CHAPTER II

REVIEW OF LITERATURE

Microencapsulation

Microencapsulation can be described as a process in which very thin coatings of polymeric materials are deposited around particles of solids or droplets of liquids. The microcapsules thus formed range dimensionally from several nanometers to several thousand micrometers (Deasy, 1984).

The microencapsulation processes that use phase separation-coacervation were developed in the early 1950's by Barrett K. Green (1957). This first successful commercial development of a product using microcapsules was carbonless paper which eliminates the need for the carbon paper in multipart business forms. In recent years, the microencapsulation processes have been used in many industries, such as food, food additives, cosmetics, adhesives, household products, and agriculture materials. Microencapsulation has been used in the pharmaceutical industry for the conversion of liquids to solids, taste-masking of bitter drugs, prolonged or sustained release, separation of incompatible component, reduced gastric irritation, and environmental protection of labile moieties to increase stability of several drugs (Bakan, 1994).

There are many other processes available to make microcapsules. Processes which are most applicable to pharmaceuticals are given in Table 1, which cites the process, the core materials which can be coated, and the approximate size range of the microcapsules that can be manufactured.

Table 1: Microencapsulation process and their application.

Process	Core Material	Microcapsule Size (nm)*
Air suspension	Solids	35–5000
Coacervation–phase separation	Liquids and solids	1–5000
Multiorifice-centrifugal	Liquids and solids	1–5000
Pan coating	Solids	600–5000
Solvent evaporation	Liquids and solids	1–5000
Spray drying and congealing	Liquids and solids	5–600

*5000 nm is an arbitrary upper size as some processes may produce larger particles.

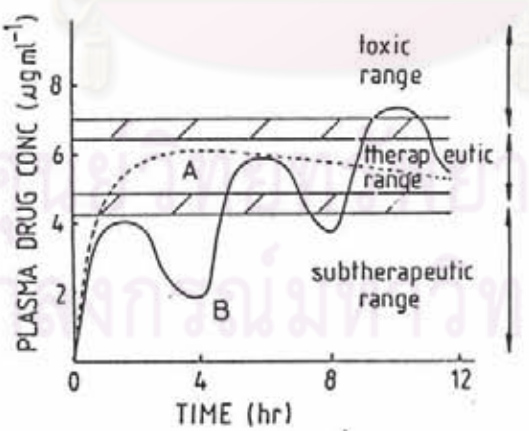

Fig. 1: Typical plasma drug concentration versus time profiles for an idealized sustained-release microencapsulated product (A) and a conventional dosage form (B) repeatedly given orally.

Figure 1 shows the typical plasma drug concentration versus time profile following an oral administration for a single dose of an idealized sustained-release microencapsulated (A) and for conventional dosage forms given repeatedly (B). With conventional dosage forms there is a peak-and-valley effect that tends toward a plateau, because most drugs exhibit exponential accumulation when given repeatedly at equal intervals. Also, the spikes associated with later doses may well account for undesirable side effects. The more frequent the dosing interval with dosages of appropriate size, the smaller will be the oscillations in the plasma drug profile and the faster the plateau will be reached. This in fact is the underlying principle of microencapsulated oral dosage forms, which often contain a portion of the dosage in a non-sustained-release form so as to establish the drug level quickly in the therapeutic range, which is then maintained over an extended period by the progressive release of drug from the various microcapsule fractions present. By combination of microcapsules with different release rates in a dosage form a pseudo-zero-order or steady state release of drug can be obtained over an extended period. The aim of these products is to make the rate-limiting step from the release of drug from the sustained-release dosage form rather than its rate of absorption. The result is improved management of the discuss state with the use of less total drug and with fewer undesirable side effects. Because of the reduced frequency of administration, sustained release products are often claimed to be convenient and to enhance patient compliance (Deasy, 1984).

1 Coacervation Technique

Microencapsulation by coacervation-phase separation was developed in 1950's. The technique was quickly developed because it can be used to microencapsulate a large number of liquids, solids and gases. The polymers used to coat the core materials can be both water soluble and water insoluble. Water-soluble core materials are microencapsulated with water insoluble polymer in organic solvents, on the other hand water insoluble core materials are microencapsulated with water soluble polymer.

There are two types of coacervation : simple and complex. Simple coacervation involves the use of only one colloid, e.g. gelatin in water, and involves removal of the associated water around the dispersed colloid by agents with a greater affinity for water, such as various alcohols and salts. The dehydrated molecules of polymer tend to aggregate with surrounding molecules to form the coacervate.

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 of the colloids carrying opposite charges rather than by dehydration.

General process of coacervation-phase separation consist of three steps (Figure 2) carried out under continuous agitation. The first step is formation of three immiscible phases, the liquid-vehicle phase, the core material, and the liquid polymer coating. The second step is deposition of liquid-polymeric

coating material on the core materials and the last step is solidification of coating material.

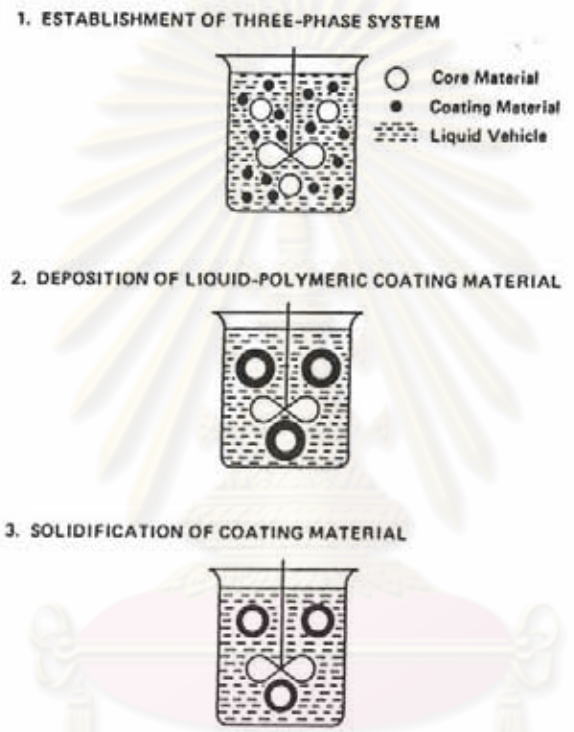

Fig. 2 : General process of coacervation technique.

In step one the three immiscible chemical phases are formed, where the core material is dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle. The core material and immiscible polymer in a liquid state is form 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 liquids polymer coating is deposited around the core material by controlled physical mixing of the coating 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 formed between the core material and the liquid manufacturing vehicle phase. 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, brought about by decrease of the coating material surface area during coalescence of the liquid polymer droplet. Step three of the process involves solidifying the coating, usually by thermal, cross linking, or desolvation methods, to form a rigid microcapsule.

2 Fluidization Technique

Fluidization may be defined as an operation in which a solid powder is made capable of behaving in many ways like a liquid. This is achieved by passing an upward current of gas through a bed of solid particles so that they are suspended in the rising stream and move rapidly. Fluidization is usually carried out in a cylindrical container or column holding the powder, which is supported when at rest on a porous plate. Gas is passed upward through the bed of powder and when the upward velocity reaches a certain critical value, "the minimum fluidization velocity", the particles are smoothly suspended. The bed of powder expands to an increased volume. It

is in visible motion, but retains a well defined upper surface. The successive stages of fluidization are shown in Figure 3 (Mathur, 1994).

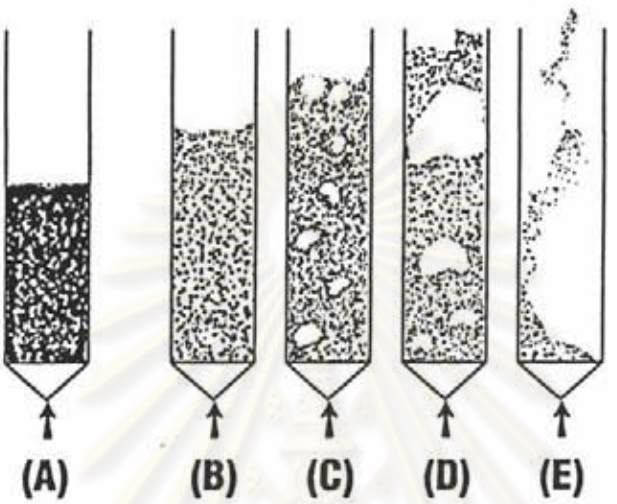

Fig 3 : Successive stages of fluidization : (A) Static bed; (B) Expanded bed; Mobile bed; (D) Bubble formation, (E) Pnuematic transport.

From Fig. 3, a bed of powder through which the fluidizing gas is introduced. As the upward flow of fluidizing gas is ionized through the stationary powder bed (A), the particle lifted upward and the bed expands (Stage B). Suddenly, there is a break in the uniform relation between the pressure applied and the flow rate produced, and the bed quickly changes over from static to mobile (stage C). Further small increases in pressure cause large increases in flow, and the bed expands considerably with an increase of voidage and usually the formation of bubbles (stage D). Eventually the lifting force of the upward gas flow causes particles to be blown out of the bed altogether and pneumatic transport occurs (stage E). For the pharmaceutical applications described here, it is generally desirable that the air velocity be

concealed at the "minimum fluidization level". Thus the upward lifting force on the bed of particles is just equal to their weight and the bed is just fluidized.

The particles in a fluidized bed are in a continual state of motion. This results in brushing together of particles, leading to static charges, especially dusting drying processes as the material reaches a dry state. Brushing of the particles can also result in granule attrition, leading to a change in the particle-size distribution and to flow problems.

There are many variables in a process affected with final microcapsules. The first is the rate of drying (dw/dt) is given by eq. (1).

$$dw/dt = hA\,\Delta T/\Delta H \qquad \text{.....(1)}$$

where dw/dt is the weight of solvent removed per unit time; h the coefficient of total heat transfer; A the area over which the mass and heat transport take place; ΔT the difference in temperature between the inlet air and the product; and ΔH the heat of vaporization of solvent being removed (Carstensen, 1973). Drying generally takes place in three stages; the constant-rate period, the falling-rate period, and the final drying period.

Since the heat required for drying is conveyed by the inlet air, the inlet air temperature should be carefully monitored and controlled.

Excessively high temperatures can lead to hardening of granules, product stickiness, decrease in product quality, and an uncrossed risk of explosion in the presence of organic solvents. The product bed temperature and the outlet air temperature serve as good indicators for the drying process. The volume of fluidization air rushing through the dryer affects the fluidization of the powder bed and the drying time. Very high flow rates can result in channeling or hole formation of the powders, occlusion of the filter bags, and severe granule attrition.

Fine powders are often processed into larger agglomerates or granules. This enhances the flow properties and handling of the powders and reduces fines and the risk of segregation. Fluid-bed granulators offer several advantages over conventional granulating equipment. They provide an efficient single-vessel process where powder can be mixed, agglomerated and dried in one operation.

There are three basic processing approaches evolved in Fig. 4. Each approach has its advantages and disadvantages depending on batch size of product being coated, functionality of the final coating and type of coating formulation being applied (Porter and Bruno, 1990).

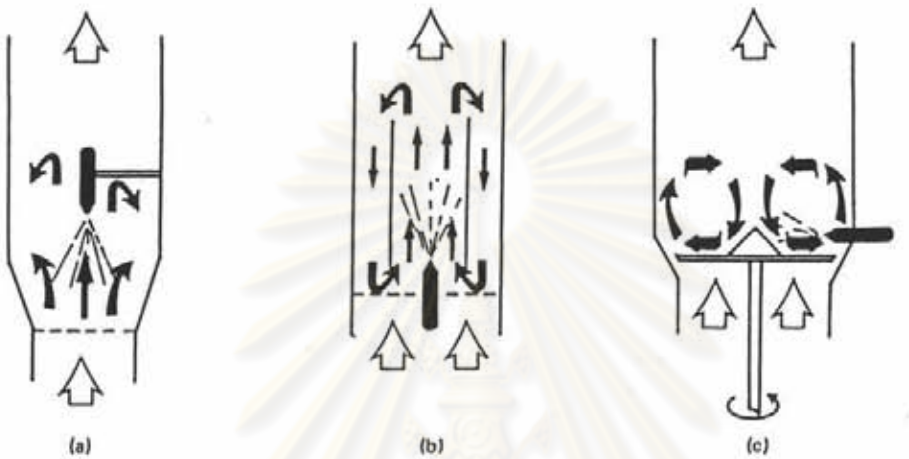

Fig. 4 : Schematic diagrams for the three basic types of fluid-bed coating processes. (a) Top spray (Glatt), (b) bottom spray (Wurster), and (C) tangential spray (Rotor-processor).

3 Spray drying Technique

The most common mechanical microencapsulation process is the spray-drying technique, which consists of rapid evaporation of the solvent from the droplets. Spray-drying technique may produce monodispersed free flowing particles which can be directly compressed into tablets, filled into capsules, and suspended in vehicle. However, the microcapsules obtained by spray drying tend to be very porous because of rapid volatilization of the solvent (Chang and Robinson, 1990).

The application of the spray-drying process to the production of microcapsules has been found to be useful for a variety of materials and can be employed to encapsulate both liquid and solids. In the case of solid, a suspension of the solid particles in a solution containing material is first prepared. Solvent removal during the spray drying process deposits the coating material on the surface of the solid particles. The spray-drying process usually produces coated aggregates rather than coated single particles. A schematic drawing of the drying equipment is presented in Figure 5 (Wurster, 1990).

It must be stated that the various instrument settings cannot be regarded in an isolated manner. All the parameters which can be adjusted are in close dependence to each other. The parameters that could be mentioned are as followed.

- Inlet/outlet temperatures

The melt temperature is defined as the temperature of the drying air which flows through the instrument with the aid of aspirator. When a dispersion is spray dried, the main aim is to remove a solvent by evaporation. In order that the solvent evaporates during the short contact time with the stream of air when the product is spray dried, the temperature of the air stream must lie a good bit above the boiling point of the solvent.

The outlet temperature is defined as the temperature of the air stream containing the solid particles before it enters the cyclone. This temperature is also not necessarily identical to be temperature of the product. This applies mainly because the solid particles do not attain the temperature of the surroundings during their brief passage through the apparatus which is usually less than 2 seconds. Contrary to the inlet temperature, the outlet temperature cannot be set arbitrarily, i.e., with a temperature regulator. The outlet temperature results out of a combination of the inlet temperature, the aspirator setting, the pump setting as well as the concentration of the substance being spray dried. In addition, it also depends on the heat of evaporation of the solvent.

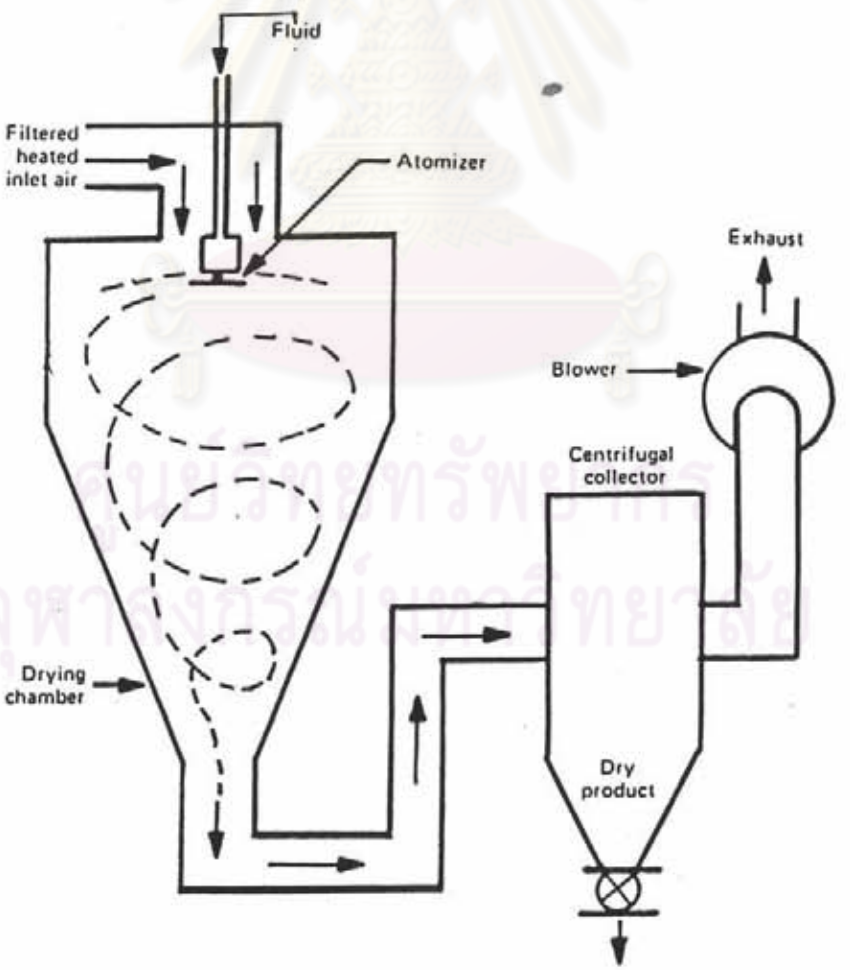

Fig. 5: Schematic diagram of spray-drying apparatus.

The optimum selection of the temperature difference between the inlet and outlet temperatures is one of the most important points in the spray drying process. As a rule, a certain latitudes still remains after the product specific factors have been taken into account. Within this range, the performance of the apparatus as well as the residual moisture content of the end product can be influenced.

- Aspirator

The aspirator sucks the drying air through the instrument and at the same time produces a partial vacuum. When the performance of the aspirator is regulated, the quantity of the heated drying air is increased or decreased on the one hand and the partial vacuum in the apparatus set within a range of approximate 70-260 mm WC (water column). Since the energy available for evaporation also varies according to the amount of air in the apparatus, the aspirator setting also has a significant influence on the spray drying performance of the unit.

- Pump performance

The setting of the feed pump influences mainly the temperature drop between the inlet and outlet temperatures. This is because the temperature as well as the quantity of drying air, and thus also the energy available for the evaporation, is defined by the perselected inlet temperature and aspirator performance. If more or less liquid is now sprayed into the chamber, more or less heat is also removed due to the evaporation. This raises or lowers the value of the outlet temperature in turn.

- Spray flow

The spray flow is defined as the necessary quantity of pressurized air for the spraying of the solution, or dispersion. The spray flow can be set on the instrument within a range of 100-800 Nl/h. With this the different spray characteristics of the samples can be taken account of, on the one hand and the particle size of the end product can be influenced.

Process control variables include feed material properties are viscosity, uniformity and concentration of core and coating material. The process procedures microcapsules approaching a spherical structure in the size range of 5 to 600 microns. Many coating materials can be applied to liquid and solid core materials by spray drying coating solutions containing the dispersed core material. The process in commonly employed in the microencapsulation of many other drugs and given free flowing powders for use in pharmaceuticals (Bakan, 1886).

Mechanism of film formation

A film forming process is very dependent upon the rate of solvent evaporation. Rate of solvent evaporation will in turn be controlled by the latent heat of vaporization of the solvent. Film formation generally comprises with initial rapid evaporation of solvent from the atomized droplets of coating liquid, causing an increase in polymer concentration and contraction in column of the droplets as shown in Fig 6. Further loss of solvent from film is occurred, that is, coalescing of film on the surface of the dosage form at a slower rate which in now controlled by the rate of diffusion of solvent

through the polymer matrix. In the last step, gradual solvent losses from the film at a very much reduced rate and the film was immobilized on the drug molecule at the solidification point. Ultimately, the amount of space between the polymer molecules becomes so small that further solvent loss is so restricted that total removal of solvent from the coating becomes almost impossible. Indeed, total solvent removal requires heating the film to a temperature significantly above the glass-transition temperature of the solvent-free polymer (Porter and Bruno, 1990).

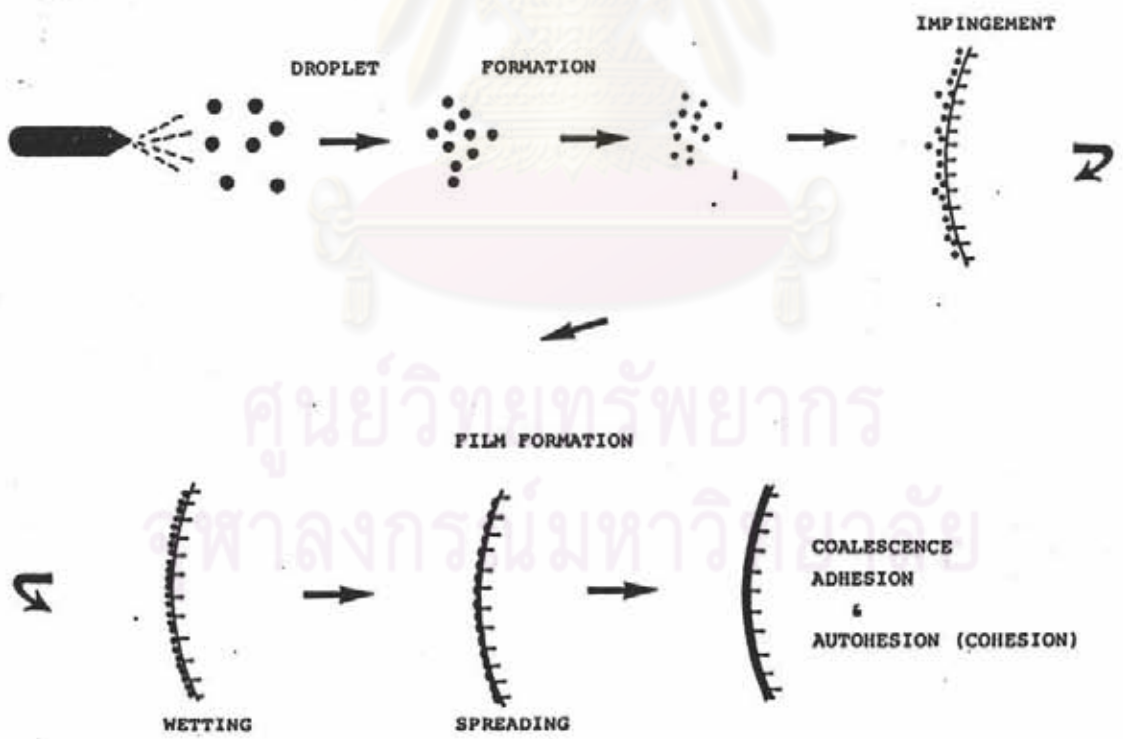

Fig.6 : Schematic representation of the film-coating process.

Effect of plasticizer on the properties of film.

Most of polymers that are used in pharmaceutical film coatings are amorphous in nature. One characteristics of these polymers is that as the temperature is lowered, a point known as the glass transition temperature (T_g) is reached, below which there is a critical cessation of molecular motion on the local scale. Under these temperature conditions, the polymer exhibits many of the properties of inorganic glasses, including toughness, hardness, stiffness, and brittleness. Because the glass transition temperatures of many of the polymers used in film coating are in excess of the temperature conditions experienced in the typical coating process, it is often necessary to modify the properties of the polymer. An appropriate modification involves the process of plasticization.

Plasticizers reduce the glass-transition temperature of amorphous polymers and impart flexibility. The basic requirements to be met by a plasticizer are permanence and compatibility. Permanence dictates that plasticizer has a low vapor pressure and low diffusion rate within the polymeric film, a requirement that favors low molecular weight plasticizers. Compatibility, the plasticizer should be miscible with the polymer, which indicates similar molecular forces in the two compartment system. It has been theorized that the most effective plasticizers will generally resemble most closely in structure the polymers they plasticize. polymeric films employ plasticizers to impart flexibility, improve flow, and reduce brittleness (Steuernagel, 1989; Porter and Bruno, 1990).

Release of Drug from Microcapsules.

Release of drug form microcapsules and microparticles is a mass transport phenomenon involving diffusion of drug molecules from a region of high concentration in the dosage form to a region of low concentration in the surrounding environment. Release of drug due to the great diversity in the physical form of microcapsules with regard to size, shape, and arrangement of core and coating materials. Also, physicochemical properties of core material, such as solubility, diffusivity, and partition coefficient, and of coating material, such as variable thickness, porosity, and inertness, make modeling of drug release difficult.

Permeation theory, where by drug molecules are transported through one or more polymeric membranes comprising the coating material, is important to an understanding of how core substances are released from microcapsules. The coating acts as a barrier the resistance of which is influenced by factors such as the identity of the film former, its degree of crystallinity, the inclusion of plasticizers or other fillers, its thickness, the occurrence of pores, and the presence of a stagnant diffusion layer in contact with the outer coating surfaces.

Flow of molecules through a barrier such as a polymeric membrane is a particularly convenient way to describe as diffusion processes. The passage of matter through a barrier (Fig. 7) may occur by simple molecular permeation or by movement through pores and channels. Molecular diffusion or permeation through nonporous media depends on dissolution of the

permeation molecules in the bulk membrane (Fig. 7 (a)), where as a second process may involve passage of a substance through solvent-filled pores of a membrane (Fig. 7 (b)) and is influenced by the relative sizes of the penetrating molecules involves dissolution of drug in the matrix of the membrane and is an example of simple molecular diffusion. Perhaps a better representation of a membrane on the molecular scale is a matted arrangement of polymer strands with branching and intersecting channels as shown in Figure 7 (c). Depending on the size and shape of the diffusing molecules, they may pass through the tortuous pores formed by the overlapping strands of polymer. If too large for such channel transport, the diffusant may dissolve in the polymer matrix and pass through the film by simple diffusion.

The release of a drug from a delivery system involves factors of both dissolution and diffusion. The foundations of diffusion and dissolution theories bear many resemblance. Dissolution rate has been discussed as it influences drug release and principles of diffusion as related to the transport of drugs from dosage matrices, through the walls of container into the body by any pathway.

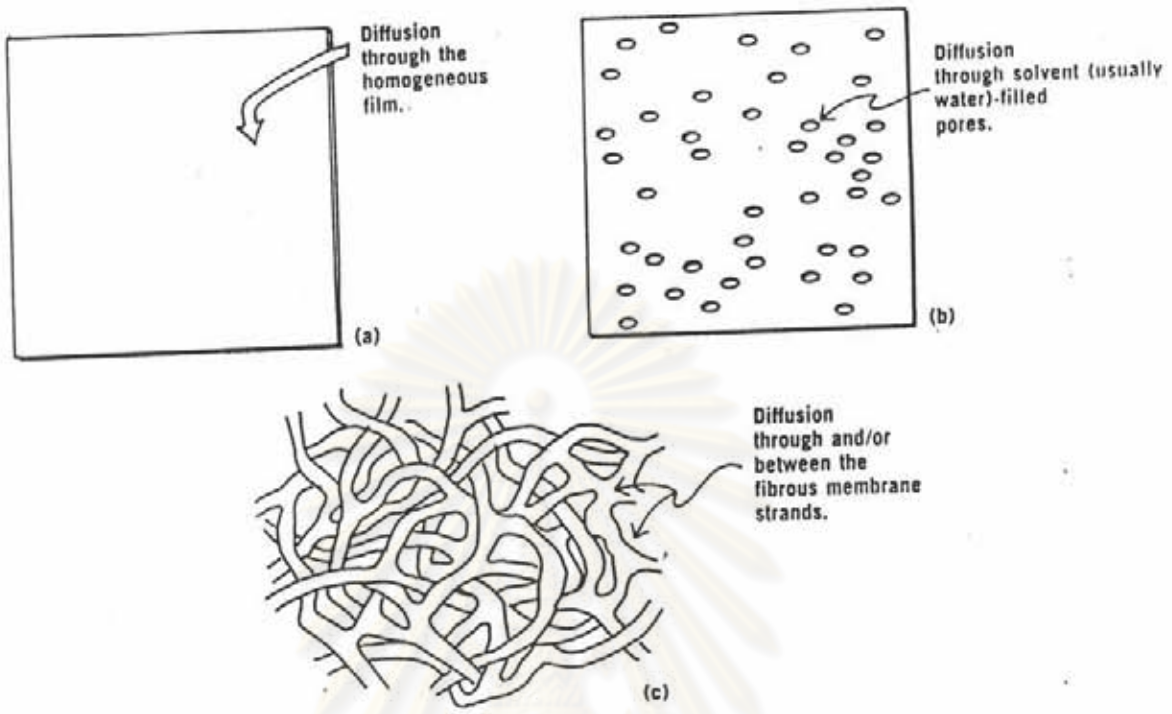

Fig.7 : (a) Homogeneous membrane without pores. (b) Membrane of dense material with straight-through pores, as found in certain filter barriers such as Nucléopore. (c) Cellulose membrane used in filtration processes, showing intertwining nature of fibers and tortuous channels.

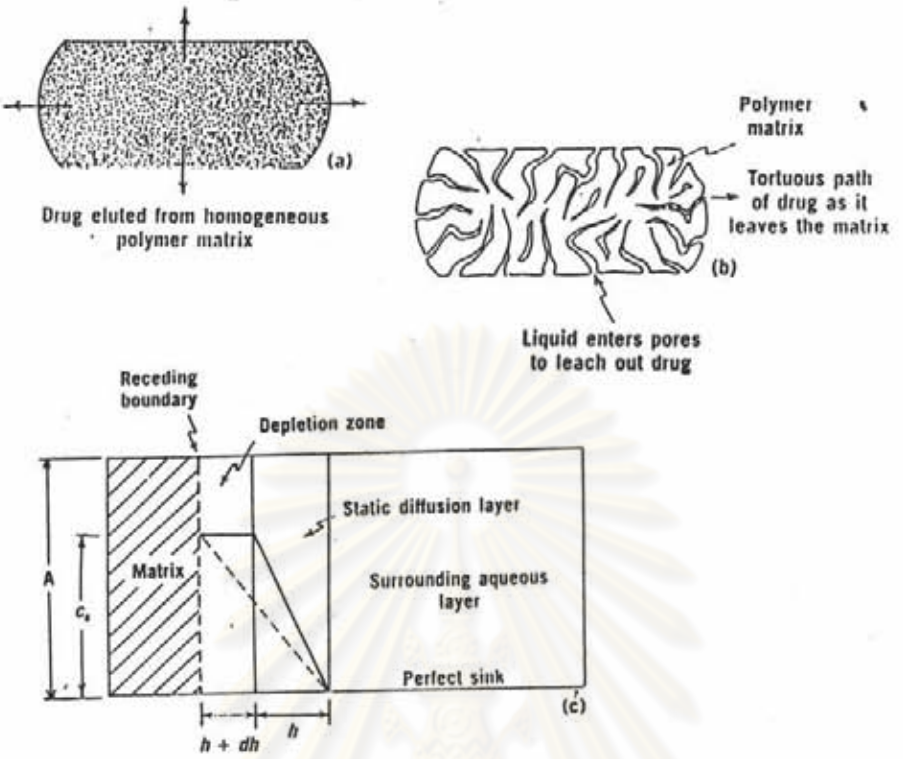

Fig. 8: The release of drug from granular matrix dosage forms. (a) Drug leached from granular matrixs, (b) Schematic of the solid matrix and (c) its receding bindery as drug diffuses from the dosage forms.

The release of a solid drug from a granular matrix (Fig. 8) involves the simultaneously penetration of the surrounding liquid, dissolution of drug, and leaching out of drug through interstitial channels or pores. A granule is, in fact defined as a porous rather than a homogeneous matrix. The volume and length of the opening in the matrix must be accounted for in the diffusion equation, leading to a second form of the Higuchi equation (Higuchi, 1967).

$$Q = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right]^{1/2} \quad \text{..... (2)}$$

in which ε is the porosity of the matrix and τ is the tortuosity of the capillary system, both parameters being dimensions quantities.

Porosity, ε, is the fraction of matrix that exists as pores or channels into which the surrounding liquid can penetrate. The porosity term, ε, found in eq. 2 is the total porosity of the matrix after the drug has been extracted. This is equal to the initial porosity, ε, due to pores and channels in the matrix before the leaching process begins, and the porosity created by extracting the drug. If A g/cm^3 of drug in extracted from the matrix and the drug's specific volume or reciprocal density is $1/\rho$ cm^3/g, then the drug's concentration, A, is converted to volume fraction of drug that will create an additional void space or porosity in the matrix once it is extracted. The total porosity of the matrix, ε, becomes

$$\varepsilon = \varepsilon_o + A\,(1/\rho\ ) \quad \text{..... (3)}$$

Granule porosity (ε) may be computed from a knowledge of the true and granule density. The porosity is given by equation

$$\varepsilon = \frac{V_g - V_\rho}{V_g} = 1 - \frac{V_\rho}{V_g}$$

$$= 1 - \frac{\text{weight / true density}}{\text{weight / granule density}} \quad \text{.....(4)}$$

or

$$\varepsilon = 1 - \frac{\text{granule density}}{\text{true density}} = 1 - \frac{\rho_g}{\rho} \quad \text{.....(5)}$$

in which V_ρ is the true volume of the solid particles and Vg is the volume of the particles together with the intraparticle pores. Equation 2 applies instead to a drug-release mechanism based upon entrance of the surrounding medium into a polymer matrix, where it dissolves and leaches out the soluble drug, leaving a shell of polymer and empty pores. In equation (2) diffusivity is multiplied by porosity, a fractional quantity, to account for the decrease in D brought about by empty pores in the matrix. The apparent solubility of the drug C_s is also reduced by the volume fraction term, which represent porosity.

Tortuosity, τ, is introduced into equation (2) to account for an increase in the path length of diffusion due to branching and bending of the pores, as compared to the shortest "straight-through" pores. Tortuosity tends to reduce the amount of drug released in a given interval of time, and so it appears in the denominator under the square root sign (Martin, 1993).

The pattern of delivery achieves by a controlled release system can vary over a wide range, but most release profiles categorized into three types :

1. Zero - order release pattern
2. Square - root - time release pattern
3. First - order release pattern

1. Zero - order model.

An ideal controlled release device is one which can deliver the drug at a constant rate until the device is exhausted of active agent. Mathemetically, the release rate from this device is given as

$$\frac{dMt}{dt} = k \qquad \text{.....(6)}$$

where k is a constant, t is time, and the mass of active agent released was Mt. This pattern of release is called zero-order release model.

3.2 Square-root-time model (Higuchi's model).

The second common release pattern, frequently referred to as square root of time release, provided compound release that was linear with the reciprocal of the square root of time the release rate then given as

$$\frac{dM_t}{dt} = \frac{k}{\sqrt{t}} \qquad \text{.....(7)}$$

In contrast to first-order release, the release rate here remained finite as the divice approached exhaustion.

The release pattern of this type can be described by Higuchi's equation refered previously as

$$Q = \left[\frac{D\varepsilon}{\tau} (2A - \varepsilon C_s) C_s t \right]^{1/2} \qquad \text{.....(2)}$$

The assumptions made deriving equation 2 are as follows

1. A pseudo-steady state is maintained during release.
2. A >> Cs, ie. excess solute is present.
3. The system is in perfectly sink condition in which C is approximately to zero at all time
4. Drug particles are much smaller than those in the matrix.
5. The diffusion coefficient remains constant.
6. No interaction between the drug and the matrix occurs.

For purpose of data treatment, Equation 2 is usually reduced to

$$Q = k_H t^{1/2} \quad \text{.....(8)}$$

were k_H was Higuchi constant. Therefore, the plot of amount of drug released from matrix versus the square root of time should be increased linearly if drug released from the matrix is diffusion controlled. Although the above equation was based on release from a single face, it may be used to describe diffusion-controlled released from all surface matrix.

3. First-order model.

The first order pattern was the third common type of the release model. the release rate in this case was proprotinal to the mass of active agent contained within the device. The rate was then given as

$$\frac{dM_t}{dt} = k (M_o - M_t) \quad \text{.....(9)}$$

where Mo was the mass of agent in the device at t = 0. On rearrangement, this gave

$$\frac{dMt}{dt} = kM_o \exp^{-kt} \quad \text{.....(10)}$$

In first order model, therefore, the rate diclined exponentially with time, approahing a release rate of zero as the divice approached exhaustion.

On the assumption that the exposed surface area of matrix decreased exponential with time, Wagner (1969) suggested that drug release from most controlled-release matrices could be described by apparent first order kinetics,

$$A_t = A_o e^{-k_1 t} \quad \text{.....(11)}$$

where k_1 = first order release constant

A_o = initial amount of drug

A_t = amount of drug remaining in the matrix at time t

simplifying and taking the logarithm of equation (11) yielded

$$\ln A_t = \ln A_o - k_1 t \quad \text{.....(12)}$$

First order pattern can be predicted by plotting the logarithm the percent of drug remaining against time. If first order model, linear relationship were obtained. Sa, Bandyopadhyay, and Gupta (1990) reported that the initial curvature of the plot

may be obtained because of the presence of surface drugs and they suggested to be ignored.

The release pattern for each classes of device is illustrated in Fig. 9 (Baker, 1987). The release patterns of zero-order, square-root of time, and first-order are depictated (Equation 6, 7 and 9), respectively.

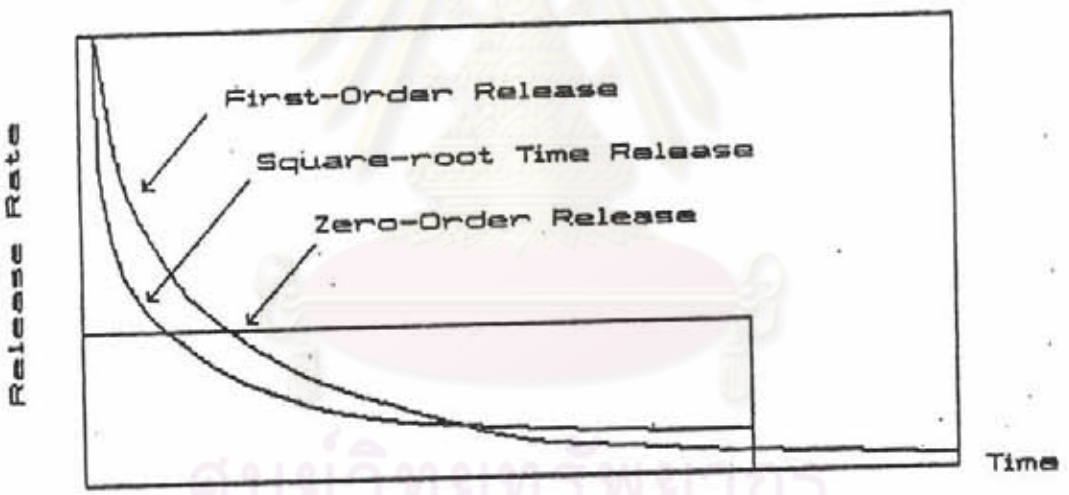

Fig. 9: Zero-order, First-order, and Square root of time release patterns form devices containing the same initial active agent content.