CHAPTER II
THEORY AND LITERATURE REVIEWS

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 [1-6]. The microcapsules consist of a solid or liquid core material containing one or more drugs enclosed in a coating as shown in Figure 2-1. The most common type is the mononuclear spherical type. The particle size of the microcapsules is defined in various ranged but can be varied from approximately 1 μm to 5,000 μm [1-2,5].

2.1 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 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 shown in Figure 2-2 [4,10,15].

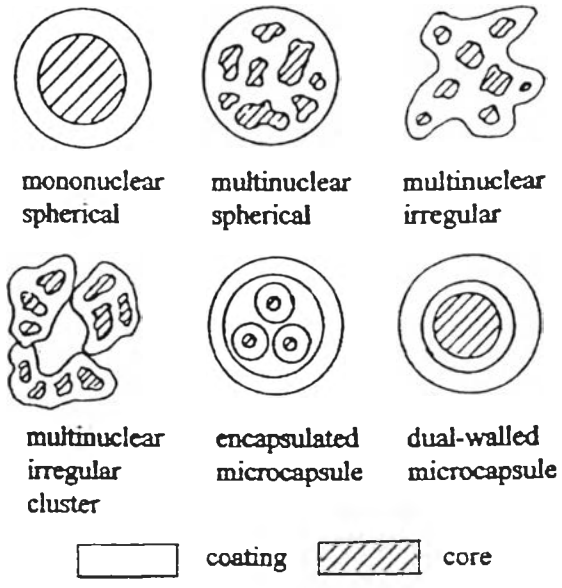


Figure 2-1 Some typical structures of microcapsules [4]

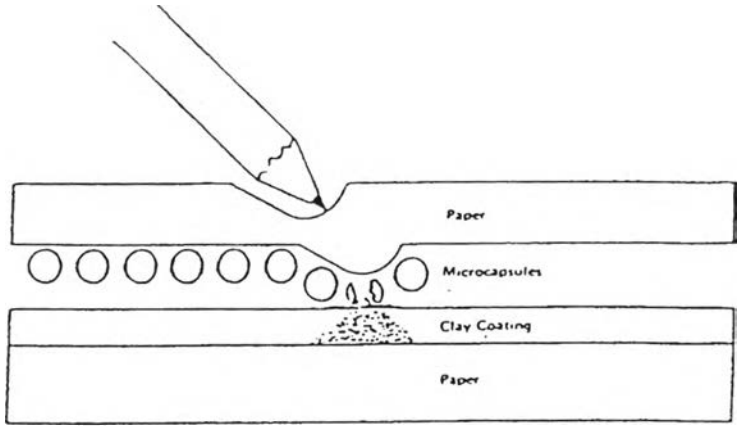


Figure 2-2 Pressure-activated release of encapsulated dye precursor to give a color reaction on paper coated with an acidic clay [15]

2.2 Reasons for Microencapsulation

The technique of microencapsulation has gained popularity because of its potential applicability in a wide variety of situations. The microencapsultion processes have been used in many industries such as food, food additives, cosmetics, adhesives, household products, agricultural materials, aerospace industry, and many others [4-6]. There are many reasons why drugs and related chemicals have been microencapsulated [1-6];

a) Microencapsulation has been employed to stabilize substances 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 the stability of drugs unstable in a biological environment, such as hydrolytic influences of enzymes and pH, and the solubilizing action of bile salts [5].

b) Microencapsulation has been used to prevent incompatibilities between drugs, such as aspirin versus chlorpheniramine 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) [6].

c) Microencapsulation has been used to reduce gastric and other gastrointestinal tract irritations from drugs; for example, ferrous sulfate, potassium chloride [4], indomethacin [14] and sodium diclofinac [16]. Coating drug particles with a thin gastrointestinal fluid-resistant film can reduce gastric irritation. 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 containing microcapsules in the gastrointestinal tract. This reduces a possibility of local high concentrations which can result in irritations or toxic effects (Bakan, 1994) [6].

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) [17]. 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) [18], sodium diclofenac (Hasan et al., 1992) [19], theophylline (Bodmeier and Wang, 1993) [20], and paracetamol (Baykara and Karatas, 1993) [21].

e) Microencapsulation has been used to modify the physical properties of chemical entities. For example, oils may be encapsulated to produce free-flowing powders that are convenient for handling and storage. Flow properties of many vitamins could be improved by microencapsulation prior to compression into tablets (Madan, 1978; Deasy, 1984) [3-4].

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. Taste can be masked because a continuous film coating the drugs particle prevents contact with the taste sensors upon ingestion. In addition, the particle sizes of the microcapsules are small enough to prevent the mouth from feeling an aftertaste (Bakan, 1994) [6].

g) Microencapsulation has been used to mask the unpleasant odor of drugs such as castor oil, cod liver oil (Deasy, 1984) [4], clofibrate (Madan, 1976) [22], etc.

h) Microencapsulation has been used to reduce the vaporization of several volatile substances such as methyl salicylate and peppermint oil (Deasy, 1984) [4].

i) Microencapsulation has been used to improve the safety in handling toxic drugs or chemical substances, e.g. antieoplastic drugs, fumigants, insecticides, herbicides, and pesticides (Madan, 1978; Deasy, 1984) [3-4].

j) Microencapsulation has also been used medically to entrap mammalian cells and tissues within polymeric microcapsules for controlled released of bioactive agents. The preparation of hepatoma cells and pancreatic islets microcapsules were carried out by enclosing those cells with calcium alginate (Lim and Moss, 1981) [23]. In the same year, Arakawa and Kondo produced the microcapsules of sheep hemolysate using interfacial polymerization between L-lysine and terephthaloyl dichloride to form poly(N^{α}, N^{ϵ}-L-lysinediylterephthaloyl) polymer to coat the dispersed core [24]. An interfacial precipitation technique was developed for encapsulating mammalian cells in polyacrylate membranes. These microencapsulated cells 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. These include powders, hard gelatin capsules, rapidly disintegrating tablets, chewable tablets, oral liquid suspensions, injections, ointments, creams, lotions, plasters, dressings, and suppositories [2,6].

2.3 Core and Coating Materials

A core material, which is defined as the specific material to be coated, plays a significant role in microencapsulation. 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 immisible liquid, 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. A partial listing of typical coating materials commonly used in the various microencapsulation methods is suggested in Table 2-1. Ethylcellulose

Table 2-1 Representatives of coating materials and their application to microencapsulation processes [5]

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

used in these 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 [5-6].

2.4 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 overlapping. However, they may be classified into 3 major categories that are physical methods, chemical methods, and mechanical methods. These major microencapsulation procedures are summarized briefly in Table 2-2 [3-6].

Various microencapsulation processes give rise to the formation of microcapsules with various characteristic size ranges as shown in Table 2-4 [4-6].

2.4.1 Coacervation/Phase Separation Procedures using Aqueous Vehicles

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 lyophillic colloids into liquid droplets rather than into solid aggregates [1,3-4,26]. Bungenberg de Jong and Kruyt first described the colloidal phenomenon of coacervation in 1963 as a process of flocculation or separation of liquids from solution in which at least one of the liquids contained a macromolecular or colloidal solute. 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 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 phenomenon of coacervation can be distinguished from the process of crytallization in the following manner. 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 [3,25].

Table 2-2 Summary of major microencapsulation processes

Process	Principle	Type of core	Type of coating
1. Physical Methods 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 drug(s).
2. Chemical Methods 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 2-3.	High-molecular weight materials such as enzymes and hemolysates.	Water-soluble and water-insoluble monomers as presented in Table 2-3.

Table 2-2 (continued)

Process	Principle	Type of core	Type of coating
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 2-4.	Non-volatile and solid drug(s).	Water-soluble or organic solvent-soluble polymer(s).
3.2 Pan Coating	Polymer solution is spray applied to the desired solid core material, which is deposited onto spherical substrates as shown in Figure 2-5.	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 2-6.	Solvent-insoluble drug(s).	Solvent-soluble polymer(s).

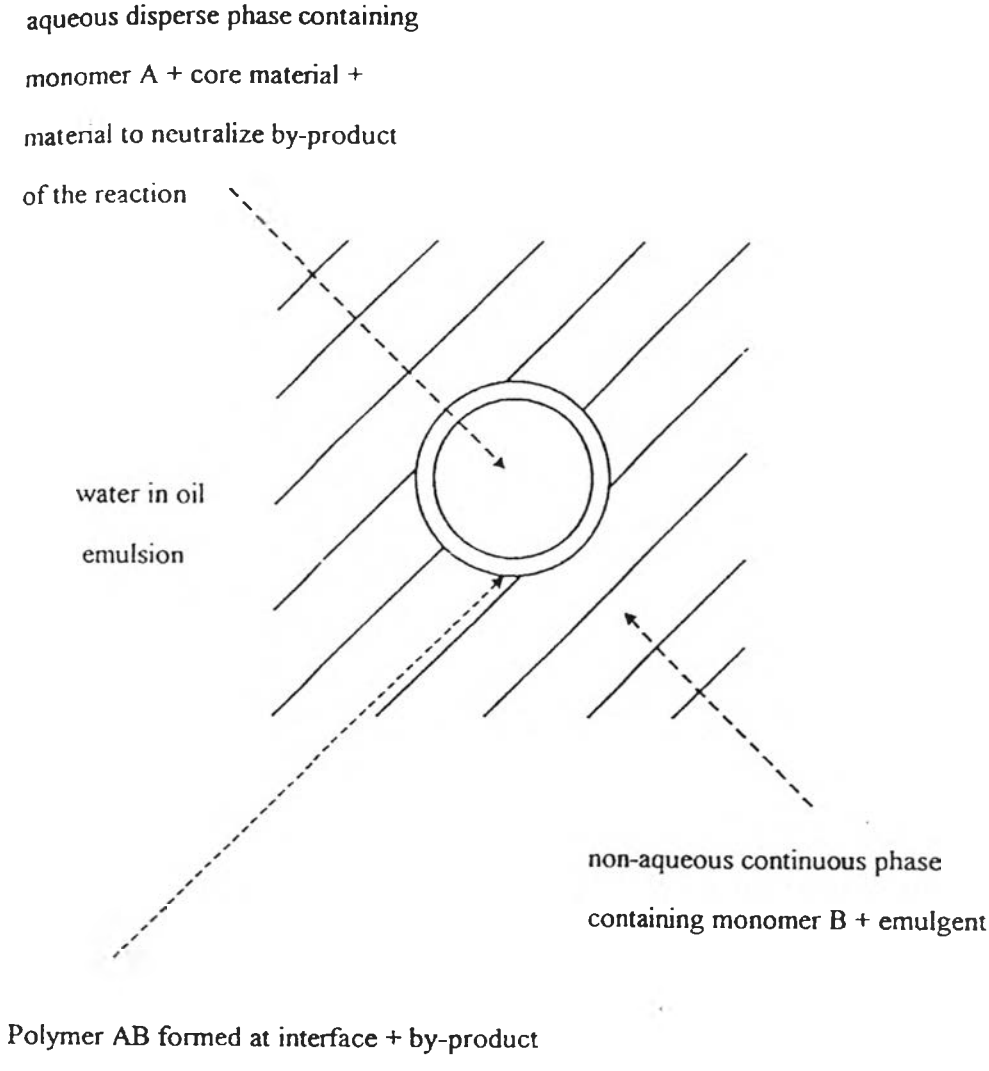


Figure 2-3 Schematic representation of microencapsulation of a droplet by interfacial polymerization [4]

Table 2-3 Principal monomer combinations investigated for the microencapsulation of pharmaceuticals by interfacial polymerization [4]

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

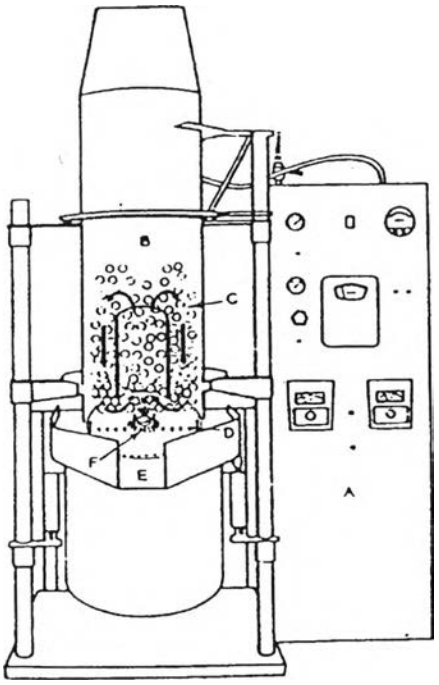


Figure 2-4 Schematic drawing of Wurster Air Suspension Apparatus: A, control panel; B, coating chamber; C, particles being treated; D, process airflow; E, air distribution plate; and F, nozzle for applying film coating [5]

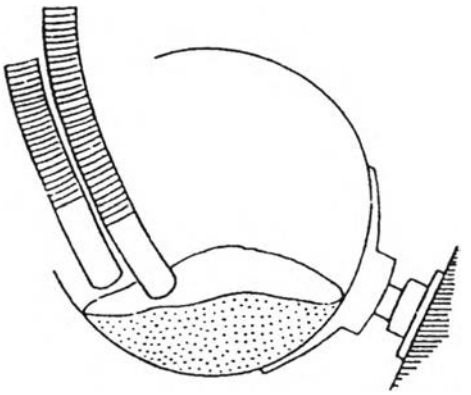


Figure 2-5 Schematic representation of an operating coating pan [4]

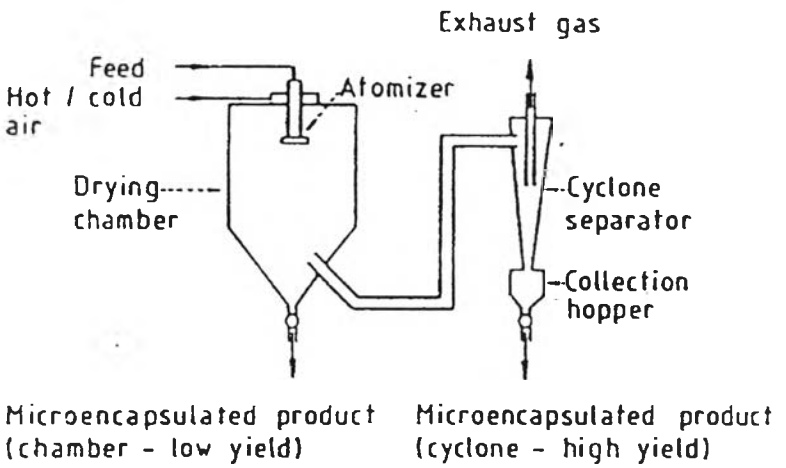


Figure 2-6 Schematic diagram of a cocurrent spray dryer [4]

Table 2-4 Microcapsule size ranges produced by various production procedures

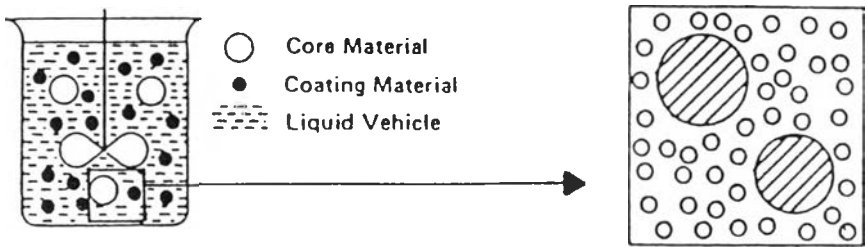
Production process	Size range (μm)
Coacervation/Phase separation	1-5000
Interfacial polymerization	2-2000
Air suspension	35-5000
Pan coating	200-5000
Spray drying	5-800

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" [3-4,6,25].

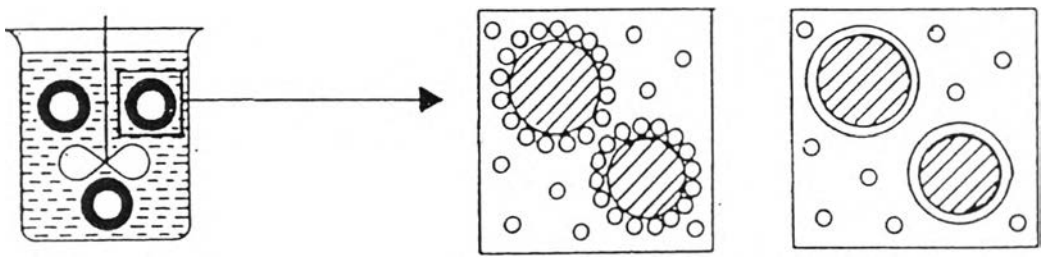
Generally, these microencapsulation processes consist of three steps (Figure 2-7) carried out under continuous agitation [3-4,6]:

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.

1. Establishment of three-phase system.



2. Deposition of liquid-polymeric coating material.



3. Solidification of coating material.

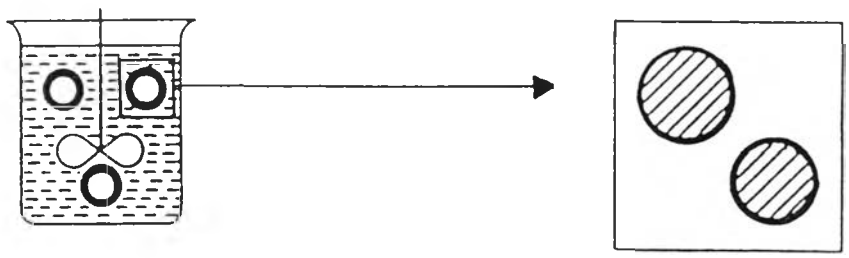


Figure 2-7 General process description of coacervation technique [11]

(core, coacervate droplets, coating, hardened 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 immisible 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 face 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 2-8 and 2-9.

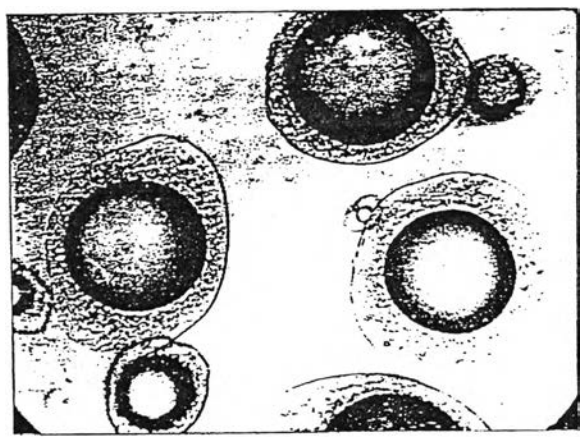


Figure 2-8 A magnified photograph of microencapsulated liquid [6]

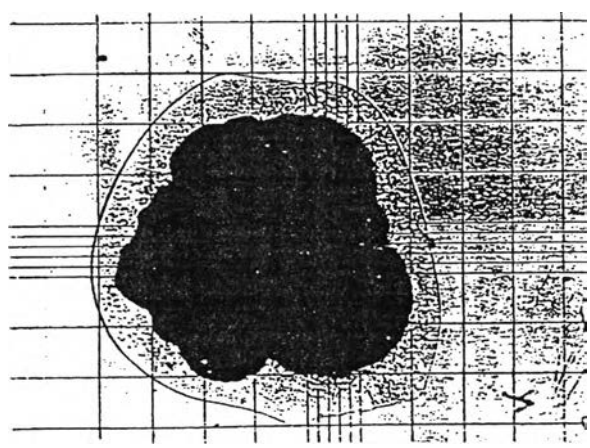


Figure 2-9 A magnified photograph of microencapsulated solid [6]

2.4.2 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 that 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 [4-6].

2.4.3 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 2-5 (Madan, 1978a) [25-26].

Table 2-5 Characteristics of simple and complex coacervations [25]

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. acacia/gelatin.
- Principal conditons.	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.	Coacrtvation occurs.
- Presence of salts.	Promotes coacervation effectiveness follows the lyotropic series.	Suppressed coacervation position of ions in lyotropic series is of minor significance.
- 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 marrow range)-also occurs at pH < isoelectric point of gelatin.

2.4.3.1 Simple Coacervation

Simple coacervation is a process ivolving 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. The typical example of this process is gelatin simple coacervation. In a system consisting of gelatin and water, coacervation is brought about by the addition of a third component which is a strongly hydrophilic substance such as ethanol or sodium sulfate When concentrations of the components in the system are suitable, microcapsules may result. In addition, methanol, isopropanol, resoreinol, acetone and

any suitable organic liquids can be used instead of ethanol to cause a similar effect and various other salts can be also used instead of sodium sulfate [1,3,5,10-11].

2.4.3.2 Complex Coacervation

Complex coacervation involves the use of more than one colloid. Gelatin and acacia in water are most frequently used. The coacervation is accomplished mainly by charge neutralization and in the appropriate concentration condition. The deposition of coacervate droplets is aided by a reduction in total free interfacial energy of the system consequent upon the decrease in the surface area of the coating material as its droplets coalesce around the core material. The coating is then gelled by lowering the temperature and hardened by the addition of a crosslinking agent such as formaldehyde and gluraraldehyde. Fimally, dried by the appropriate method, the desires microcapsules are collected [3,10-11].

2.4.4 Wall-Hardening Agents

Since the gelatin molecule contains amino and carboxyl groups, it can be insolubilized by cross-linking agents. Many different agents can be used to harden gelatin-containing walls of microcapsules formed by simple or complex coacervation. The most frequently used hardening agents for crosslinking gelatin-coated microcapsules are formaldehyde and glutaraldehyde.

The mechanisms of reaction of gelatin with formaldehyde are followed by these steps [11].

1) Formaldehyde reacts with the amino groups of the gelatin as follows :

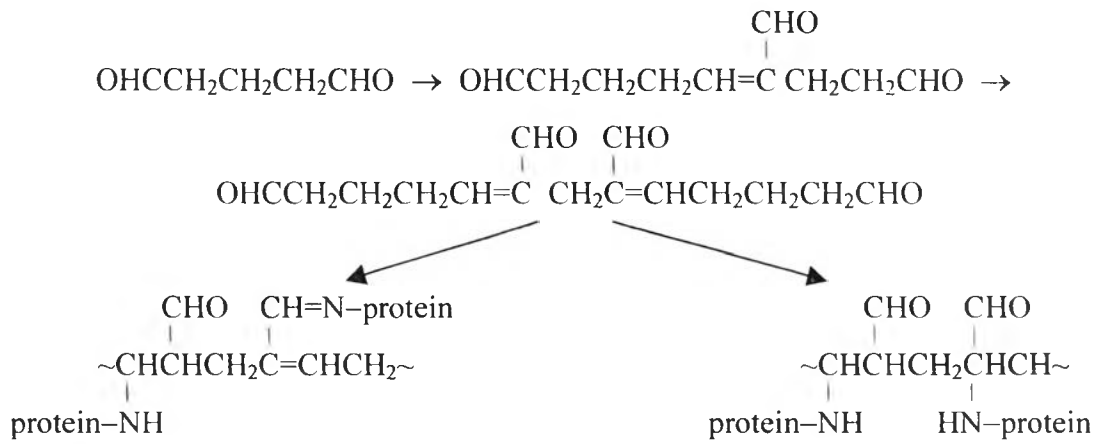
$$HCHO + \text{gelatin}\text{–}N^{+}H_3^{-} \leftrightarrow \text{gelatin}\text{–}NH\text{–}CH_2OH + H^{+}$$

2) Two molecules of the product react to crosslink by means of a dimethylene ether bridge or a methylene bridge as follows :

$$\text{gelatin}\text{–}NH\text{–}CH_2OH + \text{gelatin}\text{–}NH\text{–}CH_2OH \rightarrow$$

$$\text{gelatin}\text{–}NH\text{–}CH_2\text{–}NH\text{–gelatin} + \text{gelatin}\text{–}NH\text{–}CH_2\text{–}O\text{–}CH_2\text{–}NH\text{–gelatin}$$

Glutaraldehyde, largely polymeric and unsaturated aldehyde, reacts with protein for hardening effect as follows: [27]



2.5 Release Characteristics

2.5.1 Capsular or Reservoir Type Microcapsules

The system consists of a central core of drugs surrounded by polymeric membranes. The release of water-soluble drugs from the coating 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 [28].

The diffusion of drugs through a polymeric membrane is suitable for many applications. Figure 2-10 shows the diffusion of a salt through walled microcapsules which is dispersed in water. In the initial stage of the diffusion process, water permeates the coating into the center of microcapsule.

An aqueous suspension of the solid is formed within the microcapsule and the drug solution permeates outward to the water phase outside. Eqs. (1) and (2) express the flux:

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

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 the 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), and 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) [6].

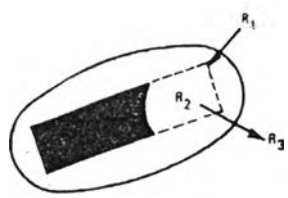


Figure 2-10 Release of drug from walled microcapsules by diffusion;
R_1 is rate of solvent permeation; R_2 is rate of drug dissolution;
R_3 is rate of solution permeation. R_r (Resultant release rate) = (R_1.R_2.R_3) [6]

For high molecular weight drugs, e.g., protein and peptide drugs, the permeability of the drug in the polymeric membrane are extremely low. Therefore, these drugs would be released 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 [28].

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

2.5.2 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 [4,29].

Higuchi (1963) has described the rate of release of drugs suspended in an inert matrix. The following two types of the release have been considered. (1) The drug particles are dispersed in a homogeneous, uniform matrix that acts as the diffusional medium (Figure 2-11(a)). (2) The drug particles are incorporated in an essentially granular matrix and released by the leaching actin of the penetrating solvent through pores, cracks, and intergranular spaces (Figure 2-11(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 [30].

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

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

Where Q is the amount of drugs 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.

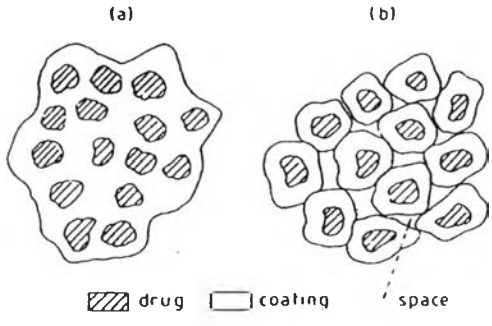


Figure 2-11 Drug releases from homogeneous matrices (a) and granular matrices (b) [4]

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

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

Where D_s is the diffusion coefficient in the release medium, C_s in 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 [4,31-32].

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

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. 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 [3,12,33].