7 DESIGN OF CONTROLLED-RELEASE DEVICES

I. MAJOR COMPONENTS OF CONTROLLED-RELEASE DOSAGE FORMS

A. CONTROLLED DRUG-DELIVERY SYSTEMS

A controlled drug-delivery system is composed of three components:

1. Drug
2. Drug-Delivery Module
    a. Rate Controller
    b. Energy Source
    c. Delivery Portal (Exit)
    d. Reservoir
3. Platform

1. Drug

The drug is, of course, the most essential component of any dosage form. The drug, in the required amount, is stored as a stable form in the drug reservoir.

2. Drug-delivery Module

The drug-delivery module is composed of four components and determines the drug-release rate as well as the duration of drug delivery. The rate controller maintains the predetermined rate of drug delivery through the operational life of the device. The drug has to be released in the most beneficial and reliable manner. Energy is required to transfer drug molecules from the reservoir to the selected site in the body. In most cases, the high concentration of drug can function as an energy source, since drug molecules move from a higher concentration region to a lower region by Brownian motion. In many cases, a rate controller also serves as an exit for the drug. Osmosis-controlled drug-delivery systems, however, have a delivery portal that is separate from a rate controller.

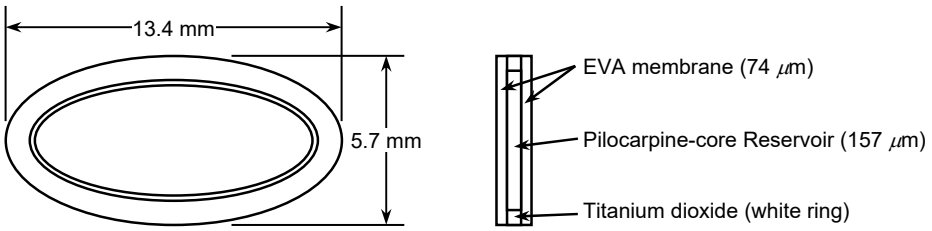
3. Platform

The platform holds the drug and delivery module to the selected body site. The adhesive of transdermal patches is a good example of a platform. The platform is an optional component in the controlled-release dosage form.

B. Examples of Controlled-release Devices

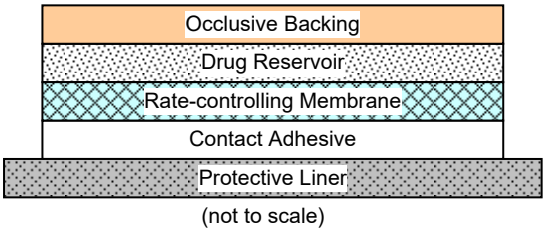
1. Ocusert®

The rate controller and the delivery portal are the same in this case. The drug itself functions as an energy source. There is no platform in Ocusert®.



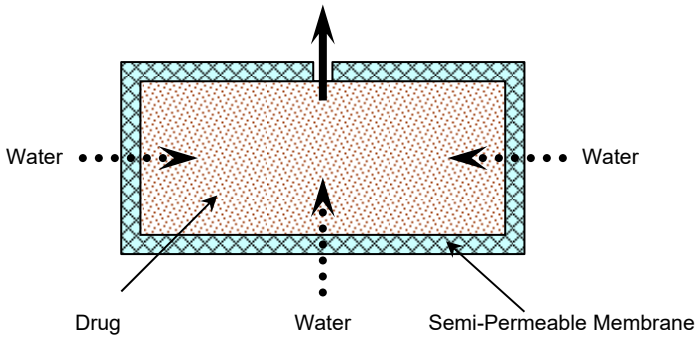
2. Transdermal Patch

For the Nicoderm® patch below, the rate controlling membrane functions as a rate controller as well as a delivery portal. The skin adhesive is a platform.



3. Osmotic Pump

In the oral osmotic (OROS) system, the delivery portal is well defined. The semi-permeable membrane is the rate controller. The drug itself functions as an energy source. In cases where additional osmotic agent is used, it works as an energy source. There is no platform in this device.



4. Infusion Device

One of the early examples of controlled-release devices is an intravenous (iv) infusion pump. The infusion pump uses positive pressure to overcome minor occlusions, which are generally associated with iv systems and viscous solutions, to overcome back pressure created by arterial lines and to accurately infuse drugs at very slow rates (Kwan, 1989). Advances

in both infusion and computer technologies resulted in production of infusion pumps with sophisticated programming and operating functions that provide multiple-rate programming and multiple-solution infusions (Kwan, 1989). The ultimate goal of controlled release is to deliver drugs at a rate that a patient needs. In this sense, patient-controlled pumps, especially analgesia pumps, symbolizes controlled drug-delivery system in its ultimate sense.

In an infusion device, the energy source is electric power and the delivery portal is a needle. The rate controller is the computerized pump system. The drug reservoir is a bottle containing the drug. Here, the platform is a table or a hanger that carries the infusion device. According to the definition of platform, any tape used to secure a needle is also a platform.

II. FACTORS TO CONSIDER IN THE DESIGN OF CONTROLLED-RELEASE DOSAGE FORMS

Development of controlled-release devices requires consideration of several factors, such as the size and shape of the controlled-release devices, the controlled drug-release mechanism, and the route of administration and targeting ability. These factors are interdependent in the design of the most useful dosage forms (Figure 7.1). Choices on the size and shape and

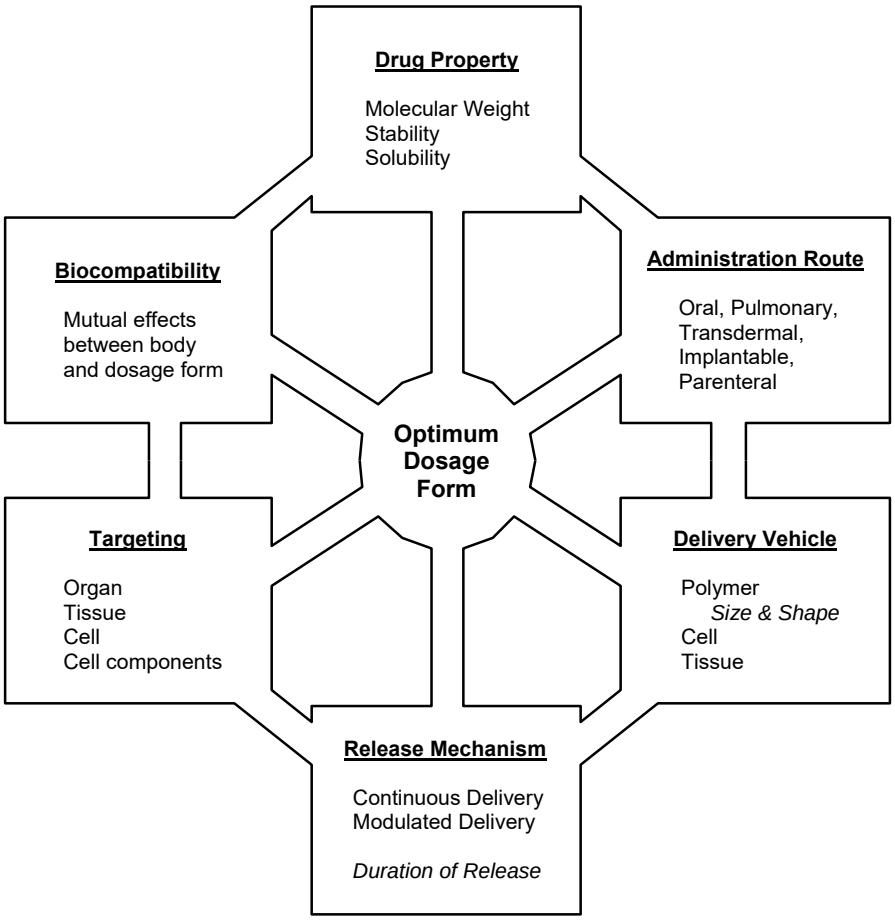


Figure 7.1 Interdependence of various factors in the design of controlled drug-delivery systems.

the release mechanism of a controlled-release device are influenced by the choice on the route of administration as well as the addition of targeting properties. Some drugs preclude selection of certain routes of administration. Oral administration is not a viable option for most peptide and protein drugs, at least up to date, owing to easy degradation in the gastrointestinal (GI) tract and poor absorption through the mucous membrane of the GI tract. This forces consideration of other routes, such as pulmonary administration, and this may dictate the choice in the size and shape of the dosage forms. For the injectable or implantable dosage forms, use of biodegradable delivery system is preferred, and this may favor drug-delivery mechanisms based on chemical or enzymatic degradation. The interdependent factors need to be considered simultaneously in the design of new controlled-release dosage forms.

III. SIZE AND SHAPE OF CONTROLLED-RELEASE DOSAGE FORMS

A. NANOPARTICLES

Controlled-release dosage forms can be made in various sizes and shapes (Figure 7.2). The size can be as small as an individual molecule and as large as a transdermal patch. Drugs can be attached to water-soluble molecules, such as antibodies, lectins (plant-derived proteins having high binding affinity to carbohydrates, such as glucose), immunotoxins,

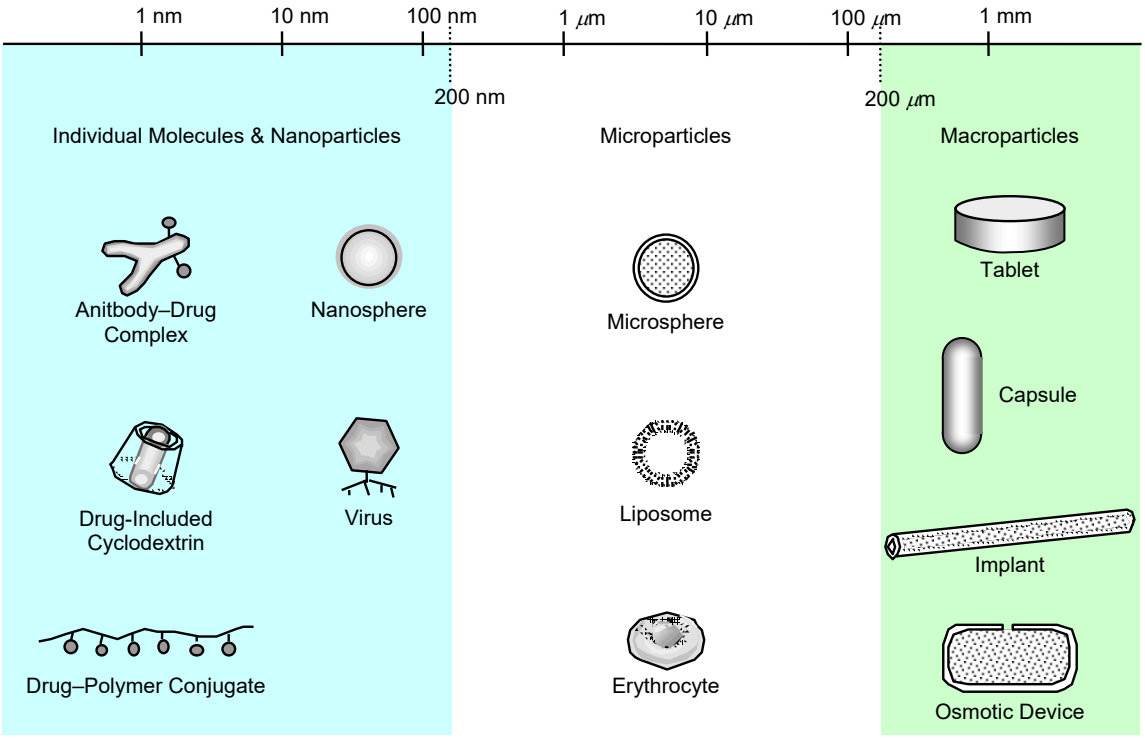
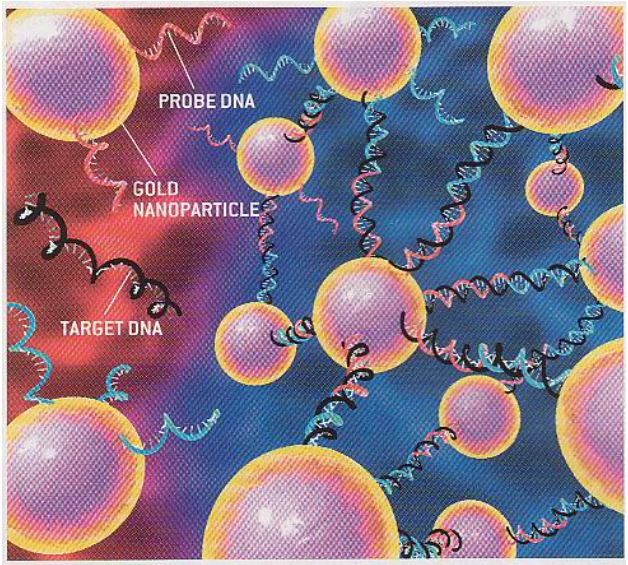


Figure 7.2 Examples of drug-delivery systems in various sizes and shapes. The size ranges from nano- to macroscale, and the shape can be fiber, spherical, film, cylindrical, and cube. The physical state can be solid, suspension, emulsion, and cream.



GOLD PARTICLES

Gold nanoparticles studded with short segments of DNA could form the basis of an easy-to-read test for the presence of a genetic sequence (*black*) in a sample under study. DNA complementary to half of such a sequence (*red*) is attached to one set of particles in solution, and DNA complementary to the other half (*blue*) is attached to a second set of particles. If the sequence of interest is present in the sample, it will bind to the DNA tentacles on both sets of spheres, trapping the balls in a dense web. This agglomeration will cause the solution to change color (*from red to blue*).

viruses, cyclodextrins, and natural or synthetic polymers. These are basically individual molecules which can release attached drug molecules at the desired site by enzymatic or hydrolytic cleavage. The dosage form can be made as nanoparticles, which are solid colloidal particles with a size less than 200 nm (0.2 μm). There is no clear-cut size range that distinguishes nanoparticles from microparticles. The 200 nm size limit is chosen here since it is the resolution limit of light microscopy. Some may call any particle smaller than 1,000 nm nanoparticles. One of the advantages of nanoparticles is that the small size allows administration by intravenous injection. They can pass through capillaries that remove larger particles that are usually taken up by the reticuloendothelial system (*i.e.*, liver, spleen, and lungs). Nanoparticles can be prepared by suspension and emulsion-polymerization techniques.

B. MICROPARTICLES

Microparticles are colloidal particles in the micrometer scale, typically in the size less than a few hundred micrometers.

1. Liposomes and Cochleates

Liposomes have been used for the delivery of drugs which are hydrophobic and/or relatively toxic. Liposomes are spherical lipid vesicles com-

posed of self-assembled amphiphilic molecules. Amphiphiles with two nonpolar tails (*i.e.*, hydrophobic chains) self-assemble into lipid bilayers where the nonpolar interior is shielded by the surface polar heads. A number of liposomal formulations of amphotericin B and daunorubicin were approved for clinical applications. Abelcet™ is a liposomal formulation of amphotericin B developed by the Liposome Company, Inc., for the treatment of invasive fungal infections, including candidiasis, cryptococcal meningitis, fusariosis, and zygomycosis in patients who are refractory to or intolerant of conventional amphotericin B therapy. AmBisome™ is another liposomal formulation of amphotericin B developed by NeXstar Pharmaceuticals Inc. for the treatment of life-threatening systemic fungal infections that fails to respond to amphotericin B. DaunoXome™ is a liposomal formulation of daunorubicin developed and marketed by NeXstar Pharmaceuticals Inc. for a primary therapy for advanced AIDS-related Kaposi's sarcoma. Cationic liposomes are effective for gene transfer into the cells. For highly negatively charged bilayers, negatively charged surfaces can be bridged together by Ca^{2+} ions to form spiral rolls, which are called cochleates. Cochleates are used for *in vivo* gene delivery via the intramuscular as well as the oral route. Phospholipid microemulsion can also be used for the delivery of hydrophobic drugs.

MINIATURIZED PEOPLE in the 1966 movie *Fantastic Voyage* swim like nanobot surgeons in a patient's bloodstream.

2. Naturally Occurring Delivery Systems

Concerns about the toxicity of the synthetic materials leads to the continued exploration of naturally occurring drug-carrier systems: platelets, erythrocytes, and lipoprotein particles (Shaw, 1991). Low-density lipoprotein (LDL) particles are the source of cholesterol supply to dividing and growing cells, and are taken up by specific receptors on the cell surface. So, there is a potential for the specific targeting of drugs to rapidly dividing cells. The problem with natural systems is that there is a limited supply of basic materials and drug loading is not simple.

a. Resealed Erythrocytes

Resealed erythrocytes can also be used as micro drug carriers. There are a few advantages of drug delivery by red blood cells. First, red blood cell drug-delivery systems are biodegradable and nonimmunogenic. Second, the entrapped drug is shielded from immunological detection and external enzymatic degradation. The system is also relatively independent of the physicochemical properties of the drug. Loading of drug into red blood cells can be accomplished by the methods described in Table 7.2. In the pre-swell dilution technique, the membrane of red blood cells can be ruptured by placing them in hypotonic media. The pores on the membrane formed during this process allow free exchange of intra- and extracellular components and this can be used to load drugs. The membrane is resealed by adjusting the solution tonicity to isotonic. In the dialysis technique, the blood cells are placed in dialysis tube immersed in a hypotonic medium. This approach allows retention of cytoplasmic components after the cells are resealed. When red blood cells are subjected to an intense electric field, pores are formed on the membrane. The membrane can be resealed after drug loading.

3. Synthetic Microparticles

Synthetic polymers have been widely used in the preparation of microparticulate drug-delivery systems. Synthetic polymers serve as a membrane or a matrix for controlling drug release (see Chapter 9). In situations where biodegradation of microparticles are desirable, biodegradable microparticles can be prepared from natural polymers (*e.g.*, albumin and gelatin) as well as synthetic polymers (*e.g.*, poly(lactic acid), poly(glycolic acid), and polycaprolactone), which are degradable *in vivo* by hydrolysis.

a. PharmaZome™

PharmaZome™ is the term used by Elan Corp. to describe its microparticulate drug-delivery technology. Each pharmazome consists of specific combinations of insoluble polymer and drug in the size range 50–125 μm.

Table 7.2 Methods of Loading Drugs into Red Blood Cells

Pre-swell dilution technique
Dialysis technique
Electric field technique

The drug is embedded uniformly throughout the polymer and can be produced using either a spray-drying or emulsion technique. The drug is released through the insoluble polymer layer by diffusion. Theo-Dur Sprinkle®, which uses Pharmazome technology, is marketed by Mitsubishi in Japan.

b. Microsponge®

Microsponge® (Advanced Polymer Systems, Inc.) is composed of thousands of small beads wrapped together to form a microscopic spheres capable of binding, suspending, or entrapping a range of substances. The outer surface is porous. Microsponges® can be incorporated into gels, creams, liquids, powders, or other formulations, and can be programmed to release ingredients depending on temperature, moisture, friction, volatility of the entrapped ingredient, or time. There are a number of products using the microsponge technology.

Exact® — a benzoyl peroxide microsponge that allows controlled release of acne medication without excessive skin drying.

EverStep® — a foot powder microsponge containing a coolant, an antifriction agent, a moisture absorber, and fragrance that releases the ingredients slowly in response to heat, moisture, and friction.

Baby Fresh® with UltraGuard™ (Scott Paper) — controlled release of water-repellant dimethicone, an ingredient to help prevent diaper rash.

ProZone® (a melanosponge sunscreen) — a microsponge system containing the skin pigment melanin).

Oil of Olay® — a microsponge product.

4. Macrodevices

Macrodevices are widely used in many applications. Considering that oral administration is the most convenient mode of administration, it is not surprising to see a large number of macrodevices designed for oral administration. For long-term applications ranging from months to years, the dosage forms may have to be implanted. Most of the implantable dosage forms are either large, single unit or small, multiple units owing to the presence of a large drug reservoir. The most widely used shapes of controlled-release devices are sphere, cylinder, and film. One of the reasons of high acceptance of these shapes is that the mathematical treatments of drug release from dosage forms of such shapes are well understood.

IV. MICROENCAPSULATION

Microencapsulation is a process of coating microparticles with a membrane layer. Microencapsulated particles (or microcapsules) are usually less than 200 μm in diameter. They can be either filled in ordinary gelatin capsules or compressed into a tablet. Microencapsulation is usually used to prepare controlled-release dosage forms. Here we will briefly review the various processes of microencapsulation. Microencapsulation methods can be divided into chemical and physical methods.

A. Coacervation (Phase Separation)

Coacervation method is based on the "salting out" or phase separation into small droplets of a polymer-rich, second liquid phase from a homogeneous solution of hydrophilic polymers rather than separating into solid aggregates. Coacervation is divided into simple and complex coacervation.

1. Simple Coacervation

When an aqueous polymer solution (*e.g.*, gelatin, PVA, or carboxymethylcellulose) is partially dehydrated (or desolvated) by adding a strongly hydrophilic substance (*e.g.*, ethanol, acetone, dioxane, isopropanol, propanol, or sodium sulfate), the water-soluble polymer is concentrated in water by the action of the water-miscible, non-solvent and a polymer-rich phase is formed. Under suitable conditions, microcapsules result.

The following is a typical example of making microcapsules by simple coacervation:

a. Prepare a 10% dispersion of gelatin in water at 40 °C.
b. Add 20% sodium sulfate solution or ethanol (final concentration of 50–60% v/v) with constant stirring.
c. Cool to 5 °C.
d. Insolubilize the coacervate capsules by adding a hardening agent such as glutaraldehyde.
e. Wash, dry, and collect.

2. Complex Coacervation

Complex coacervation can be induced in systems having two dispersed hydrophilic polymers (colloids) of opposite electric charges. Neutralization of the overall positive charges on one of the colloids by the negative charge on the other is used to bring about separation of the polymer-rich complex coacervate phase. Since electrostatic interactions are involved, the pH of the medium is very important. For example, in the gelatin–gum arabic (or gum acacia) system, pH should be below the isoelectric point of gelatin to make the gelatin positively charged.

An example of complex coacervation:

a. The core material is emulsified or suspended in a gelatin solution. The aqueous solution of both the gelatin and gum arabic (or gum arabic) should be below 3% by weight.
b. Then the gum arabic (or gum arabic) solution is added to the gelatin system at > 35 °C and at pH 3.8–4.3 with continuous mixing.
c. Cool the system to 5 °C.
d. Crosslink the gelled-coacervate capsule walls with glutaraldehyde.
e. Wash, dry, and collect.

3. Commercial Products

The first commercial product based on microcapsules prepared by the complex coacervation was carbonless copy paper developed by National Cash Register Corp. in the 1940s and 1950s. The back side of the first page is coated with microcapsules in the size 3–10 μm 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. Writing ruptures microcapsules in both sheets of paper to release the colorless color-forming agent which, upon reacting with the developing layer, develops color (*e.g.*, by breaking the lactone ring).

Examples:

Purdue forms with carbon papers

Form 3 — Printing Service Work Order

Purdue forms with carbonless copy paper

Form 56 — Invoice Voucher
DSP Form 1 — Proposal transmittal check sheet.

Recently, microcapsules have also been used in Scratch-N-Sniff® scent strips, and Snap-N-Burst® fragrance samplers. It is used to prepare scented inserts in magazines and for department store bill mailings. Scratch-N-Sniff® is used for sales promotion efforts by fragrance marketers.

Other examples of controlled-release dosage forms will be dealt with in depth in later chapters.

B. Solvent Evaporation and Extraction

1. Solvent Evaporation

The polymer is dissolved in a volatile organic solvent, such as methylene chloride. The therapeutic or diagnostic agent, either in soluble form or dispersed as fine particles, is added to the polymer solution, and the mixture is suspended in an aqueous phase that contains a surface-active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporates leaving solid microspheres that may be washed with water and dried overnight in a lyophilizer. An example of the double emulsion solvent evaporation method is shown in Figure 7.3. The model protein, leuprorelin acetate, was mixed with dicholomethane in which poly(lactide–co-glycolide) (PLG) was dissolved to form a w/o (water/oil) emulsion. This emulsion is added to PVA solution to form a w/o/w (water/oil/water) double emulsion. At elevated temperatures, dichloromethane is evaporated through the aqueous phase. The drug-containing PLG microparticles are freeze-dried.

2. Solvent Extraction

Solvent removal was primarily designed for use with less-stable polymers, such as the polyanhydrides. In this method, the agent is dispersed or dissolved in a solution of a selected polymer in a volatile organic solvent, like methylene chloride. The mixture is then suspended in oil, such as silicon oil, by stirring to form an emulsion. Within 24 h, the solvent diffuses into the oil phase and the emulsion droplets harden into solid polymer microspheres. Unlike solvent evaporation, this method can be used to make microparticles from polymers with high melting points and different molecu-

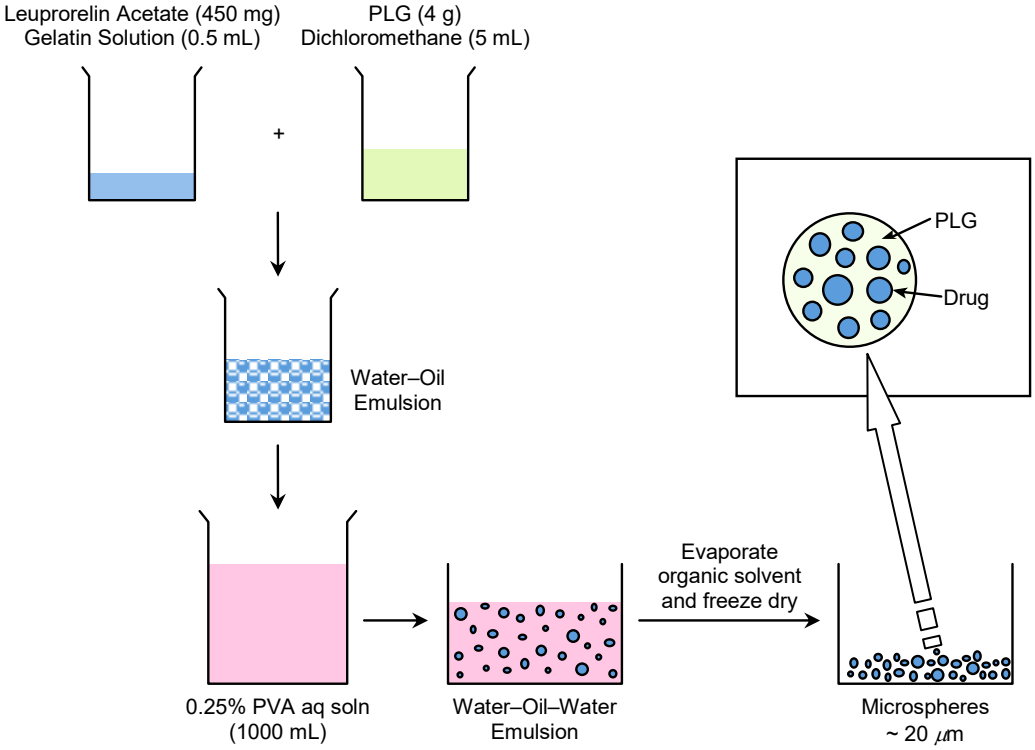


Figure 7.3 An example of the double emulsion solvent evaporation method.

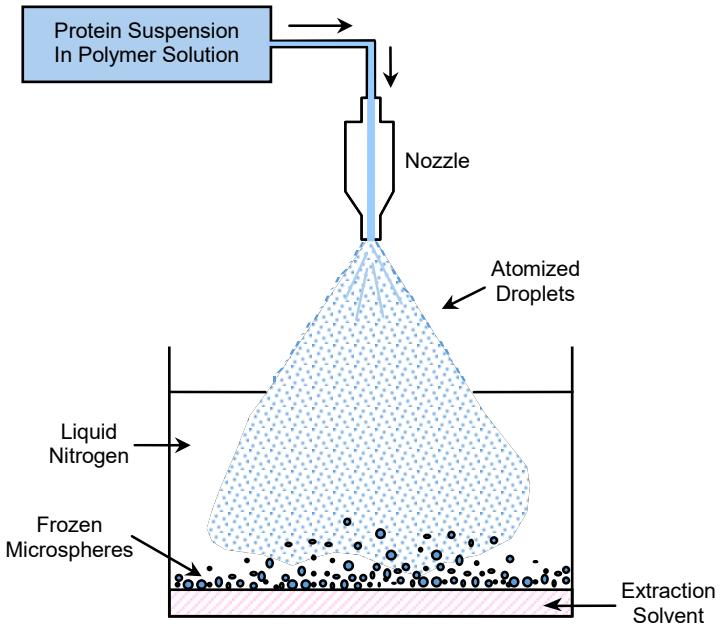


Figure 7.4 The Prolease® process.

lar weights. A variation of this method was developed for microencapsulation of protein drugs with minimal exposure of the protein drugs to denaturing conditions. In the Prolease® process shown in Figure 7.4, protein powders are dispersed into the organic solvent, such as dichloromethane containing PLG, and the whole polymer solution is sprayed into liquid nitrogen for immediate freezing of the polymer microdroplets. The

frozen microparticles are collected on top of the alcohol present at the bottom of the liquid nitrogen container. The organic solvent is extracted to the alcohol to result in microparticles.

3. Interfacial Crosslinking

In some cases, the homogeneous microparticles can be crosslinked only at the surface to form thin membranes. For example, alginate microcapsules are made this way. Sodium alginate solution can be dropped or sprayed into a calcium chloride solution (Figure 7.5). An alginate solution containing a drug in a 10-mL syringe is infused, using a syringe pump, into a gas-atomizing device to be sprayed into a pan containing calcium chloride (1.5%) solution. Pressurized nitrogen is introduced into the atomizer through the gas inlet. In the inside of the atomizer, the pressurized gas is mixed with incoming alginate liquid to break the liquid into tiny droplets, which are forced out through the orifice of the nozzle. The calcium ions crosslink the alginate molecules on the surface of microparticles immediately on contact (see Figure 5.2). By controlling the time of diffusion of calcium ions into the alginate particles, only the outer layer of the alginate particles can be crosslinked. Alternatively, the calcium crosslinked-alginate particles can be further crosslinked with poly-L-lysine. Since poly-L-lysine is a polymer, it does not go into the alginate particles, and only the outside of the particle is crosslinked. These alginate particles can be exposed to citric acid or EDTA solution to replace the calcium ions.

Other polymer systems that can be used for interfacial crosslinking include chitosan–tripolyphosphate, carboxymethylcellulose–lead ions, and alginate–polyethylene imide systems.

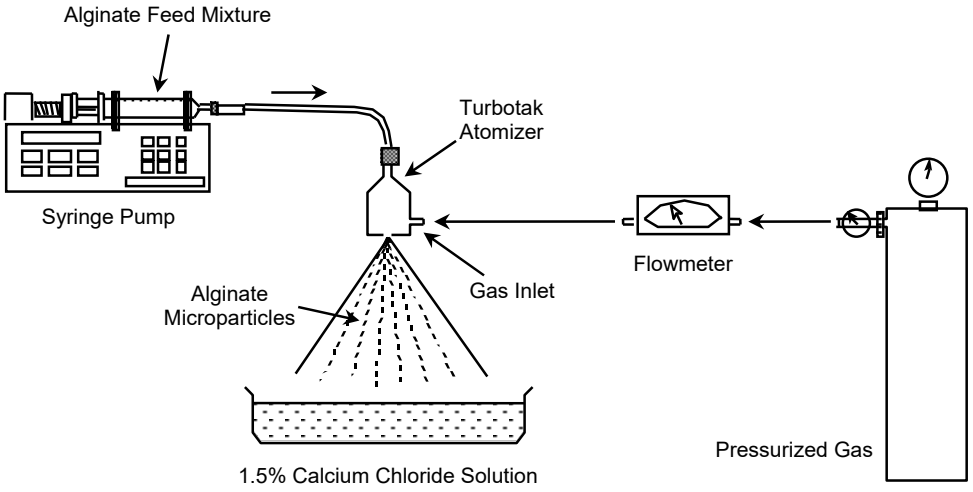


Figure 7.5 Set-up for alginate solution atomization. Pressurized gas source, syringe pump for continuous liquid feed, atomizer, and receiving solution are required. Optional gas flow meter is connected between the gas source and the atomizer to accurately control the flow of the gas. Calcium chloride solution is placed 45 cm below the atomizer nozzle orifice.

D. 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 at the interface.

E. Hot-Melt Microencapsulation (Congealing)

In hot-melt microencapsulation, the polymer is first melted and then mixed with the solid particles of the solid or liquid drug. The mixture is suspended in a non-miscible solvent (such as silicon oil), and, while stirring continuously, heated to 5 °C above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify.

F. Spray Drying

Spray drying is a single-step, closed-system process applicable to a wide variety of materials, including heat-sensitive materials (Burgess & Hickey, 2002). The drug is dissolved or suspended in a suitable (either aqueous or non-aqueous) solvent containing polymer materials. The solution is atomized and the microspheres are dried by heated carrier gas. The size of microspheres is controlled by the rate of spraying, the feed rate of the drug-polymer solution, the nozzle size, and temperature in the drying and cooling chambers,

Polylactide microspheres can be prepared by dissolving the drug and polymer in methylene chloride, while microspheres of methylcellulose and sodium carboxymethylcellulose (CMC) can be prepared by dissolving the polymer in aqueous systems.

G. Spray Coating

1. Fluid-Bed Coating (Air-Suspension Technique, Wurster Processing)

There are three commonly used spraying methods for coating in fluid-bed processing: top, tangential, and bottom spray methods (Figure 7.6).

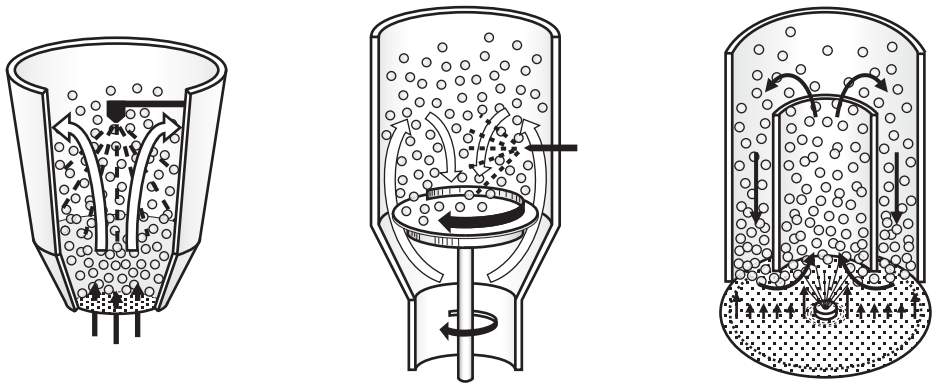


Figure 7.6 Schematic diagrams of spraying methods for coating in fluid-bed processing: top spray (left), tangential spray (center), and bottom spray (right).

When the granules are coated by the top-spray granulator system, granules are usually characterized by a porous surface and by an interstitial void space that results in increased wicking of liquid into the granules and improved disintegration of dispersibility. In addition, the bulk density of the produced granules is generally lower than that attainable by other techniques of granulation.

A rotating-disk method (also called a tangential-spray coating process), which combines centrifugal, high-intensity mixing with the efficiency of fluid-bed drying, yields a product that has a higher bulk density but still results in some interstitial void space. In addition, this method results in particles that are less friable and are more spherical in shape.

The Wurster system is similar to the rotary coater in that the coating solution is applied concurrently with the flow of product. The Wurster process combines a partition (coating partition) and an orifice plate (air distribution plate) to organize the flow of particles in close proximity to the nozzle. Solid, particulate core materials are suspended on a supporting air stream designed to induce smooth cyclic flow of the particles past a bottom-positioned nozzle that atomizes the coating material up into a fluidized bed of core particles. Because the nozzle is immersed in the airflow to spray concurrently into the fluidized particles, the solution droplets travel only a short distance before contacting the substrate. 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 out, and then descend to begin another cycle. The cycles continue until the desired film thickness is achieved. Because the particles actually separate from each other as they are carried on the air stream during coating, even very small particle can be coated while controlling agglomeration. The process is able to use a wide variety of coating materials. Thus, one can tailor-coat particles to specific requirements. The Wurster process is particularly well suited for the uniform coating of particles with a polymeric membrane in a single operation.

2. Pan Coating

Relatively large particles can be microencapsulated by the pan method. Solid particles greater than 600 μm in size are essential for effective coating by this method. This is the typical method used to apply coats of sugar on candy (such as M&Ms and jelly beans) and employs a rotating drum containing the candy cores to be coated (see Figure 7.7). As the pan slowly rotates, a warm syrup of sucrose and water is ladled onto the contents. 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. The equipment resembles a large clothes dryer with a perforated drum and slanting baffles to achieve better agitation of the cores (see Figure 7.8)

Figure 7.7 A small pan coater used in sugar coating candy.

Figure 7.8 A 42-in perforated coating pan with spray nozzles (upper left) and tumbling cores (lower right).

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