CHAPTER II

LITERATURE REVIEW

Microencapsulation can be described as a process in which very thin coatings of polymeric material(s) are deposited around particles of solids or droplets of liquids, and the products from this process are called microcapsules or microspheres (Luzzi, 1970, 1976; Madan, 1978b; Deasy, 1984; Li et al., 1988; Bakan, 1986, 1994). The microcapsules developed for use in medicine consist of a solid or liquid core material containing one or more drugs enclosed in a coating as shown in figure 1. The core may also be referred to as the nucleus or fill; the coating, the wall or shell. Depending on the manufacturing process, various types of microcapsule structure can be obtained as illustrated in figure 1. The most common type is the mononuclear spherical. The particle size of microcapsules is defined in various ranges but can be varied from approximately 1 μm to 5,000 μm (Bakan and Sloan, 1972; Luzzi, 1976; Deasy, 1984; Bakan, 1986; Li et al., 1988).

1. History of Microencapsulation Techniques

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kaas in 1931 and dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating. In the late 1930s and 1940s, Green and co-workers

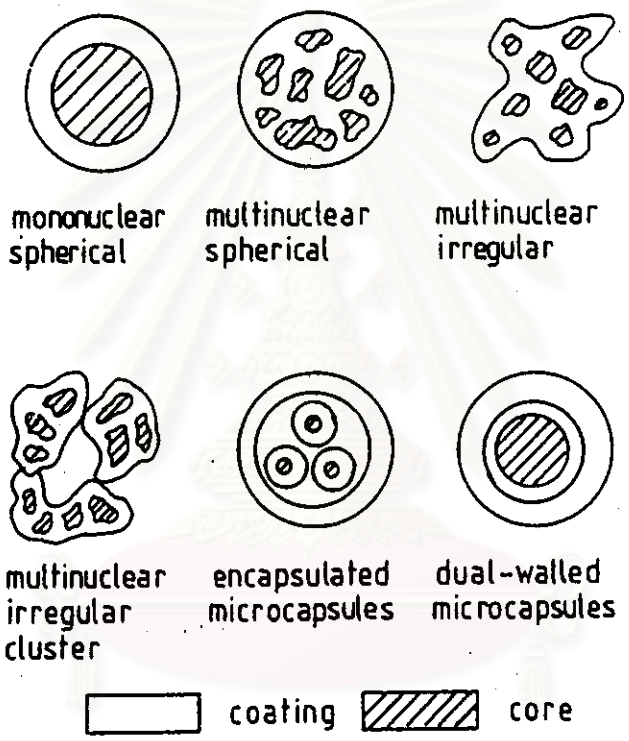


Figure 1. Some typical structures of microcapsules (Deasy, 1984).

of the National Cash Register Co. developed the gelatin coacervation process to prepare carbonless carbon paper. The microcapsules containing a colorless dye precursor (3,3-bis-(p-dimethylaminophenyl)-6-dimethylamino phthalide) were affixed to the under surface of the top page and released the dye precursor upon rupture by pressure from the tip of a writing tool. The liberated dye precursor then reacted with an acidic clay (attapulgite) coating on the top surface of the underlying page to form a copy image, dark blue color, as illustrated in figure 2 (Fanger, 1974; Deasy, 1984).

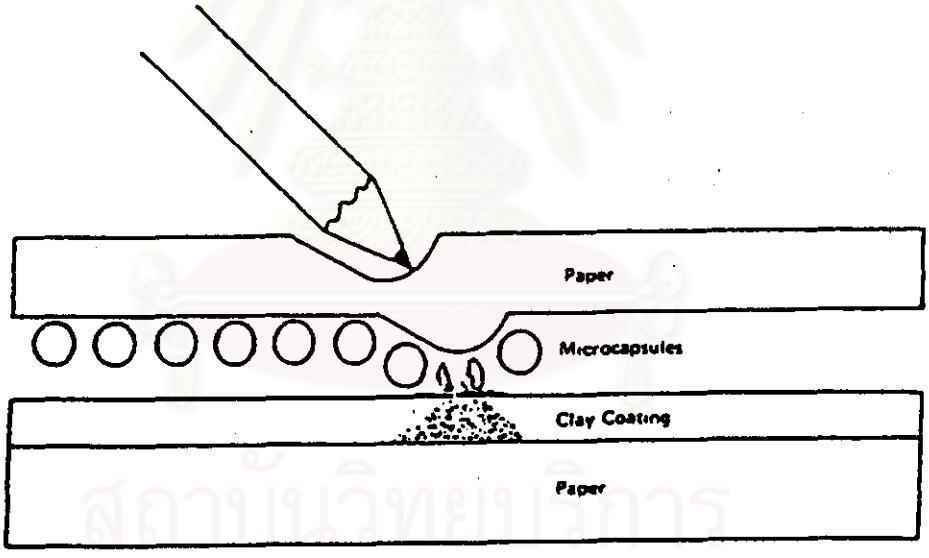


Figure 2. Pressure-activated release of encapsulated dye precursor to give a color reaction on paper coated with an acidic clay (Fanger, 1974).

2. Reasons for Microencapsulation

The technique of microencapsulation has gained popularity because of its potential applicability in a wide variety of situations. The microencapsulation processes have been used in many industries such as food, food additives, cosmetics, adhesives, household products, agricultural materials, an aerospace industry, and many others (Deasy, 1984; Bakan and Doshi, 1991; Bakan, 1994). In the pharmaceutical industry, the microencapsulation processes have been used since the 1960's, and there are many reasons why drugs and related chemicals have been microencapsulated (Luzzi, 1970; Bakan and Sloan, 1972; Madan, 1978b; Deasy, 1984; Bakan, 1986, 1994):

a) Microencapsulation has been employed to stabilize drugs sensitive to environment such as moisture, light, oxygen, etc. Bakan (1986) reported that microencapsulated vitamin A palmitate had enhanced the stability of the drug compared with the unencapsulated control. In addition, the microencapsulation technique has also been used to improve stability of drugs unstable in a biological environment such as hydrolytic influences of enzymes and pH, and the solubilizing action of bile salts.

b) Microencapsulation has been used to prevent incompatibilities between drugs such as aspirin versus chorpheniramine maleate, and aspirin versus propoxyphene HCl. Pharmaceutical eutectics have been microencapsulated to separate them. This is because when the microcapsules are properly produced, all the particles are coated (Bakan, 1994).

c) Microencapsulation has been used to reduce gastric and other gastrointestinal tract irritations from drugs, for example, aspirin, ferrous sulfate, and potassium chloride. Gastric irritation can be reduced by coating drug particles with a thin gastrointestinal fluid-resistant film. The film, deposited by microencapsulation, separates the irritant particles from the mucosal lining and thus minimizes the irritant effects. In addition, a microencapsulated product allows a dispersion of drug-containing microcapsules in the gastrointestinal tract. This reduces a possibility of local high concentrations which can result in irritations or toxic effects (Bakan, 1994).

d) Microencapsulation has been used to prolong the action of drugs, and it may also be useful for improving the bioavailability of lipophilic drugs (Jizomoto et al., 1993). The controlled release products usually consist of a large number of microcapsules having variable release rates due to the composition or amount of the coatings applied. Many drugs have been produced in the microcapsule form to prolong their actions such as furosemide (Gohary and Gamal, 1991), theophylline (Bodmeier and Wang, 1993), aspirin (Nikolayev and Gebre, 1993), and 5-fluorouracil (Zinutti et al., 1994).

e) Microencapsulation has been used to modify the physical properties of chemical entities. For example, oils may be encapsulated to produce free-flowing powders which are convenient for handling and storage. Flow properties of many vitamins could be improved by microencapsulation prior to compression into tablets (Madan, 1978b; Deasy, 1984).

f) Microencapsulation has been used to disguise the objectionable taste of a number of drugs such as fish oil, naproxen, aspirin, acetaminophen, dicloxacillin, sulfa drugs, etc. Tastes can be masked because a continuous film coating the drug particle

prevents contact with the taste sensors upon ingestion. In addition, the particle sizes of microcapsules are small enough to prevent mouth feel and aftertaste (Bakan, 1994).

g) Microencapsulation has been used to mask the unpleasant odor of drugs such as castor oil, cod liver oil, clofibrate, etc. (Deasy, 1984).

h) Microencapsulation has been used to reduce the vaporization of several volatile substances such as methyl salicylate and peppermint oil (Deasy, 1984).

i) Microencapsulation has been used to improve safety in handling of toxic drugs or chemical substances, e.g. antineoplastic drugs, fumigants, insecticides, herbicides, and pesticides (Madan, 1978b; Deasy, 1984).

Microencapsulation has also been used medically to entrap mammalian cells and tissues within polymeric microcapsules for controlled release of bioactive agents (Lim and Moss, 1981; Sefton et al., 1992; Uludag et al., 1993). The capsule membrane (e.g. hydroxyethyl methacrylate-methyl methacrylate copolymer) constitutes a physical permeability barrier that restricts the survival of cell mass in a confined space but allows the release of cell-derived products (Sefton et al., 1992; Uludag et al., 1993). An interfacial precipitation technique was developed for encapsulating mammalian cells in polyacrylate membranes. These microencapsulated cells constitute a novel form of controlled release device in which the therapeutic agent (such as insulin, dopamine, etc.) is produced by naturally or genetically engineered cells which are transplanted into a host and isolated from the immune system by the permselective capsule wall. A permselective polymeric membrane acts as a permeability barrier for large molecules (such as antibodies) but it has high permeability for small molecules (such as nutrients, hormones, etc.).

The microcapsules can be formulated into a variety of useful dosage forms (Bakan and Sloan, 1972; Bakan, 1994). These include powders, hard gelatin capsules, rapidly disintegrating tablets, chewable tablets, oral liquid suspensions, injections, ointments, creams, lotions, plasters, dressings, and suppositories.

3. Core and Coating Materials

A core material, which is defined as the specific material to be coated, plays a significant role in microencapsulation (Bakan, 1986, 1994). It dictates the process as well as the polymer used as a coating material. It should be insoluble and nonreactive with the coating material and the manufacturing vehicle. Water soluble and insoluble solids, water immiscible liquids, solutions, and dispersions of solids in liquids can be microencapsulated. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients, and release rate retardants or accelerators.

The microcapsule coating can be chosen from a wide variety of natural and synthetic polymers (Bakan, 1986, 1994). A partial listing of typical coating materials commonly used in the various microencapsulation methods is suggested in table 1, and ethylcellulose used in this studies will be presented in more details. The selection of the appropriate coating material dictates, to a major degree, the resultant physical and chemical properties of the microcapsules, and consequently, the selection must be given due consideration. The coating material should be capable of forming a film that is adhesive with the core material, should be chemically compatible and nonreactive with the core material, and provides the desired coating properties such as strength, flexibility, permeability, optical properties, and stability.

Table 1. Representative coating materials and applicable microencapsulation processes.

Coating materials	Processes				
	Coacervation	Solvent evaporation	Air suspension	Pan coating	Spray drying
Water soluble resins					
Gelatin	✓	✓	✓	✓	✓
Gum arabic	✓	✓	✓	✓	✓
Starch	✓		✓	✓	✓
Polyvinylpyrrolidone	✓		✓	✓	✓
Carboxymethylcellulose	✓		✓	✓	✓
Hydroxyethylcellulose	✓	✓	✓	✓	✓
Methylcellulose	✓		✓	✓	✓
Arabinogalactan	✓		✓	✓	✓
Polyvinyl alcohol	✓	✓	✓	✓	✓
Polyacrylic acid	✓	✓	✓	✓	✓
Water insoluble resins					
Ethylcellulose	✓	✓	✓	✓	✓
Polyethylene		✓	✓		
Polymethacrylate	✓	✓	✓	✓	✓
Polyamide (Nylon)		✓	✓		
Poly [ethylene-vinyl acetate]	✓	✓	✓	✓	✓
Cellulose nitrate	✓	✓		✓	✓
Silicones				✓	✓
Poly (lactide-co-glycolide)	✓	✓		✓	
Waxes and lipids					
Paraffin	✓	✓	✓	✓	✓
Carnauba			✓	✓	✓
Spermaceti	✓		✓	✓	✓
Beeswax			✓	✓	✓
Stearic acid				✓	✓
Stearyl alcohol			✓	✓	✓
Glyceryl stearates			✓	✓	✓
Enteric resins					
Shellac	✓		✓	✓	✓
Cellulose acetate phthalate	✓	✓	✓	✓	✓
Zein	✓		✓		

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets, granules, and microcapsules. Ethylcellulose coatings are used to modify the release of drug, to mask an unpleasant taste, or to improve the stability of a formulation. An example of the use of ethylcellulose, which is dissolved in isopropanol, is to coat ascorbic acid granules to prevent oxidation (Wade and Weller, 1994c). Ethylcellulose, which is dissolved in an organic solvent or a solvent mixture, can be used on its own to produce water-insoluble films. Higher viscosity ethylcellulose grades tend to produce stronger and tougher films. Ethylcellulose films may be modified to alter their solubilities by the addition of hydroxypropyl-methylcellulose or a plasticizer.

Ethylcellulose alone yields very tough films of excellent tensile strength, flexibility, and elongation characteristics; yet, such films lack suppleness. Also, ethylcellulose alone softens and flows at too high a temperature to be practical in molding operations or in other applications requiring good thermo-plasticity. Therefore, plasticizers or softening agents are added to ethylcellulose to obtain the proper degree of suppleness, to increase segmental mobility, to impart flexibility, to reduce brittleness, and to increase resistance of the film coating to failure produced by mechanical stress (Deasy, 1984; McGinity, 1989; Rekhi and Jambhekar, 1995).

Ethylcellulose is additionally used in cosmetics and food products. It is not metabolized following oral consumption and is therefore a noncaloric substance. It is generally regarded as a nontoxic, nonallergenic and nonirritant material.

4. Microencapsulation Procedures

Many microencapsulation procedures have been developed for the coating of pharmaceuticals. There are difficulties to classify simply under any one heading because the techniques employed in these methods exhibit a large degree of overlap; however, they may be classified into 3 major categories that are physical methods, chemical methods, and mechanical methods (Madan, 1978b; Deasy, 1984; Bakan, 1986, 1994). These major microencapsulation procedures are summarized briefly in table 2. The coacervation or phase separation and solvent evaporation techniques using non-aqueous vehicles will be presented in more details in the next topic.

Various microencapsulation processes give rise to the formation of microcapsules with various characteristic size ranges as shown in table 4 (Deasy, 1984; Bakan, 1986, 1994).

4.1 Coacervation/Phase Separation Procedures

Coacervation is one of the oldest and most common microencapsulation techniques in current use. The term 'coacervation' is used to describe the phenomenon of salting out or phase separation of lyophilic colloids into liquid droplets rather than into solid aggregates (Luzzi, 1970; Madan, 1978a, 1978b; Deasy, 1984; Bakan and Doshi, 1991). The colloidal phenomenon of coacervation was first described by Bungenberg de Jong and Kruyt in 1963 as a process of flocculation or separation of liquids from a solution in which at least one of the liquids contained a macromolecular or colloidal solute (Madan, 1978a, 1978b). If one starts from a solution of a colloid in an appropriate solvent, then, according to the nature of the colloid, various changes (e.g. temperature, pH, addition of certain substances) can bring about a reduction of

Table 2. Summary of major microencapsulation processes.

Process	Principle	Type of core	Type of coating
1. Physical Methods			
1.1 Coacervation/ Phase Separation (using aqueous and nonaqueous vehicles)	The solvation of polymeric solute(s) in a medium is reduced to form coacervate droplets to deposit and coat the dispersed phase.	Vehicle-insoluble drug(s).	Vehicle-soluble polymer(s).
1.2 Solvent Evaporation	A polymer solution containing drug is emulsified into an immiscible liquid phase to form a dispersion and the solvent is removed from the dispersed droplets to leave a suspension of drug containing polymer microcapsules.	Solvent-soluble and solvent-insoluble drug(s), but insoluble in manufacturing vehicle.	Solvent-soluble polymer(s), but insoluble in manufacturing vehicle.

Table 2. (continued)

Process	Principle	Type of core	Type of coating
2. Chemical Methods 2.1 Interfacial Polymerization	Various monomers are reacted at the interface of two immiscible liquid phases to form a film of polymer that encapsulates the dispersed phase as illustrated in figure 3.	High-molecular-weight materials such as enzymes and hemolysates.	Water-soluble and water-insoluble monomers as presented in table 3.
3. Mechanical Methods 3.1 Air Suspension	Polymer solution is spray-applied to the suspending and moving particles in the coating zone portion of the coating chamber of air suspension apparatus as shown in figure 4.	Non-volatile and solid drug(s).	Water-soluble or organic solvent-soluble polymer(s).

Table 2. (continued)

Process	Principle	Type of core	Type of coating
3.2 Pan Coating	Polymer solution is spray-applied to the desired solid core material, which is deposited onto spherical substrates, e.g. nonpariel seeds or other solid substrates, in the coating pan while rotating as shown in figure 5.	Non-volatile and solid drug(s).	Water-soluble or organic solvent-soluble polymer(s).
3.3 Spray Drying	A core material is dispersed into a coating solution and then the mixture is atomized into a hot air stream to remove the solvent from the coating material as shown in figure 6.	Solvent-insoluble drug(s).	Solvent-soluble polymer(s).

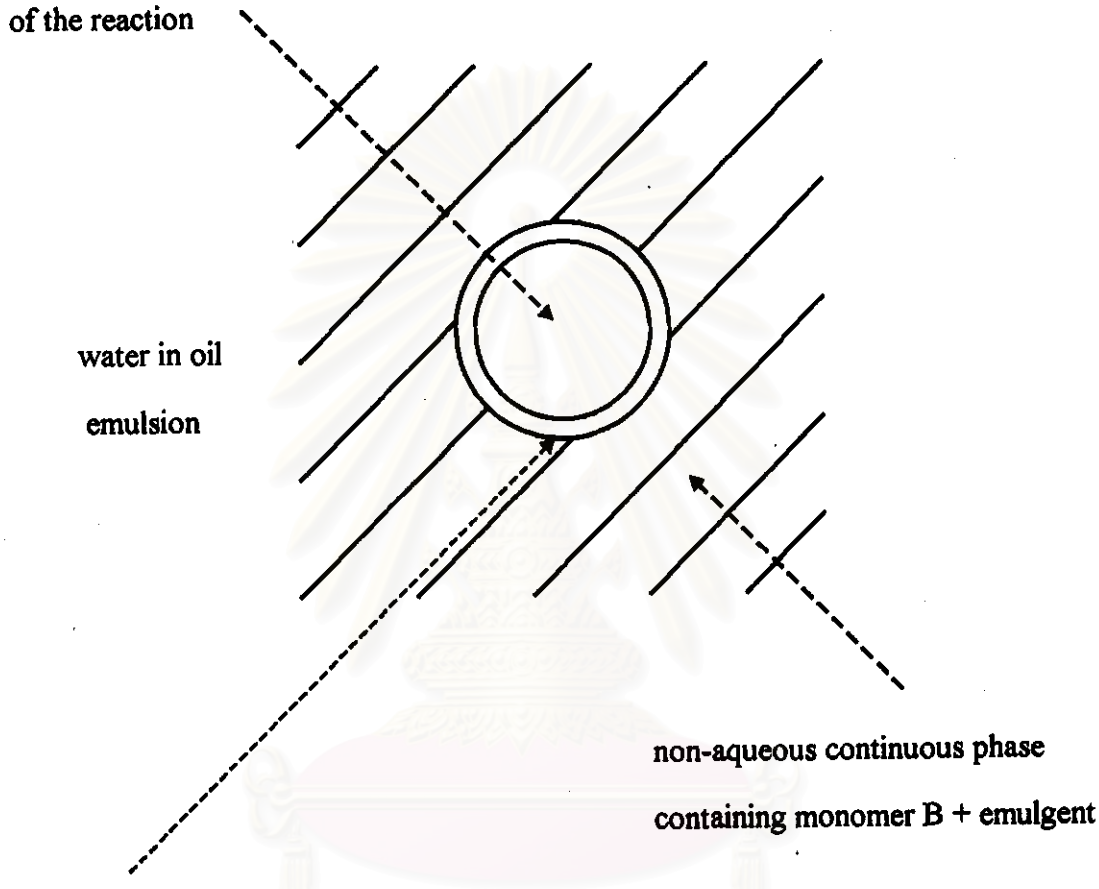


Figure 3. Schematic representation of microencapsulation of a droplet by interfacial polymerization (Deasy, 1984).

Table 3. Principal monomer combinations investigated for the microencapsulation of pharmaceuticals by interfacial polymerization (Deasy, 1984).

Aqueous phase monomer A		Nonaqueous phase monomer B	→	Polymer AB wall material formed
1. Polyamine, e.g.	+	Polybasic acid halide, e.g.	→	Polyamide, e.g.
1,6- hexamethylene diamine	+	sebacoyl chloride	→	nylon 6-10
piperazine	+	terephthaloyl cholride	→	polyterephthalamide
L-lysine	+	terephthaloyl cholride	→	poly(terephthaloyl L-lysine)
2. Polyphenol, e.g.	+	Polybasic acid halide, e.g.	→	Polyester, e.g.
2,2-bis(4-hydroxy-phenol)propane	+	sebacoyl chloride	→	polyphenyl ester
3. Polyamine, e.g.	+	Bischloroformate, e.g.	→	Polyurethane, e.g.
1,6-hexamethylene diamine	+	2,2-dichlorodithyl ether	→	polyurethane

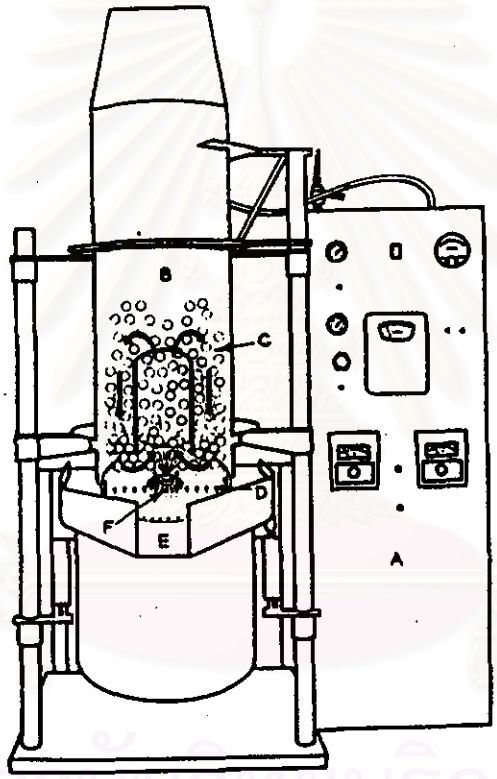


Figure 4. Schematic drawing of Wurster Air Suspension Apparatus: A, control panel; B, coating chamber; C, particles being treated; D, process airflow; E, air distribution plate; and F, nozzle for applying film coatings (Bakan, 1986).

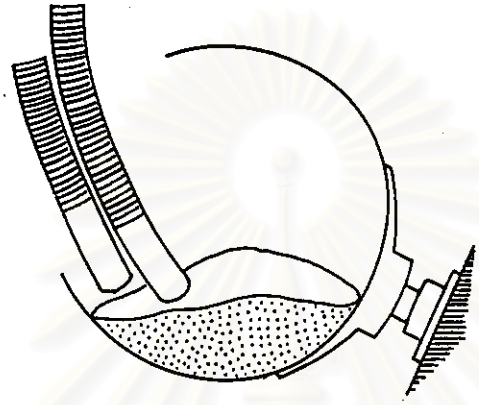


Figure 5. Schematic representation of an operating coating pan (Deasy, 1984).

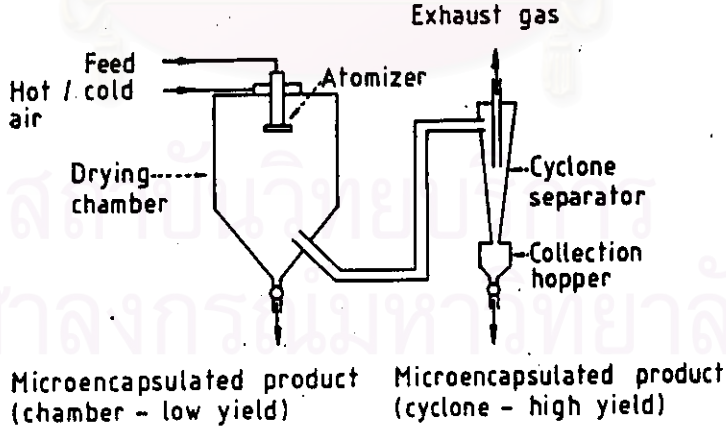


Figure 6. Schematic diagram of a cocurrent spray dryer (Deasy, 1984).

Table 4. Microcapsule size ranges produced by various production procedures.

Production process	Size range (μm)
Coacervation/Phase separation	1-5000
Solvent evaporation	1-5000
Interfacial polymerization	2-2000
Air suspension	35-5000
Pan coating	200-5000
Spray drying	5-800

the solubility of the colloid. As a result of the solubility reduction of the colloid, a large part of the colloid will separate out in a new phase. Thus, the original one-phase system is divided into two phases; one of them is rich in colloid (the coacervate phase), and the other contains very little colloid (the equilibrium liquid). The phenomenon of coacervation can be distinguished from the process of crytallization in the following manner (Madan, 1978a, 1978b). In crystallization, the colloid-rich phase appears in a low-dispersed state and microscopic examination reveals the presence of crystalline entities. Whereas, in coacervation, the colloid-rich phase appears in a more highly dispersed state and microscopic examination reveals the presence of amorphous liquid droplets or coacervate droplets. In dealing with polymers and solvents, a form of phase separation can occur wherein the polymer in solution can be made to separate as a liquid phase rather than a flocculate or a precipitate.

For microencapsulation of water-insoluble core materials, the wall-forming polymer is dissolved in water. This process is termed 'aqueous phase separation'. When the substance to be encapsulated is water-soluble and the wall-forming polymer is dissolved in an organic hydrophobic solvent, the microencapsulation process is called 'nonaqueous phase separation' or 'Dobry effect' (Madan, 1978a, 1978b; Deasy, 1984; Bakan, 1994).

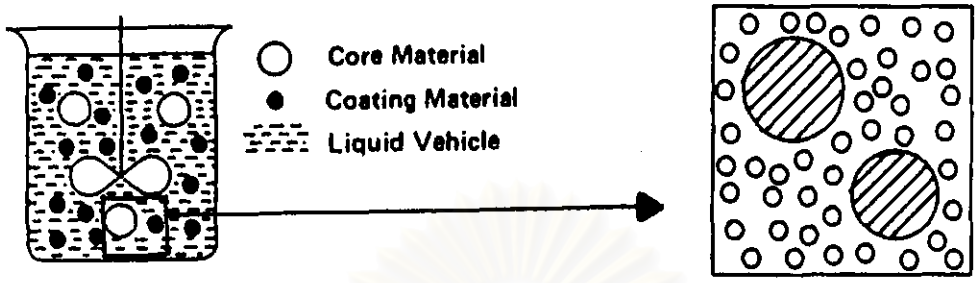
Generally, these microencapsulation processes consist of three steps (figure 7) carried out under continuous agitation (Madan, 1978b; Deasy, 1984; Bakan, 1994):

1. Formation of three immiscible phases: the liquid-vehicle phase, the core material, and the liquid polymer coating.
2. Deposition of the coating.
3. Solidification of the coating.

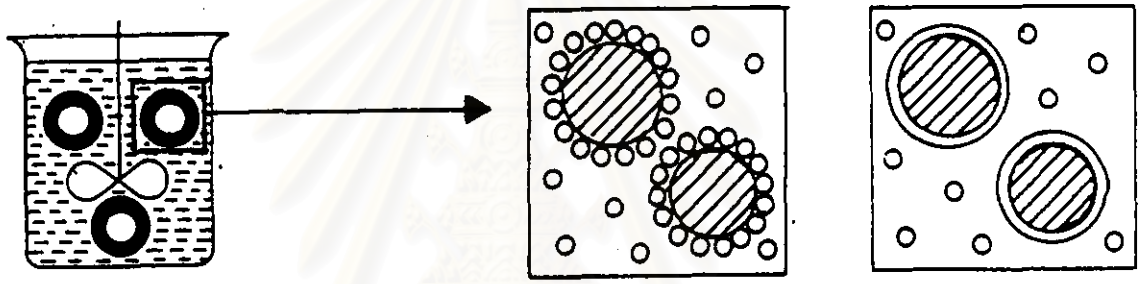
In step one, the three immiscible chemical phases are formed. The core material is dispersed in a solution of the coating polymer. The solvent for the polymer is the liquid manufacturing vehicle. The coating material, the immiscible polymer in the liquid state, is formed as coacervate droplets of colloid-rich phase by utilizing one of the methods of phase separation or coacervation, that is, by simple or complex coacervation, temperature change, addition of a nonsolvent, or polymer-polymer incompatibility.

In step two, the liquid polymer coating (coacervate droplets) is deposited around the core material by controlled physical mixing of the coating (while fluid) and the core material in the liquid manufacturing vehicle. Deposition of the liquid polymer coating around the core material occurs if the polymer is adsorbed at the interface

1. Establishment of three-phase system.



2. Deposition of liquid-polymeric coating material.



3. Solidification of coating material.

Figure 7. ·General process description of coacervation technique (Adapted from Deasy, 1984, and Swarbrick and Boylan, 1994).

(core, coacervate droplets, coating, hardened coating)

formed between the core material and the liquid manufacturing vehicle. This sorption phenomenon is a prerequisite to effective coating. The continued deposition of the coating is promoted by a reduction of the total free interfacial energy of the system which is brought about by a decrease in the coating material surface area during coalescence of the liquid polymer droplets.

Step three of the process involves solidifying of the coating which is usually induced by thermal, cross-linking, or desolvation methods to form rigid microcapsules. The desolvation can be performed by addition of a non-solvent or phase-inducing polymer or by a change in pH. Photograph examples of the rigid and uniformity coated microcapsules formed are shown in figures 8 and 9.

4.1.1 Types of Coacervation

Coacervation has been subdivided into two catergories: simple coacervation and complex coacervation. Briefly, simple coacervation usually deals with systems containing only one colloidal solute and depends primarily on the degree of hydration produced. Whereas complex coacervation usually deals with systems containing more than one colloidal solutes and depends on the formation of electrical charge interaction between macromolecules. Some basic characteristic features of the two systems are summarized in table 5 (Madan, 1978a).

Simple coacervation is a process involving the addition of a strongly hydrophilic substance to a solution of a colloid. This added substance causes two phases to be formed; one phase is rich in colloidal droplets and the other is poor in such droplets. This process depends primarily on the degree of hydration produced.

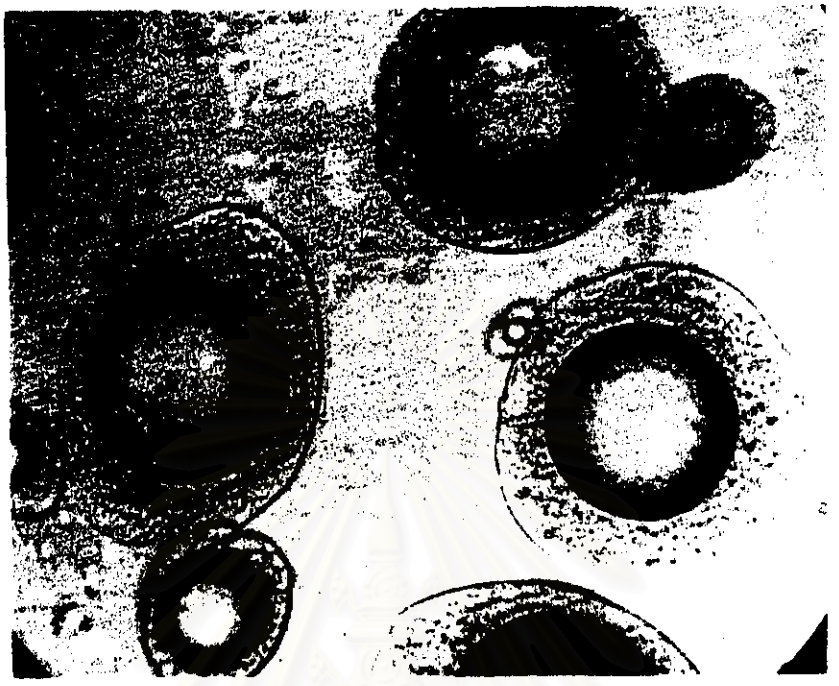


Figure 8. A magnified photograph of microencapsulated liquid (Swarbrick and Boylan, 1994).

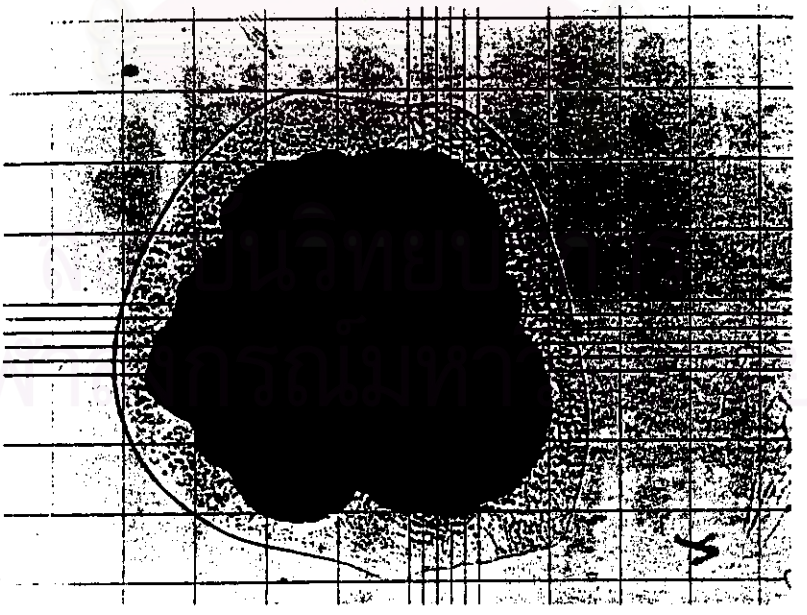


Figure 9. A magnified photograph of microencapsulated solid (Swarbrick and Boylan, 1994).

Table 5. Characteristics of simple and complex coacervation.

Characteristics	Simple Coacervation	Complex Coacervation
- Components needed.	At least one must be a macromolecule, e.g. gelatin.	Two macromolecules capable of carrying opposite charges, e.g. gum arabic/gelatin.
- Presence of charge on the macromolecules.	Has no consequence in inducing coacervation.	Determines whether or not coacervation will take place.
- Principal conditions.	Insufficiency of water in a part of the total system.	Sufficient water for adequate charge interaction.
- Concentration of components.	Must be high, usually between 20% and 40%.	Must be low, preferably less than 5%.
- Effect of dilution.	Coacervation does not occur.	Coacervation occurs.
- Presence of salts.	Promotes coacervation–effectiveness follows the lyotropic series.	Suppresses coacervation–position of ions in lyotropic series is of minor significance.
- Application of direct current electric field.	Coacervate drops do not exhibit disintegration phenomenon.	Coacervate drops exhibit disintegration phenomenon.
- pH of coacervation.	Not of great significance (usually a very large margin)–also occurs at pH > isoelectric point of gelatin.	Highly dependent on pH (usually a very narrow range) –also occurs at pH < isoelectric point of gelatin.

For example, an addition of alcohol or sodium sulfate, as typical hydrophilic substances, to an aqueous solution of gelatin can lead to the two phase formation. When suitable conditions including the presence of suitable nuclei are prevalent, microcapsules may result.

4.1.2 Coacervation/Phase Separation Procedures Using Non-aqueous Vehicles

Many drugs are moderate to very water-soluble and would be unsuitable for encapsulation by procedures using aqueous vehicles, especially for drugs sensitive to moisture. Accordingly, various techniques have been developed for coating such drugs. The techniques employ organic liquids in which the drug is insoluble but the coating polymer is soluble under certain conditions. Phase separation of the polymer may be induced by different methods such as temperature change, addition of incompatible polymer, or non-solvent addition (Deasy, 1984; Bakan, 1986, 1994). The coacervated polymer encloses the core material to form the microcapsule wall. Usually, low polymer concentrations are required for encapsulation by the coacervation technique involving separation into polymer-rich and polymer-poor regions. The phase separation must be gradual; this enables the concentrated polymer solution to deposit and flow uniformly over the surface of the core material to form a satisfactory coating. Higher polymer concentrations tend to give a rapid demixing effect upon phase separation which is unsuitable for microencapsulation. Suitable polymers must be water-insoluble so that drug release from such microcapsules in aqueous environments is controlled mainly by diffusion of the drug through the coating rather than by dissolution or erosion of the coating.

A. Coacervation Induced by Temperature Change

Microencapsulation by temperature change involves a polymer soluble in a solvent at elevated temperature but insoluble in the same solvent at room temperature. When certain polymers are dispersed in a cold solvent with a core material present, heating the mixture with agitation to a selected temperature and slowly cooling the dispersion back to room temperature can result in the microencapsulation.

Figure 10 illustrates a general temperature-composition phase diagram for a binary system comprised of a polymer and a solvent. A system having an overall composition represented as point X on the abscissa exists as a single-phase, homogeneous solution at all points above the phase-boundary or binodal curve, FEG. As the temperature of the system is decreased from point A along the arrowed line AEB; the phase boundary is crossed at point E and the two-phase region is entered.

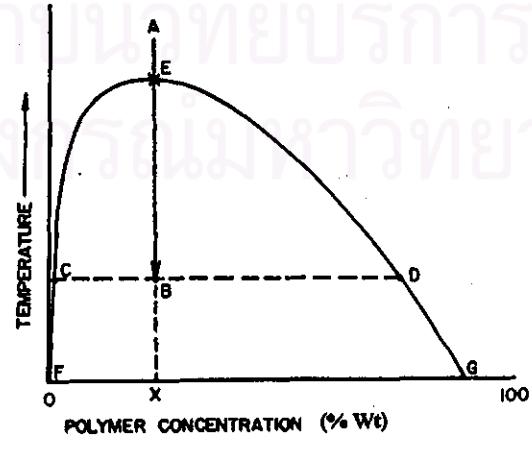


Figure 10. General phase diagram of thermally induced coacervation (Bakan, 1986).

The phase-boundary curve indicates that with decreasing temperature, one phase becomes polymer-poor (the microencapsulation vehicle phase) and the second phase becomes polymer-rich (the coating material phase). At point B, for instance, the segmented tie-line suggests that vehicle phase is essentially pure solvent, point C, whereas the coexisting phase, point D, is a concentrated polymer-solvent mixture.

A commonly used microencapsulation system involves the release of ethylcellulose from cyclohexane to form a liquid envelope on a water-soluble solid core. It, then, is converted into a hard-walled microcapsule. The process involves dissolving ethylcellulose in cyclohexane at 80 to 81°C (boiling point of cyclohexane) and the solution is gradually cooled so that the polymer separates as a liquid coacervate and encloses particles of core material that are dispersed by vigorous agitation in the system. The deposited wall material may be hardened by continued lowering of the temperature while maintaining vigorous agitation to prevent coalescence of microcapsules. When the system reaches the temperature of 20 to 25°C, the microcapsules can be filtered off from cyclohexane and dried.

When ethylcellulose is precipitated by cooling or coacervation, it comes out solvated with cyclohexane. In such case, the final washed and filtered cakes of microcapsules are difficult to dry. Tray drying leads to dry cakes of microcapsules. Breaking the cakes into lumps, following by drying, lead to dry lumps of microcapsules. Drying method of ethylcellulose microcapsules can be improved by displacing residual solvating cyclohexane in the ethylcellulose by reslurrying with pentane, hexane, heptane, octane, or mixtures thereof, such as petroleum ether, prior to the drying stage. The product obtained has less tendency to clump, giving small discrete microcapsules (Gutcho, 1979; Deasy, 1984).

B. Coacervation Induced by Addition of Incompatible Polymers

Microencapsulation by polymer-polymer incompatibility is probably the most classical method to produce microcapsules using the Dobry effect to induce liquid polymer phase separation. The Dobry effect primarily uses organic liquids as the solvents for the polymers. The Dobry effect involves the cohesive energy density and/or solubility parameters of polymers (tables 6-7). As the numerical values of the solubility parameters of polymers and solvents move away from each other, incompatibility occurs.

When dissimilar polymer pairs are dissolved in a common solvent, incompatibility is the rule; compatibility, the exception. In many cases, when two solutions of different kinds of polymers dissolved in the same kind of solvent are mixed, liquid-liquid phase separation occurs. If this is done with agitation in the presence of a core material, microcapsules form. The polymer that is most tenaciously sorbed at the core material-solvent interface becomes the coating, and the microcapsules thus formed are dispersed in a solution of the other polymer. The noncoating material can be removed from the microcapsules by washing them with a solvent for this polymer in which the coating is insoluble. Typical coating polymers include ethylcellulose, cellulose nitrate, cellulose acetate, polymethyl methacrylate, and polystyrene. Polymers that can be used to induce phase separation include polyethylene, polybutadiene, and polymethylsiloxane. Common solvents such as cyclohexane, toluene, ethanol, acetone, and methyl ethyl ketone are used in many processes. Consequently, this process is best used to microencapsulate solvent-insoluble or, more specifically, water-soluble solids.

Table 6. Solubility parameters of selected polymers (Bakan and Doshi, 1991).

Polymer	Solubility Parameter
Silicone, polydimethyl	7.3
Polyethylene	7.9
Polyisobutylene	8.1
Natural rubber	8.3
Polybutadiene	8.6
Polystyrene	9.1
Neoprene GN rubber	9.2
Polyvinyl acetate	9.4
Polymethyl methacrylate	9.5
Polyvinyl chloride	9.7
Polymethyl chloroacrylate	10.1
Ethylcellulose	10.3
Cellulose dinitrate	10.6
Polymethacrylonitrile	10.7
Cellulose diacetate	10.9
Cellulose nitrate, 1/2s	11.5
Polyvinylidene chloride	12.2
Nylon type 8	12.7
Nylon 66	13.6
Polyacrylonitrile	15.4

Table 7. Solubility parameters of selected solvents arranged by chemical types (Bakan and Doshi, 1991).

Solvent	Solubility Parameter
Isobutylene	6.7
Petroleum ether	7.1
Hexane	7.3
Diethyl ether	7.4
Octane	7.6
Diisobutyl ketone	7.8
Methyl amyl acetate	8.0
Butyl butyrate	8.1
Cyclohexane	8.2
Isobutyl acetate	8.3
Isopropyl acetate	8.4
Butyl acetate	8.5
Carbon tetrachloride	8.6
Xylene	8.8
Toluene	8.9
Ethyl acetate	9.1
Diacetone alcohol	9.2
Methyl ethyl ketone	9.3
Tetrachloroethylene	9.4
2-Ethylhexanol	9.5
Methyl acetate	9.6
Methylene chloride	9.7
Ethylene dichloride	9.8
Acetone	10.0
n-Octanol	10.3
2-Ethylbutanol	10.5
n-Hexanol	10.7
Sec. butanol	10.8
n-Butanol	11.4
Isopropanol	11.5
n-Propanol	11.9
Ethanol	12.7
Ethylene glycol	14.2
Methanol	14.5

C. Coacervation Induced by Nonsolvent Addition

Microencapsulation by nonsolvent addition is a classical example of using the Dobry effect. Phase separation is induced by adding an organic solvent that must be miscible with the first organic solvent but must be a nonsolvent for the polymer to a solvent solution of the polymer. The ability of the nonsolvent to cause the polymer to separate is measured by the solubility parameter (tables 6-7). As the difference of solubility parameters of the nonsolvent vehicle and the polymer surpasses 1.1, liquid phase separation occurs. Thus, due to the decreased solubility of the polymeric wall material in the new solvent system, the wall material is phased out and forms a film around the hydrophilic nucleus particles. This process is designed to produce microcapsules of solids which are insoluble in the solvent-nonsolvent pairs. Many polymers can be used as coating including cellulosics, acrylics, styrene, rubbers, vinyl acetates, and others.

4.2 Solvent Evaporation Procedures

Microencapsulation by solvent evaporation is conceptually a simple procedure (Bakan, 1986; Watts et al., 1990). It involves, first, the emulsification of a polymer solution containing drug (either dissolved or dispersed) into the other immiscible liquid phase containing an emulsifier to form a dispersion of drug-polymer-solvent droplets. In the second step, the solvent is removed from the dispersed droplets by application of heat, vacuum, or by allowing evaporation at room temperature to leave a suspension of drug containing polymer microcapsules or microspheres that can then be separated by filtration or centrifugation; the microcapsules or microspheres are then washed and dried (figure 11). In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core. In the case in which the core material is

dissolved in the coating polymer solution, a matrix-type microspheres is formed. This technique can be tailored to produce microspheres over a wide size range, from less than 200 nm to several hundred microns. By choice of suitable solvent and polymer systems, drugs encapsulated can have high or low aqueous solubilities. The structure of microspheres produced by this technique is that the drug is essentially dispersed through a matrix as a solid or a molecular dispersion, whereas those produced by coacervation are essentially capsular in structure.

4.2.1 Factors Affecting Microencapsulation of Pharmaceuticals Using Solvent Evaporation Technique

A. Selection of Solvents

Central to this procedure is the selection of the two liquid phases, one to contain drug and polymer (dispersed phase) and one to contain the emulsifier (continuous phase).

Important criteria for the dispersed phase solvent are:

1. Ability to dissolve a chosen polymer.
2. Ideally, ability to dissolve the drug.
3. Immiscibility with the continuous phase solvent.
4. Lower boiling point than continuous phase solvent.
5. Low toxicity.

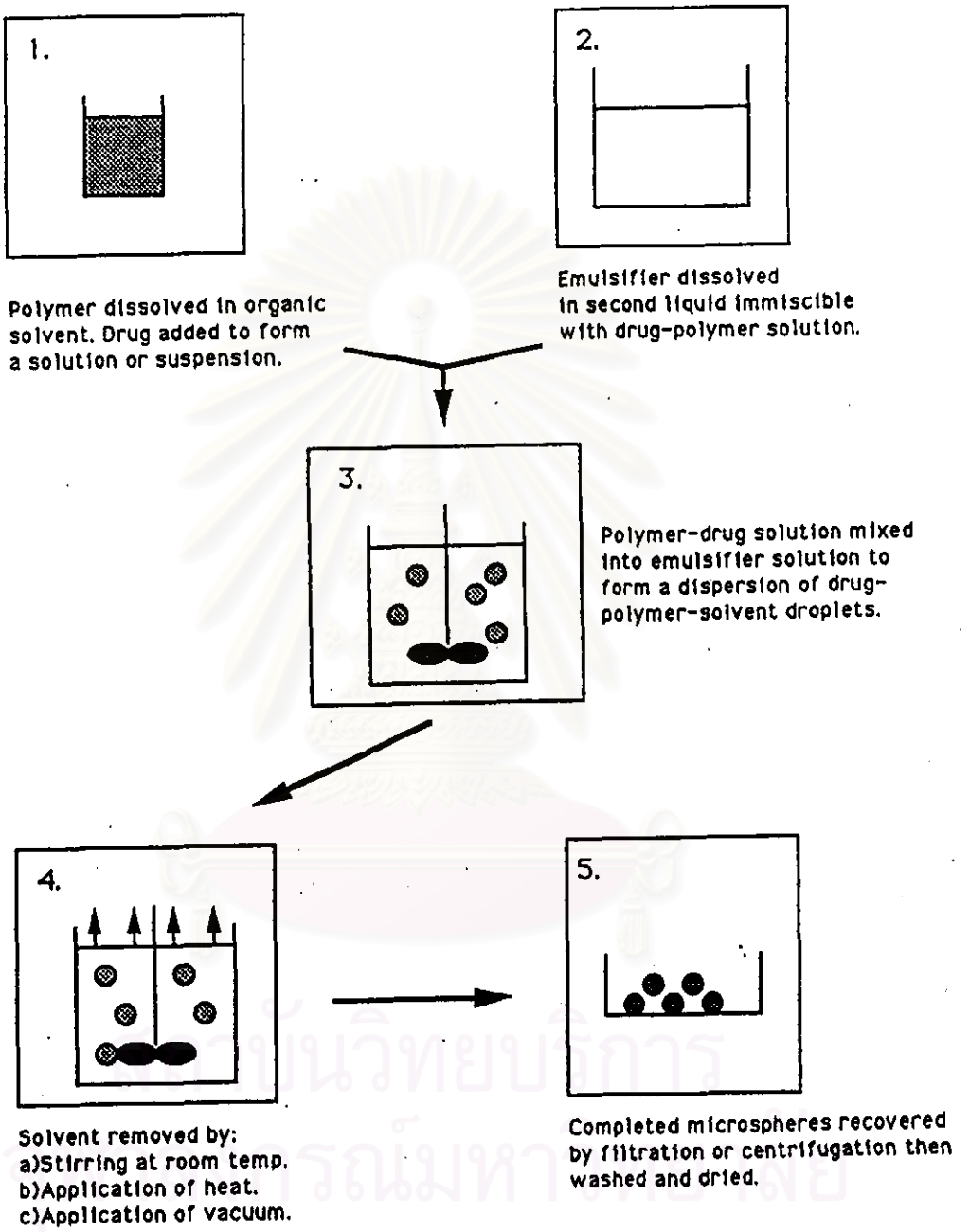


Figure 11. Schematic diagram of microsphere formation by solvent evaporation procedure (Watts et al., 1990).

Important criteria for the continuous phase solvent are:

1. Immiscibility with the dispersed phase solvent.
2. Inability to dissolve polymer.
3. Low solubility toward drug.
4. Higher boiling point than the dispersed phase solvent.
5. Low toxicity.
6. Easy recovery and clean-up of microspheres.

The final structure and composition of microsphere results from a complex interplay between polymer, drug, solvent, continuous phase, and emulsifier. Since the drug and polymer to be used are usually fixed, solvent choice can be of crucial importance. The effect of solvent properties on the microencapsulation by aqueous solvent evaporation technique was investigated on poly(lactic acid) microspheres (Bodmeier and McGinity, 1988). A high efficiency of quinidine sulfate entrapment was favored by dissolving the drug and polymer in water-immiscible solvents with sufficient water solubility. Such solvents caused rapid precipitation of polymer at the droplet interface, thereby creating a barrier to drug diffusion out of the forming microsphere. The solvent able to achieve the highest drug loading was methylene chloride. If water-miscible solvents such as acetone were used to dissolve the drug and polymer, large polymer agglomerates would be formed on mixing.

Methylene chloride is the most widely used solvent for producing microspheres using the aqueous solvent evaporation technique. This solvent has high volatility that facilitates easy removal by evaporation and also shows good solubility toward a range of encapsulating polymers.

For drugs with high water solubility and moisture sensitivity, the emulsification into an aqueous phase is, not unexpectedly, generally unsuccessful in producing entrapment of drug since the drug will rapidly partition from the more hydrophobic polymer-solution phase into the aqueous surroundings. This problem can be solved by the use of oil-in-oil (o/o) type emulsion systems or nonaqueous solvent evaporation technique (Huang and Ghebre-Sellassie, 1989; Watts et al., 1990; Bodmeier et al., 1994). The polymer and drug, which are contained in a polar solvent such as acetone, ethanol, and solvent mixture, are emulsified into an immiscible lipophilic phase; mineral oil is commonly used. The wall material used is hydrophobic and practically water insoluble such as ethylcellulose (Zinutti et al., 1994; Palomo, Ballesteros, and Frutos, 1996). Ethanol and acetone are immiscible with mineral oil, and permit emulsion formation with the polymeric solution before solvent diffusion occurs. However, ethanol diffuses faster than acetone; this results in faster polymer precipitation (thus creating microcapsules). Acetone has a slow diffusion that produces microspheres instead of microcapsules (Palomo et al., 1996). The matrix structure of microspheres prepared using ethanol as a solvent is more porous than with acetone (Zinutti et al., 1996).

B. Emulsifier

The role of emulsifier in microsphere production by solvent evaporation is the short-term stabilization of the suspended polymer droplets. Stabilization to prevent aggregation and coalescence is only a short-term requirement. Once adequate solvent evaporation has taken place to produce some hardening of the drug-polymer droplets, coalescence and aggregation should not occur.

Most published oil-in-water techniques utilize polymeric stabilizers such as gelatin, polyvinyl alcohol (PVA), and methylcellulose. These polymers increase solution viscosity that may affect microsphere properties. For example, the use of methylcellulose 400 as the stabilizer produces a high-viscosity external phase that results in distorted, ovoid-shaped microparticles (Cavalier, Benoit, and Thies, 1986). The use of PVA as the emulsifier has been found to have dramatic effects on the release of ibuprofen from cellulose acetate butyrate and ethylcellulose microcapsules (Kristmundsdottir and Ingvarsdottir, 1994). The emulsifier is thought to promote drug crystal growth by solubilization at the microsphere surface and this results in a marked 'burst' effect. Other o/w stabilizers used include polysorbate80 (Bodmeier and McGinity, 1987a) and sodium dodecyl sulfate (SDS) (Spenlehauer et al., 1988).

The emulsifiers used in microencapsulation by o/o type solvent evaporation technique include sorbitan trioleate (Ghorab, Zia, and Luzzi, 1990; Zinutti et al., 1994), Span80 (Huang and Ghebre-Sellassie, 1989; Bodmeier et al., 1994), and Tween80 (Amperiadou and Georgarakis, 1995). The effect of Span80 concentration on drug content of the microspheres was investigated on chlorpheniramine maleate-ethylcellulose microspheres (Bodmeier et al., 1994). The drug content of the microspheres decreased slightly with increasing concentration of Span80 in the oil phase. The solubility of the drug and the organic solvent in the oil phase was probably enhanced through solubilization; thus, it resulted in a more favorable partitioning of the drug into the oil phase and hence lowered drug loadings with increasing surfactant concentrations.

C. Mixing Conditions

The principal controlling parameters of particle size are the speed, equipment, and technique used for mixing the two phases and the concentration of polymer in the dispersed phase.

The particle size tends to decrease exponentially with increasing mixing speed accompanied by a narrowing of the particle size distribution (Benita et al., 1984; Huang and Ghebre-Sellassie, 1989).

In general, the particle size increases with polymer concentration (Pongpaibul, Price, and Whitworth, 1984). There are two contributing factors. (1) The increase in concentration of polymer in the dispersed phase increases the solution viscosity so that for a given set of mixing conditions, droplet sizes and final microsphere sizes tend to be larger. (2) The increase in concentration of polymer inside the droplet increases the volume occupied by the polymer during solvent evaporation, although this may be offset to a certain extent by a reduction in the microsphere porosity with increasing polymer concentration.

5. The Release of Water-Soluble Drugs from Ethylcellulose Walled Microcapsules

5.1 Capsular or Reservoir Type Microcapsules

The system consists of a central core of drug surrounded by a water-insoluble polymeric membrane. The release of water-soluble drugs from the water-insoluble coating such as ethylcellulose follows three pathways: 1) through the continuous polymer phase, 2) through inter-connecting channels such as fine pores or minute cracks existing in the membrane, and 3) through parallel pathways of continuous polymer phase and channels (Koida et al., 1987).

The diffusion of water-soluble drugs through a polymeric membrane is suitable for many applications. Figure 12 illustrates the diffusion of a water-soluble salt through ethylcellulose walled microcapsules which is dispersed in water. In the initial stage of the diffusion process, water permeates the coating into the center of

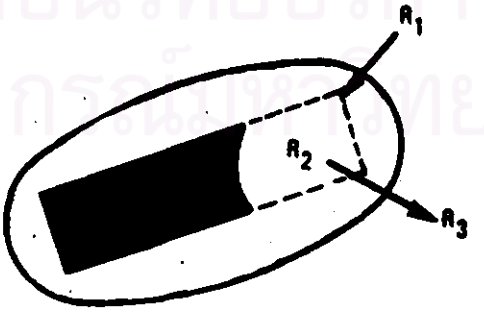


Figure 12. Release of water-soluble drug from ethylcellulose walled microcapsules by diffusion; R_1 is rate of solvent permeation; R_2, rate of drug dissolution; R_3, rate of solution permeation. R_r (Resultant release rate) $= (R_1.R_2.R_3)$.

microcapsule. An aqueous suspension of the water-soluble solid is formed within the microcapsule and the drug solution permeates outward to the water phase outside. The flux is expressed by Eq. (1) and (2):

$$dQ/dt = PD_mA(C_i-C_o)/l_m \quad (1)$$

under sink condition, $$dQ/dt = PD_mAC_s/l_m \quad (2)$$

where Q is the amount of drug permeated at time t. The release rate is a function of the partition coefficient of the drug between membrane and bulk solution (P), the diffusion coefficient of the drug in the membrane (D_m), the surface area of the microcapsule (A), the concentration gradient across the membrane (C_i-C_o), the film thickness (l_m), the solubility of the salt in water (C_s). The release rate also depends on temperature and other factors. The release mechanism is independent of pH if the solubilities of the drug and polymer are independent of pH. The resultant release rate, R_r, can usually be described as a first-order rate process. However, in large microcapsules (above 1000 μm), the release rate tends to be of zero order (Bakan, 1994).

For high molecular weight water-soluble drugs, e.g., protein and peptide drugs, the permeability of the drug in the polymeric membrane is extremely low. Therefore, these drugs would release through pores or water-filled channels in the membrane. Large pores in adequate numbers provide a release mechanism that is apparently independent of the coating and is controlled by the rate of drug dissolution. In the case of small pores that are only slightly larger than the drug molecules, significant resistance to mass transport is offered by the coating. Often drug release through the pores occurs simultaneously with drug diffusion through the polymeric

membrane. For drugs transporting through water channels, the flux is expressed by Eq. (3); where ε is the porosity of the matrix, τ is the tortuosity and D is the diffusion coefficient of the drug in the aqueous phase (Koida et al., 1987).

$$dQ/dt = (\varepsilon/\tau)DAC_s/l_m \qquad (3)$$

5.2 Matrix or Monolithic Type Microcapsules

In a monolithic microcapsule, the diffusion path length does not remain constant since the drug in the center has a longer path to travel than the drug near the surface, and therefore the rate of release decreases exponentially with time (Deasy, 1984; Burgess and Hickey, 1994).

The rate of release of drugs suspended in an inert matrix has been described by Higuchi (1963). The following two types of the release have been considered. (1) The drug particles are dispersed in a homogeneous, uniform matrix which acts as the diffusional medium (figure 13(a)). (2) The drug particles are incorporated in an essentially granular matrix and released by the leaching action of the penetrating solvent through pores, cracks, and intergranular spaces (figure 13(b)). The drug is presumed to dissolve slowly into the permeating fluid phase and diffuse from the system along the cracks and capillary channels filled with the extracting solvent.

The release from a planar system having a homogeneous matrix can be presented by (Higuchi, 1963):

$$Q = [D_a C_a(2C_{tot} - C_a)t]^{1/2} \qquad (4)$$

where Q is the amount of drug released after time t per unit exposed area, D_a is the diffusion coefficient of the drug in the homogeneous matrix phase, C_a is the solubility of the drug in the matrix substance, and C_{tot} is the total amount of drug present in the matrix per unit volume.

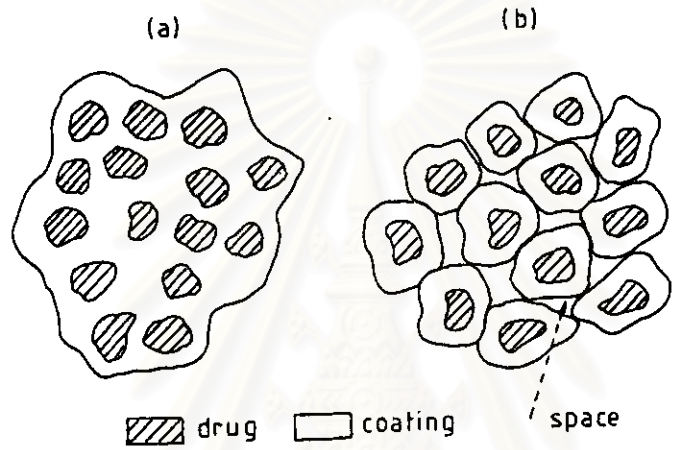


Figure 13. Drug releases from homogeneous matrices (a) and granular matrices (b).

The release from a planar system having a granular matrix can be described by (Higuchi, 1963):

$$Q = [D_s C_s(2C_{tot} - \varepsilon C_s)(\varepsilon/\tau)t]^{1/2} \quad (5)$$

where D_s is the diffusion coefficient in the release medium, C_s is the solubility of the drug in the release medium, ε is the porosity of the matrix, and τ is the tortuosity of the capillaries through which the drug diffuses.

Equation (4) and (5) are conveniently reduced to Eq. (6); where K is the release rate constant (Deasy, 1984; Park, Wood, and Robinson, 1984; Washington, 1990).

$$Q = Kt^{1/2} \qquad (6)$$

Therefore, a plot of amount of drug released vs the square root of time should be linear if the release of drug from the matrix is diffusion controlled. Jalsenjak, Nicolaidou, and Nixon (1976), Madan (1980), and many others have reported that the drug release from microcapsules produced by coacervation is proportional to the square root of time because the prepared microcapsules form clusters during preparation. The approximately spherical units formed are usually composed of solid drug particles dispersed in the coating material.