause a number of undesirable events. First, the acidic conditions can facilitate hydrolysis of peptide bonds and disulfide exchange.[58] Second, some proteins can undergo conformational transition at low pHs and induce noncovalent aggregation.[49] Third, it was shown that an acidic environment developed within microspheres contributed to deamidation and covalent dimerization of insulin.[59] Fourth, lactic acid and glycolic acid units accumulated within degrading microspheres can induce acylation of peptides.[60] On the other hand, adsorption of proteins to the polymer surface is another potential source that disturbs structural integrity of the encapsulated protein.[56,61] Among various interactions involved in the protein adsorption, hydrophobic interactions are generally regarded as the main driving force of adsorption and aggregation causing incomplete release.[62]

Strategies to address the instability issues

Different approaches have been pursued in an attempt to improve stability of the encapsulated drugs. Table 2 summarizes various approaches according to inactivation sources.

Recent approaches include a new microencapsulation method that was developed in an attempt to accommodate most of the above strategies.[71,72] This new method called the ''solvent exchange method'' is based on interfacial mass transfer between two contacting liquids, which results in reservoir-type microcapsules. Fig. 3 describes one method of making microcapsules. Series of polymer solution droplets and aqueous drug solution droplets are separately produced using ink-jet nozzles, and then are induced to collide in air. Following the collision, the two liquid phases are separated as a core and a membrane within the merged microdroplets due to the surface tension

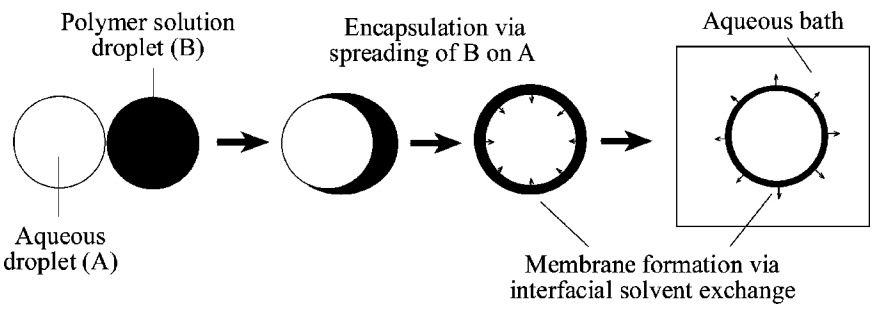

Fig. 3 Microencapsulation based on the solvent exchange method.

difference as well as incompatibility of the two liquids. There are several potential advantages of this method. First, the process does not include potentially damaging conditions such as an emulsification step but employs a mild drop generation protocol. Second, in the mononuclear microcapsules, undesirable interactions between protein and organic solvent or polymer matrix are limited only to the interface at the surface of the core. A recent study showed that these reservoir-type microcapsules were able to release the encapsulated lysozyme at a near zero-order kinetics for over 50 days. The released lysozyme remained functionally intact, which suggests that the protein survived the microencapsulation process without losing its biological activity. Third, the organic solvent for polymers can be chosen with more flexibility than in conventional methods. Hence, toxicity concerns over residual solvents, in particular, methylene chloride, can be avoided.

Control of Drug Release

Drug release from biodegradable polymer microparticles is determined by the polymer degradation kinetics, structural features of the microparticles, and distribution of the drugs within the particle matrix. The ultimate goal of microparticle systems in the controlled drug delivery is to achieve readily tunable release profiles, which has been pursued in various perspectives.

Polymer chemistry

Polyanhydrides[73] and poly(ortho esters)[74] are alternative biocompatible, biodegradable polymers that have obtained the FDA approval for the treatment of a brain tumor (Gliadel® wafer, approved in 1996) and are currently under the clinical phase II trial as of 2004 for the treatment of postsurgical pain management,[75] respectively. Unlike PLGA polymers, which undergo bulk degradation, these polymers have in common that their erosion processes are confined to the surface layers. Consequently, the drug release is primarily controlled by erosion of the surface. The interior of the matrix remains essentially neutral in pH because the hydrolysis products diffuse away from the device.[74] Microparticles fabricated using poly (ortho esters) showed lower initial bursts and sustained release profiles of a model protein.[76] Hybrids of existing biodegradable polymers were introduced in order to increase versatility of the polymeric systems taking advantage of different attributes of the participant polymers. For example, copolymers of polyesters and polyanhydrides were synthesized to achieve better control over the degradation properties and drug encapsulation.[77]

Formulation efforts

If a high initial dose is not an intended effect as in the vaccine or antibiotic delivery, the initial burst is, in most cases, an undesirable form of drug release. However, it is often true that microparticle systems containing hydrophilic drugs, such as proteins, display a large initial burst before they can reach a stable release rate. Initial burst is generally ascribed to two possible causes. First, drug distribution in the matrix is heterogeneous. Drugs that are either loosely associated with the surface or embedded in the surface layer are responsible for the burst release.[78] Second, the microparticles may have porous structure. Drugs can escape through the pores and cracks that form during the microparticle fabrication process.[79,80]

One way of reducing the surface-bound drugs is to make a blank layer on the microparticle surface. In this regard, it is worthy to note the recent efforts to make multiwall polymeric microparticles. The additional layers have traditionally been made using the spray coating method. However, the major disadvantages are relatively large size of the resulting particles and low production efficiency. Alternatively, double-walled microparticles can be prepared utilizing phase separation of constituent polymers[81,82]: A mixture of two polymer solutions, such as polyanhydride and PLA, is emulsified in an aqueous continuous phase. As the solvent evaporates, the polymer solution concentration increases to the point where they are no longer mutually soluble and begin to separate. However, since the location of individual polymer in the microparticles mainly depends on the thermodynamics of the phase separation, there is not much control over the wall composition of the microparticles. On the other hand, a recent study showed that this limitation could be overcome by utilizing multiple concentric nozzles and controlling the flow rates and concentrations of the polymer solutions (Fig. 4).[83] Another way of making coated microparticles involves sequential formation of a matrix core containing drugs and a wall polymer coating.[84] An in vitro release study using tetanus toxoid as a model drug showed that the coating was effective in suppressing the initial burst.[84]

Migration of drugs during drying and storage steps is sometimes responsible for a heterogeneous drug distribution in the polymer matrix.[79] During the air or vacuum drying process, the residual solvent (usually water) flows to the matrix surfaces before evaporation. Here, drugs also diffuse toward the surface along with water and result in heterogeneous drug distribution in the polymer matrix. In this case, the drying method can make a difference: For example, the burst release was significantly reduced[78] or almost entirely eliminated[85] by the freeze-drying.

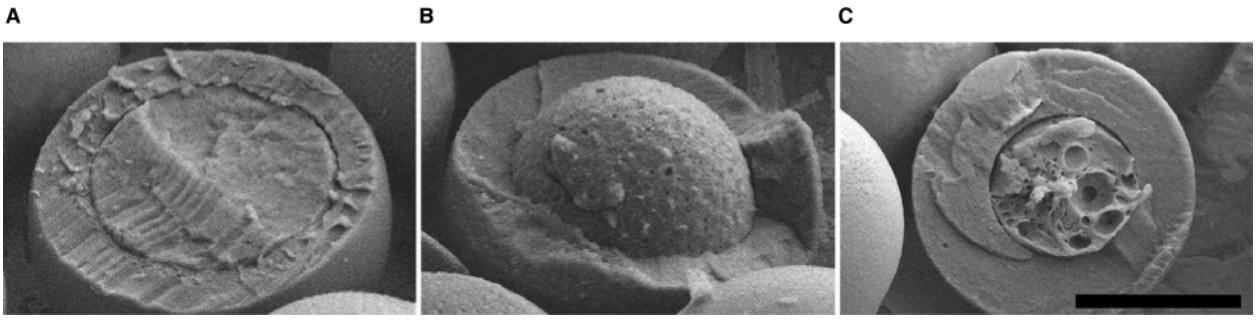

Fig. 4 Scanning electron micrographs of PLGA encapsulating poly[(1,6-*bis*-carboxyphenoxy)hexane] (PCPH) (A), PCPH encapsulating PLGA (PCPH : PLGA mass ratio = ~2 : 1) (B), and PCPH encapsulating PLGA (PCPH : PLGA mass ratio = 3 : 1) (C). Scale bar = 25 μm. (From Ref.[83].)

High affinity of the encapsulated drug to the continuous phase is another reason for heterogeneous drug distribution. For efficient internalization of the drug within the polymer matrix, formulation and fabrication parameters are varied. Addition of a small fraction of glycerol into the discontinuous phase was found to be effective in enhancing internalization of the drug (insulin) to the polymer phase.[86] The initial burst decreased from 40% to 10% by this approach. In another example, increasing hydrophilicity of the encapsulating polymer by polyethylene glycol (PEG) modification contributed to reducing the presence of the surface-associated drug and the initial burst.[87] Relatively homogeneous drug distribution can also be achieved by generating a fine primary emulsion.[88,89] The fine primary emulsion was obtained using a high energy homogenization method such as sonication[89] or high shear rate application.[88]

In alternative approaches, improvement of the structural features of microparticles was sought through various formulation parameters. In general, low molecular weight polymers result in high burst release.[80] It is partly because the low molecular weight polymer is more soluble in the organic solvent and undergoes slow solidification to produce more porous microparticles. Polymer concentration,[90] composition of the copolymer,[91] and hydrophilicity of the polymer[92] also affect the degree of initial burst by governing the rate of polymer solidification. In case of the emulsion method, composition of the continuous phase influences particle size, encapsulation efficiency, and/or initial burst.[80,93] High concentration of PVA suppresses the initial burst because the viscosity of the continuous phase prevents migration of the internal aqueous phase toward the continuous phase.[80] Addition of salt or sugar into the continuous phase can also contribute to suppression of the initial burst.[94] The presence of salt or sugar increases the osmotic pressure across the polymer phase, which is in essence a semipermeable membrane in the semisolid state. This increase in osmotic pressure prevents influx of the continuous phase into the dispersed phase and reduces the formation of water channels, which often results in a high initial burst.

Size control

Particle sizes are known to have significant influences on the release rate.[95,96] The effects vary depending on the drug release mechanism. When the drug release is mainly controlled by diffusion, which is usually the case of the early stage of release from polymeric microparticles or hydrogel-based microparticles, smaller microparticles tend to release the drugs at a relatively high rate due to the large surface area and the short diffusion distance.[97] On the other hand, when the release depends on the polymer degradation, the particle size controls the release rate by affecting additional features such as drug distribution and polymer degradation rate.[98]

In this regard, a variety of efforts have been made to obtain microparticles of monodisperse and controllable sizes. A common feature of these approaches is that the dispersed phase is formed by fragmentation of a liquid jet, which is a more readily controllable process as compared to emulsification. A few examples have shown promising results in controlling the particle size distribution.

A method developed by Amsden and Goosen[99] involves extruding a solution through a needle and then an electric field, which pulls the droplets off the end of the needle. Applicability of this method to microparticle fabrication for the controlled release was demonstrated using a solution of ethylene vinyl acetate and BSA. It was shown that the particle size could be controlled by varying size of the needle and strength of the electric field. However, this method was not effective in reducing the mean diameter maintaining a narrow size distribution. This limitation was later alleviated using a continuous phase flowing perpendicularly past the needle tip, which aids in overcoming interfacial tension between the polymer solution and the needle tip.[100]

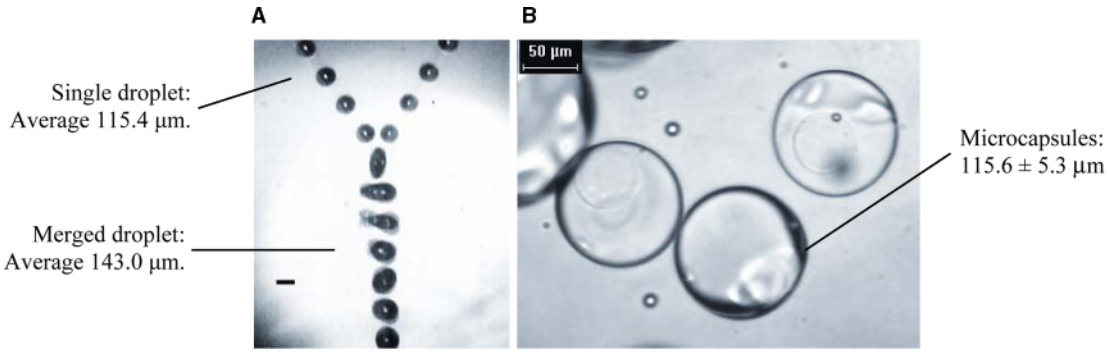

Fig. 5 Stroboscopic images of microcapsule formation via midair collision between two component liquids (scale bar = 100 μm) (A) and bright-field microscope images of microcapsules (B). The left and streams are 0.25% alginate solution and 4% PLGA solution, respectively. The nozzle orifice diameter d = 60 μm; volumetric flow rate Q = 0.6 ml/min; and forcing frequency f = 10.6 kHz. (From Ref.[71].) *(View this art in color at www.dekker.com.)*

Researchers at the University of Illinois utilize a small-gauge needle that vibrates at an ultrasonic frequency for this purpose.[101] A jet of a polymer solution passing the needle breaks up into uniform droplets, which becomes solidified micromatrices after solvent removal. The droplet size can be precisely controlled as a function of orifice size, solution flow rate, and vibration frequency. An optional carrier stream enables further reduction of the particle size. In vitro release studies using microparticles of different mean diameters demonstrated the dependence of the diffusion-dependent release profiles on the particle size.[97]

The solvent exchange method utilizing the dual microdispenser system also demonstrates a good potential of controlling the microcapsule size.[71] Here, two ink-jet nozzles carrying a polymer solution and an aqueous drug solution, respectively, are arranged in a way that two emerging liquid jets can collide resulting in reservoir-type microcapsules (Fig. 5A). The ink-jet nozzles operate in the same mechanism as the small-gauge needle described above to generate homogeneous microdroplets. The size of merged droplets, i.e., the microcapsules, is 1.26 times of the single droplets, when measured right after the collision, indicating that there is no volume loss upon the collision (Fig. 5A). On the other hand, the majority of microcapsules collected in the water bath were close to single droplets in size, and the membrane existed only as a thin membrane (Fig. 5B). It is likely that the polymer layer shrank as the solvent that constituted the majority of the polymer phase was extracted into the aqueous phases by the solvent exchange.[71]

RECENT APPLICATIONS OF THE MICROPARTICLE SYSTEMS

Use of microparticle systems is not limited to the sustained or local delivery and has a wide range of applications. A limited number of examples are introduced below.

Since it was first noticed that bioerodible hydrophobic polyanhydrides [e.g., poly(fumaric-co-sebacic anhydride)] exhibited strong bioadhesiveness, microparticles made of these polymers have been investigated as potential oral drug delivery systems.[102] The bioadhesiveness in this case comes from the hydrogen bonding interactions between mucin and carboxylic acid groups that form during the polymer erosion.[103] Furthermore, the small size of microparticles provides additional advantages by promoting cellular uptake of the formulation. Taking advantage of both the small size of microparticles and the chemical attributes of the polymeric system, the bioadhesive microparticles have shown enhanced oral bioavailability of dicumarol,[104] insulin, and DNA.[102]

Polymeric microspheres have been used for delivery of DNA vaccines, which enable prolonged immune responses through sustained release of DNA encoding a protein antigen. It has been known that <10 μm particles are preferentially internalized through phagocytosis by macrophages and antigen-presenting cells.[92] Poly(lactic-co-glycolic acid) was used as an encapsulating polymer in the initial research with promising results.[92] On the other hand, disadvantages of PLGA particles in delivering DNA vaccines were acidification of microenvironment, which can inactivate encapsulated DNA,[50] and slow release rate, which does not catch up with the life span of the target cells such as dendritic cells. In order to provide for rapid and tunable release and to avoid internal acidification, use was recently made of pH-triggered biodegradable polymers based on poly(ortho esters)[51] and poly-β-amino esters.[105] These microparticles loaded with DNA were successfully internalized into the antigen-presenting cells, enhanced immune response, and suppressed in vivo tumor challenges significantly.[51,52]

CONCLUSIONS

The microencapsulation technology, which started as a way of encapsulating dyes and flavors, has now become one of the most intriguing fields in the area of controlled drug delivery systems. The encapsulation techniques have been advanced to such a level that not only small molecular weight drugs but also macromolecules, such as proteins and genes, can be delivered via microparticle carriers. Although the technological advances have led to commercialization of several microparticulate products in recent years, many technical problems are to be overcome yet. Examples of such hurdles are maintaining the stability of encapsulated drugs throughout the lifetime of the products, manipulating release rates according to the applications, and transferring bench scale processes to the manufacturing scale. Some of the answers to those problems have been provided by advances in polymer chemistry, formulation efforts, and recent progresses in new microencapsulation techniques. The microencapsulation technology will remain as one of the most important areas in drug delivery and various other applications.

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