CHAPTER I

INTRODUCTION

Development of controlled-release dosage form for oral administration aim to control the amount release of the therapeutic agent in order to obtain suitable therapeutic range and duration of action for consideration to improve efficacy in drug therapy. The release of several drugs in conventional dosage forms can be controlled to promote the patient compliance by taking the fewer dose per day and reduce the frequency of unwanted side effects.

Diltiazem HCl (DTZ HCl) is a calcium channel blocker that has been widely used in the treatment of various cardiovascular disorders such as angina pectoris, cardiac arrythmias and hypertension. The usual dose of DTZ HCl in adults is 30 mg 4 times a day. The maximum dose that can be consumed daily is 360 mg (Reynolds, 1993). None of the conventional formulations are able to keep the plasma concentration of DTZ HCl in the therapeutic range for a long period of time owing to short biological half-life of the drug. Reported half-lives for the elimination phase of DTZ HCl ranged from 2 to 7 hours (average about 4.5 hours). The repeated administration of conventional formulations will produce many peaks and valleys in the plasma concentration as a function of time. The properties of DTZ HCl found to be (a.) short elimination half-life, (b.) highly water soluble and (c.) therapeutic use in chronic diseases, make it suitable as a candidate for sustaining of its release from dosage forms. In order to maintain plasma concentration in the therapeutic range, many attemps have been made to sustain the therapeutic concentration of DTZ HCl. The sustained-release formulations have advantages of patient compliance, less variable in releasing and less dependent on gastric transit time. The use of sustained-release formulations will improve the efficiency of treatment. In addition, sustained-release dosage forms are somewhat important for

patient that must take the drug for a long period of time. There are several ways to develop the controlled release drug delivery systems. One method is forming release-controlling membranes around drug-containing pellets or granules (Harris and Ghebre-Sellassie, 1989).

Multiparticulate dosage forms such as pellets as a drug delivery system offer both therapeutic and technological advantages. In the first case, pellets have less irritation to gastro-intestinal tract and also lowered risk of side effects due to dose dumping (Bechgaard and Hegermann Nielsen , 1978). In the second case, pellets have advantages in flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing. The reproducibility of the drug in blood levels is an additional advantage to the use of pellet formulation. The commercially available pellet formulations are mainly coated with a polymer film in order to obtain a controlled release effect. The thickness and composition of the film found to influence the release pattern, so by mixing different type of coated pellets the desired release profile can be obtained (Yuen, Deshmukh, and Newton, 1993).

The present works are to studies on the preparation of pellets which containing highly water soluble drug (DTZ HCl) by extrusion-spheronization process and observe the effects of drug concentration, amount of water content and binder concentrations on appearance and some physical properties of obtained pellets.

For coating process, ethylcellulose (EC) was chosen to be a coating polymer due to the most widely used as water insoluble polymer membrane for film coating and has good film-forming properties that enable tough, flexible coatings to be produced (Porter, 1989). The evaluation of mechanical properties of EC film is important by determination of the film resistance to the mechanical stress. EC is giving a satisfactory

control of the drug release pattern as well as inexpensive and easy to prepare into a coating solution. An attempt to control release of selected pellets by means of encapsulating with EC polymer using the fluidized bed coating technique and the satisfy formula was the one that its release pattern became the same as a commercial product, Herbesser® 90 SR. Finally, the release mechanisms of the prepared pellets were observed.

Objectives of the Study

On the basis of the rationale mentioned above, the objectives of this study were to;

1. Study the concentration of hydroxypropylcellulose medium grade (HPC-M®) and amount of water content on appearance and physical properties of DTZ HCl core pellets by using extrusion spheronization process.
2. Determine the mechanical properties of film casting with various types and amount of plasticizers for selection the suitable coating film formula to use in coating process.
3. Prepare controlled-release DTZ HCl pellets by coating with suitable amount of EC solution by using fluidized bed technique and compare the release profiles of prepared film coated DTZ HCl pellets to commercial product, Herbesser® 90 SR.
4. Study the possible mechanisms that involve in releasing of DTZ HCl from prepared coated pellets.

Literature Reviews

Pellets Prepared by Extrusion-Spheronization Process

Multiparticulates or pellets offer many advantages over other solid oral dosage forms in term of drug release. They are suitable for drug combinations when incompatability problems exist or when drugs are to be released at different rates from the same dosage form. They can be filled into capsules or compressed into tablets and retain their respective drug releasing characteristics.

Pelletization is an agglomeration process that converts fine powder or granule of bulk drugs and excipients into small, free-flowing, spherical or semi spherical units, refer to as pellets. Pellets typically range in size between 0.5-1.5 mm (Ghebre-Sellassie, 1989). There are many methods to produce multiparticulates or pellets. For example, spraying a solution or suspension of a binder and drug on to an inert core for building the pellet layer after layer (Li et al., 1989), spraying a melt of fats and waxes from the top into a cold tower (spray-congealing) to form pellets by the hardening of the molten droplets (Ghebre-Sellassie, 1989), spray-drying a solution or suspension of the drug forming pellets due to the evaporation of the fluid phase (Ghebre-Sellassie, 1989) and spraying a binder solution into the whirling powder using a fluidized bed (Olsen, 1989) etc. However, The most popular method of producing pellets is by the extrusion-spheronization technique.

The extrusion-spheronization process involves five unit operations. These are blending, granulation, extrusion, spheronization and drying (Figure 1). The moistened pre-compacted mass is extruded into strands, which are then rounded into pellets in a spheronizing machine, dried and subjected to further processing.

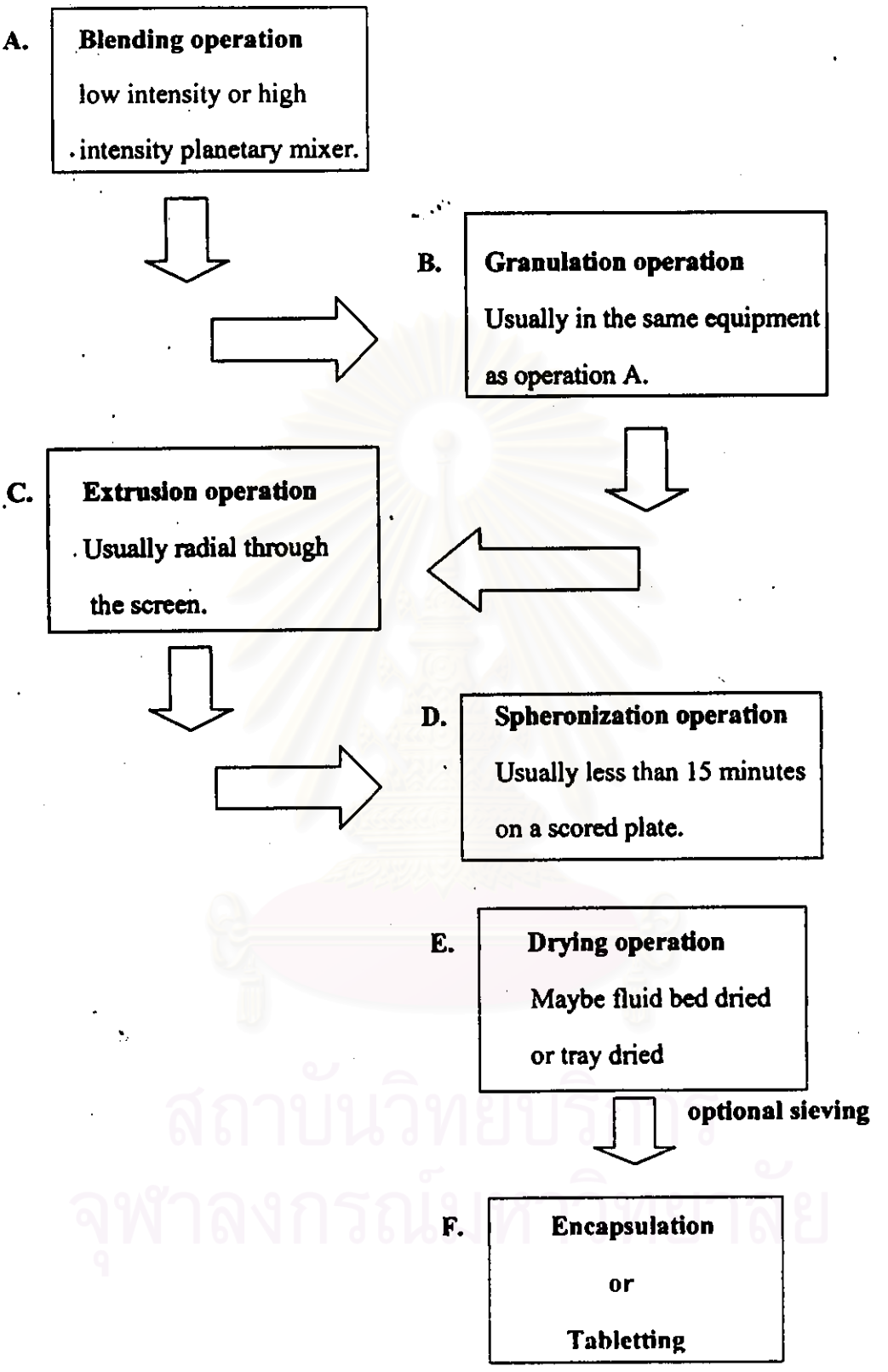

Figure 1. Illustrate flow chart for the spheronization process using the extruder/spheronizer

Granulation

Granulation is the first step consisting of the preparation of the plastic mass by mixing of the powder blend and the granulation liquid. The most commonly used granulator is a planetary mixer although the use of high shear or sigma blade mixers has also been reported (Vervaet et al., 1995).

Extrusion

Extrusion is an operation where a plastic deformable mass is forced through small openings under pressure. The pressure is created by a screw/ conveyer, which produces a steady material flow (Figure 2). The wet mass is shaped into long rods during this step.

Spheronization (Merumerization® is trademark of the Fuji Denki Kogzo Co. in Osaka).

In the spheronizer, the extrudate is initially broken down into short equal lengths. These are transported by centrifugal forces to the edge of the spinning plate, called the friction plate, where this spining motion causes them to rise up the vertical wall and then fall as there momentum is lost. This movement along with the angular velocity causes the moving mass to form a toroidal rope like shape. The friction plate has a grooved surface to increase the frictional forces. Two types of geometry of the grooves exist, cross-hatch geometry where the grooves form right angles and radial geometry where a radial pattern is used (Figure 3).

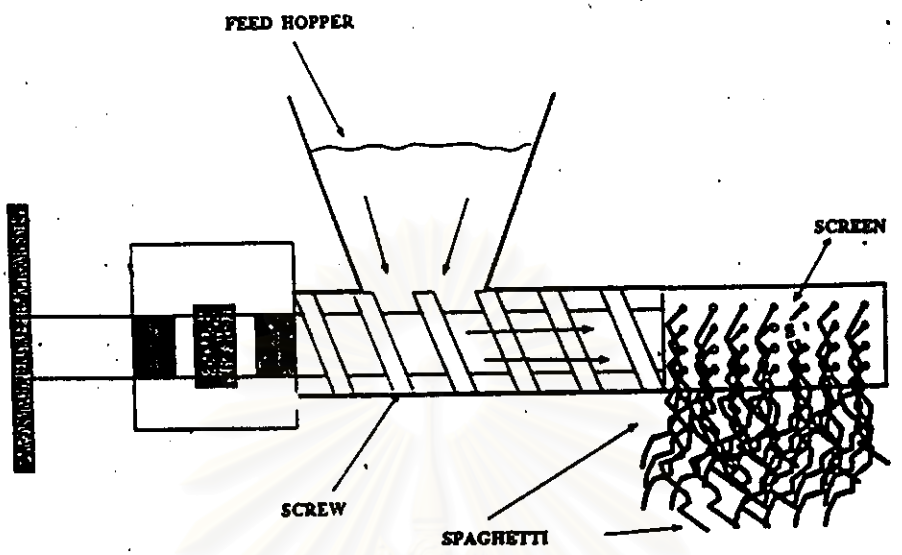

Figure 2. Schematic of extruder

Figure 3. Geometry of the spheronization plate

The pellet-forming mechanism may be divided into two types. The different stages can be distinguished depending on the shape of the particles. The first mechanism, according to Rowe (1985) starts from a cylinder over a cylinder with rounded edges, dumbbells and elliptical particles to eventually perfect spheres (Figure4a). Baert and Remon (1993) suggested that another mechanism might exist. In this mechanism a twisting of the cylinder occurs after the forming of cylinders with round edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have around and flat side. Due to the rotational and the frictional forces involved in the spheronization process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets (Figure4b). The overall process usually takes less than 15 minutes.

Drying

Drying is the final step to eliminate the excess of the solvent used in granulation liquid. The pellets can be dried at room temperature or at elevated temperature in a fluidized bed, a hot air oven or a microwave oven. Comparing a formulation dried in a microwave and ordinary oven, the pellets dried with microwave differed from those dried in the oven as their surface was rougher, more porous and lesser hardness (Bataille et al., 1993)

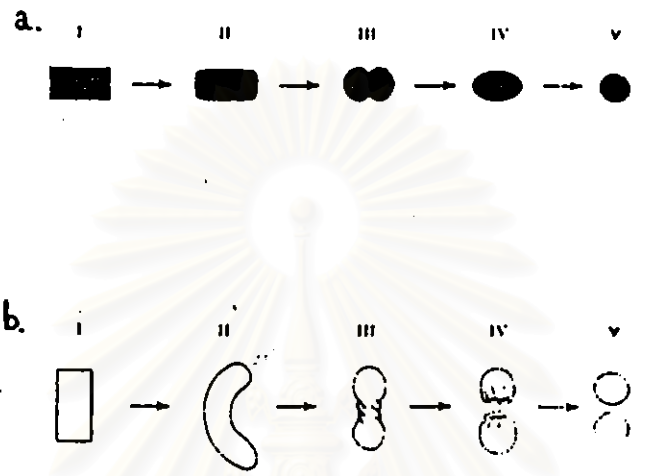

Figure 4. Pellet-forming mechanism according to: (a) Rowe; I cylinder, II cylinder with round edges, III dumb-bell, IV ellipse, V sphere (b) Baert; I cylinder, II rope, III dumb-bell, IV sphere with cavity outside, V sphere

Shape of the Pellets

One of the most important characteristics of a pellet is its roundness. The main claim of benefit which the process gives is spherical shape with uniform sized, better flow properties, uniform packing and a smooth minimum surface area for efficient film coating to provide uniform control of drug release.

Pellets can be divided into six shape groups (I-VI) by visual inspection (Figure 5), the shape varied from long, cylindrical rods through dog-bones and ellipsoids to almost spherical pellets (Hellen et al., 1993c).

There are seven tested parameters (Eqns1-7) indicating shape were derived from size data measured by OPT/IA (optical microscopy/Image analysis) (Hellen et al., 1993b). The purpose of these parameters was to emphasis the degree of sphericity of the pellets. The value close to 1 which calculated from each parameter model represented the most spherical pellets (Hellen et al., 1993c). These parameters were as follows:

$$Circularity = \frac{4 \times \pi \times A}{(perim)^2} \quad (1)$$

$$Roundness = \frac{A}{\pi \times (d_{max}/2)^2} \quad (2)$$

$$Elongation = \frac{d_{max}}{d_{min}} \quad (3)$$

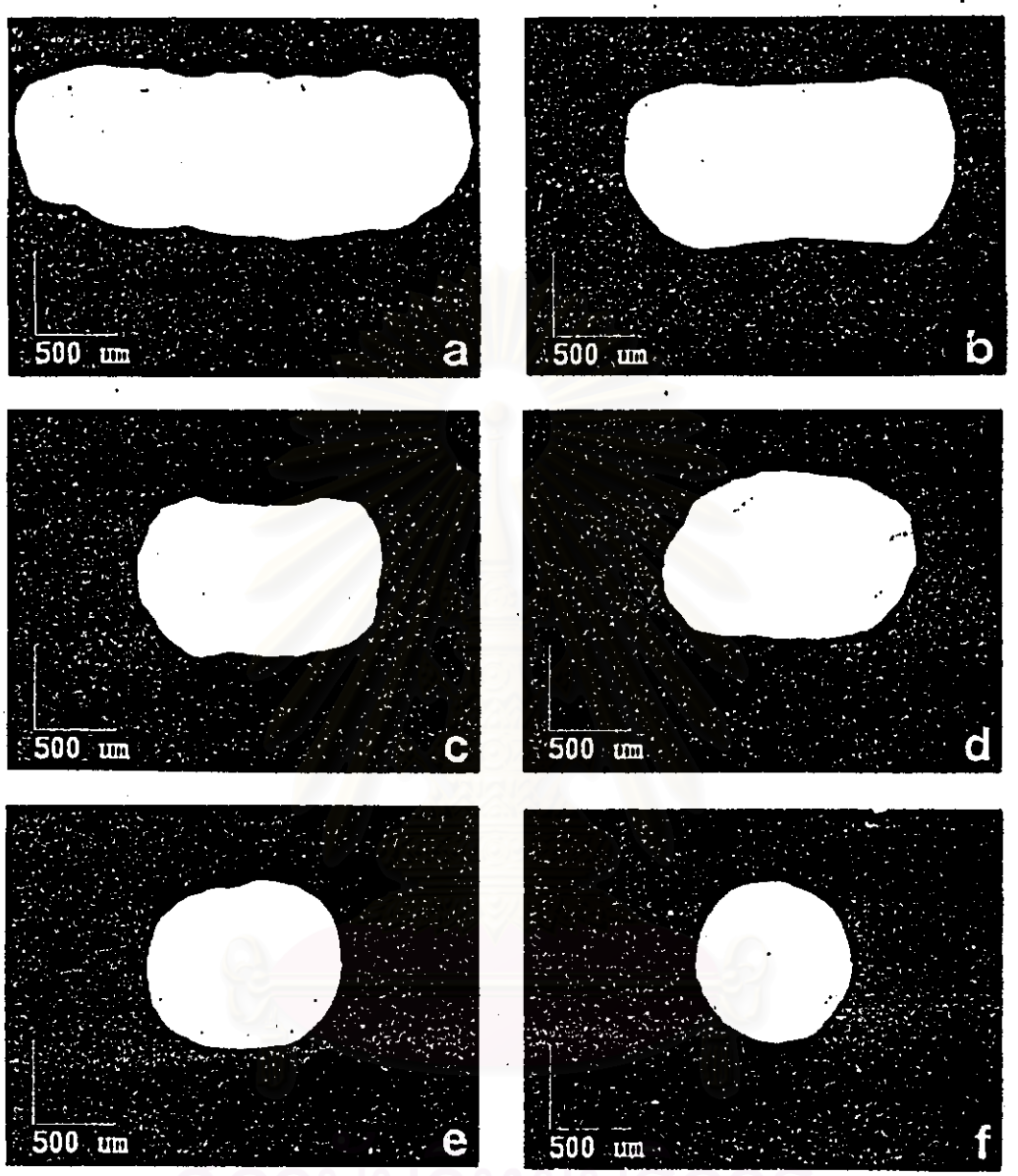

Figure 5. Pellets representing shape group I –VI which varied from long , cylindrical rod, dog-bone, ellipsoid, almost spherical and spherical, respectively.

$$Pellips = \frac{perim}{\pi \times d_{max}} \quad (4)$$

$$\mathrm{Re}ctang = \frac{A}{d_{max} \times d_{min}} \quad (5)$$

$$Modelx = \frac{perim \times d_{max}}{4 \times A} \quad (6)$$

$$Roughness = \frac{perim}{cperim} \quad (7)$$

Where A, $perim$, $cperim$, d_{max} and d_{min} are two-dimensional area of the projection of the pellet (mm^2), perimeter of the object which is the length of the outline of the projection (mm), convex perimeter of the object which is the length of a regular polygon with 64 corners stretched around the object, maximum Feret's diameter and minimum Feret's diameter, respectively (Feret's diameter is the perpendicular projection, on to a fixed direction, of the tangents to the extremities of the particle profile (Figure 6).

The calculated shape parameters for the six shape groups of pellets I-VI (VI refer to roundest pellet) are evaluated (Hellen et al., 1993c). The circularity parameter seemed to be limited in the evaluation of the shape of pellets this parameter could not distinguish the difference between the three roundest pellets shape groups IV-VI. The roundness parameter was more sensitive and could classify the pellets clearly according to visual observation. The roundness parameter increased as pellets shape became more spherical and the value was close to 1.0. The pellips parameter increased as the shape of pellets became more spherical like circularity and roundness parameter.

The elongation and modelx parameters behaved very similarly. The numerical value of both these parameters decreased systematically as the pellets became rounder and the value was close to 1.0. The rectang parameter was somewhat limited because it was able to classify these six pellets only in two categories. Shape groups I-III had slightly higher rectang values than shape groups IV-VI because the first group really had a more rectangular shape on the basis of the pictures presented earlier. The roughness parameter could not distinguish the different shapes or surface structures from each other. Hence, due to its insensitivity, the roughness parameter cannot be used as an indicator of shape or surface structure in the case of pellets (Hellen et al., 1993b).

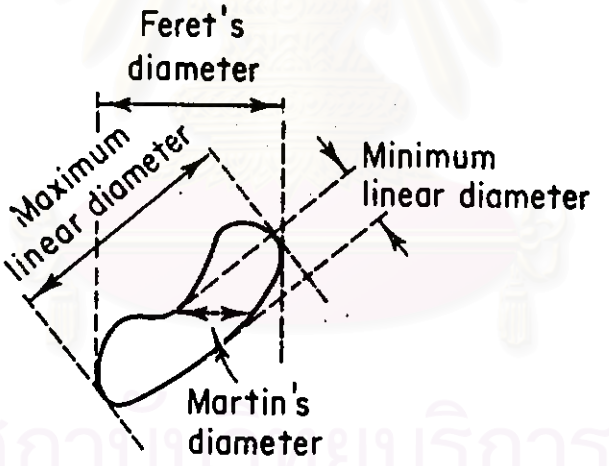

Figure 6. Various dimensions of an irregular particle (Chemical Engineering, 1970).

Coating pellets.

Fundamentals of film formation

Application of a film to a solid is indeed very complex. A layer of coating does not occur during a single pass through the coating zone, but relies on many such passes to produce complete coverage of the surface. Generally, formation of coatings from polymer solutions involves conversion of a viscous liquid into a visco-elastic solid. In the spray-application process bulk coating liquids are finely atomized to droplets and delivered in such a state that droplets retain sufficient fluidity to wet the surface of core being coated, spread out, coalescence and evaporation to form film, as illustrated in Figure 7.

The rapid evaporation of solvent causes an increase in polymer concentration in the solution and contraction in volume of the coating liquid. Further loss of solvent after the solvent has diffused to the surface of the coating. Concentration of the polymer in the coating increases to the point where the polymer molecules ultimately become immobilized (solidification point). Additional loss of solvent result from the slow diffusion of residual solvent through the dry coating and it ultimately causes shrinkage stresses to develop within the coating (Porter, 1989). These processes are occurring almost simultaneously during coating. Because of the highly adhesive nature of partially dried droplets, it is imperative that the droplet of coating liquid dry almost instantaneously at the moment they contact the surface of the substrate; otherwise sticking and picking may occur. The air used for atomization also contributes to evaporation of the coating solvent. This evaporation results in increasing the droplet's viscosity, thus inhibiting spreading and coalescence upon contact with the core material. Another factor affecting the droplet's viscosity is the distance that the droplets travel

through the primary evaporation media (the fluidization air) before impinging on the core. Hence, there is a need to strike an appropriate balance between liquid application rate and drying process.

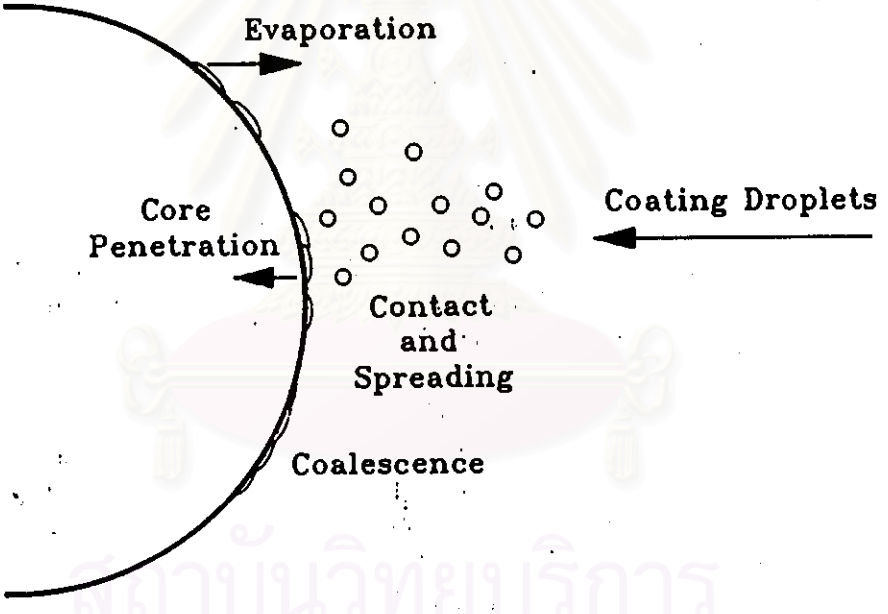

Figure 7. Dynamics of film coating on surface solid

Fluidized bed coating.

The fluidized bed is well known for its drying efficiency, as it has been used for drying and granulating for many years. It has recently been given increased interest owing to its ability to apply virtually any type of coating system (solution, suspension, emulsion, latex and hot melt) to a wide range of particle sizes. Equipment of this type has proven to be particularly suitable for coating pellets. Coatings can be applied to fluidized particles by a variety of techniques, including spraying from the top, from the bottom, or tangentially. The three fluidized bed equipment types, top spray, tangential spray and bottom spray (Wurster type) method are illustrated in the Figures 8, 9 and 10, respectively. The basic features of these techniques and their relative advantages and disadvantages are described in Table 1. In rationalizing the suitability of any one type of coating process compared to another, many factors may well have to be considered during the selection process. When considering the performance of the final coated product, the quality of the coating that is to be deposited will be a major key to success. The influence of various types of coating process on the quality of applied modified-release film coatings can be arranged from good to bad quality as follows: Wurster $\approx$ Tangential spray > Side-vented pan >> Conventional pan (Mehta et al., 1985).

There is no doubt that the fluidized bed process posses the best drying characteristics and that the proximity of the spray nozzle to the product being coated when using the Wurster or tangential spray process helps to control deposition of the coating fluid and evaporation of the solvent/vehicle in that fluid and thus maximize quality of the final coating.

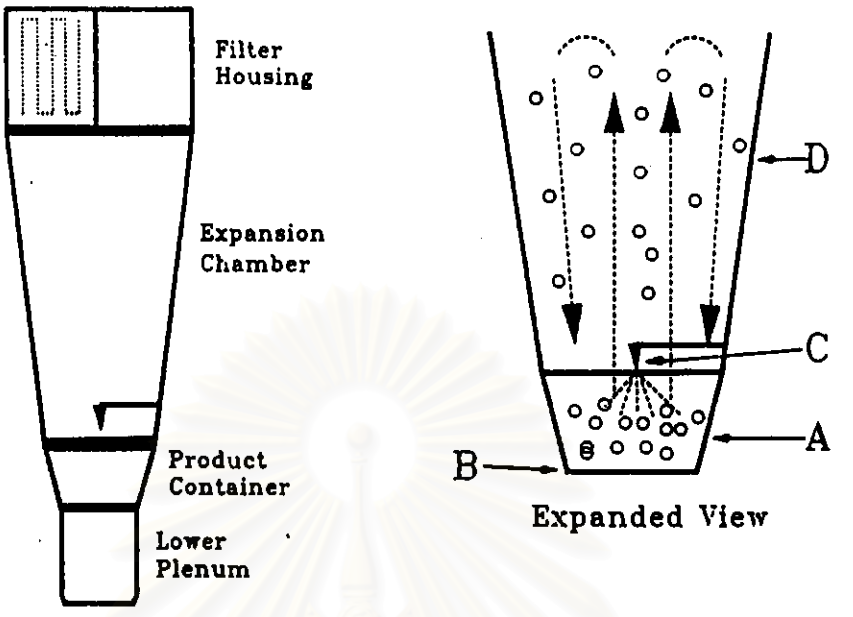

Figure 8. Top spray coater: (A) product container; (B) air distribution plate; (C) spray nozzle; (D) expansion chamber.

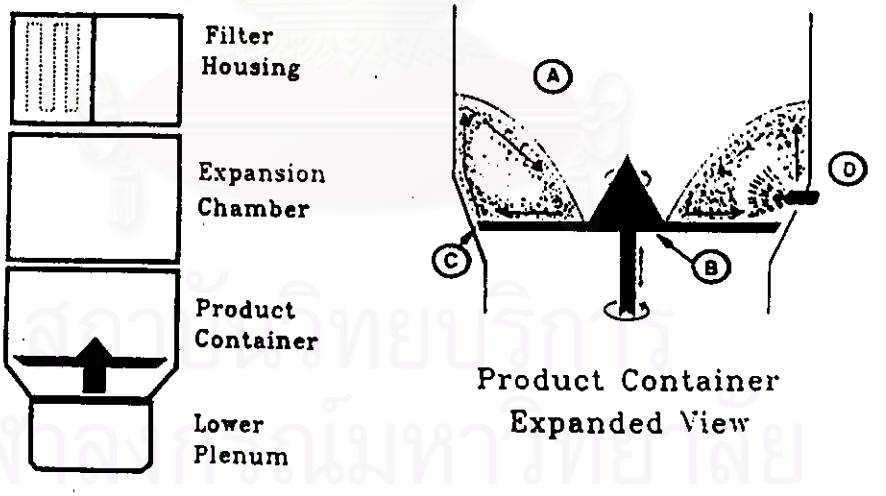

Figure 9. Rotor tangential spray coater: (A) product chamber; (B) variable speed disc; (C) disc gap or slit; (D) spray nozzle.

Table 1. Characteristics of three fluidized beds coating process.

Processing method	**Advantages**	**Disadvantages**	**Applications**
Top-spray coating (conventional mode)	Accommodates large batch sizes, is simple to set up, and allows easy access to nozzle.	Limited in its applications.	Hotmelt coating and aqueous enteric coatings. Not recommended for sustained-release products.
Bottom-spray coating (Wurster)	Accommodates moderate batch sizes, produces uniform and reproducible film characteristics, and allows for widest application range.	Tedious to set up, does not allow access to nozzles during processing, and is the tallest fluid-bed machine for coating fine particles.	Sustained-release, enteric-release, and layering. Poor for hotmelt coating.
Tangential-spray coating (rotary mode)	Simple to set up, allows access to the nozzle during processing, permits higher spray rates, and is the shortest fluid-bed machine for coating fine particles.	Puts mechanical stress on the product.	Very good for layering, sustained-release, and enteric-coated products. Hotmelt coating is possible. Not recommended for friable products.

When comparing two fluidized-bed processes used in the application of organic solvent-based polymer solutions. The Wurster process claimed to be more efficient (in terms of actual amount of coating deposited) than the top spray process. (Li et al., 1989).

Porter (1982) described the concept of Wurster design that a moving particle continuously passes up the central column where the spray gun situated. At the top of expansion chamber, the particle drop back to the bottom between the walls of the inner and the outer chamber, as a result of reducing air velocity. The moving particle continuously passed through the spray path with every particle capturing some of the coating and at the same time ensuring that little or no solution reaches the wall of the inner column (Figure 11).

Mechanical properties of free film

The physical-mechanical properties of coating films is an important characteristic with help to predict the stability and release property of release dosage forms and also provides information concerning possible interactions between the component in coating films. Such studies are usually used with free films (S.Obara et al., 1994). The release characteristics of film-coated extended release formulations are strongly dependent on the properties of the film such as film permeability and its mechanical strength (O'Donnell and MacGinity, 1997).

Traditionally, stress-strain testing in the tensile mode has been a popular and widely used mechanical test for the polymeric films. The tensile test gives an indication not only of the elasticity and strength, but also of the toughness of the film.

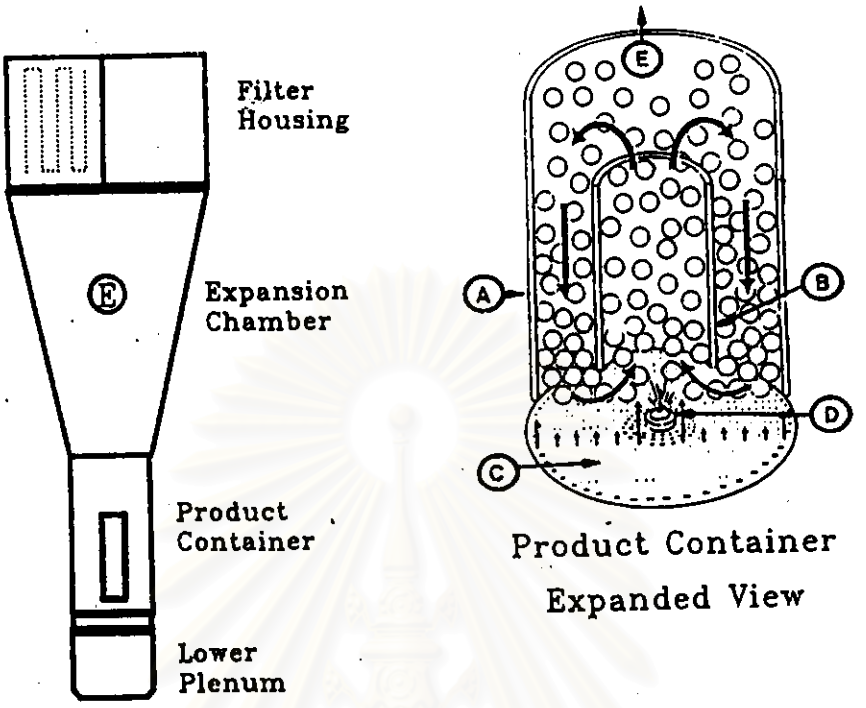

Figure 10. Wurster bottom spray coater: (A) coating chamber; (B) partition; (C) air distribution plate ; (D) spray nozzle; (E) expansion chamber.

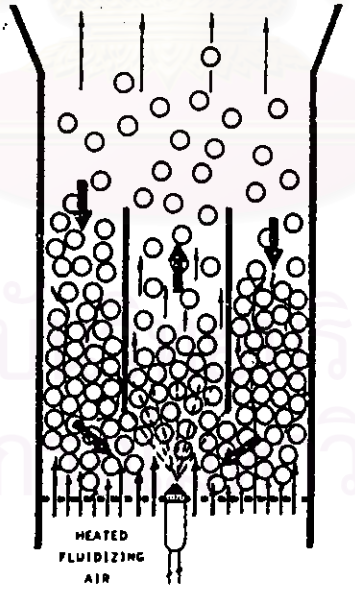

Figure 11. The direction of particle movement in Wurster fluidized bed coater.

In the development of a film coating system, the evaluation of free films has been established as a valuable tool because it can readily used to characterize and evaluate the fundamental properties of the coating (Li and Peck, 1989).

Tensile testing

The method of preparing tested film has two choices. One is sprayed film another is cast film method.

Sprayed films are more realistic but cast film method gives a more perfect specimen, uniform thickness and free from bubbles and defects. Cast films are reproducible because environmental factors affect the film preparation less than with sprayed films. Casting is therefore a better means of obtaining accurate data on the fundamental properties of the polymer and polymer formulation (Aulton, 1982).

An ideal film coat with respect to retaining its physical continuity should be hard and tough without being brittle. Polymers are divided into five categories according to a qualitative description of their mechanical behavior and corresponding stress-strain characteristics as showed in the Table 2 and Figure 12.

Hard or stiff polymers are characterized by high moduli as opposed to soft ones. Strong (as opposed to weak) polymers have high tensile strengths. Tough (as opposed to brittle) polymers have large areas under their stress-strain curves and require large amounts of energy to break under stress, combining high or at least moderate tensile strength with high elongation. The desirable hard, tough film must have a high yield stress large extension before breaking and a high elastic modulus (Aulton, 1982).

Table 2. Qualitative description of polymer and it's stress-strain characteristics.

Polymer Description	Characteristics of stress- strain curve			
	Young's Modulus	Yield Stress	Tensile Strength	Elongation To break
Soft, weak	Low	Low	Low	Low to moderate
Soft, tough	Low	Low	Moderate	Very high(20-1000%)
Hard, brittle	High	None (break around yield point)	Moderate to high	Very low(<2%)
Hard, strong	High	High	High	Moderate(~5%)
Hard, tough	High	High	High	High

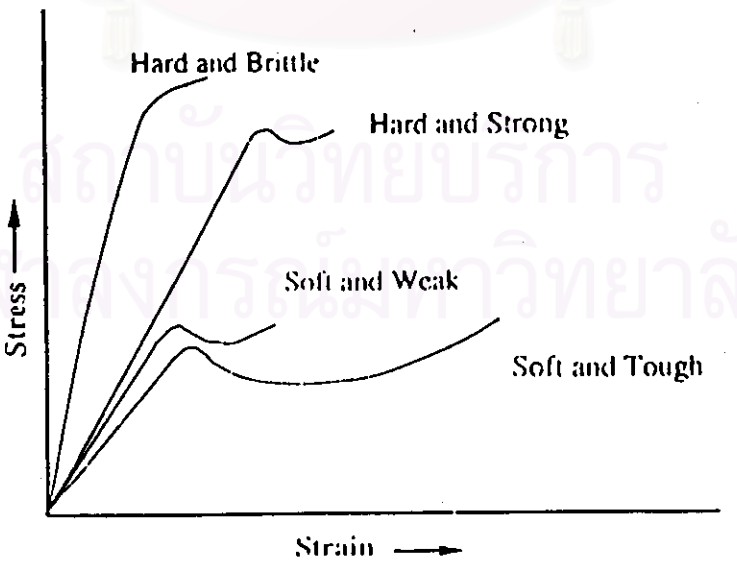

Figure 12. Characteristic of polymer properties in stress-strain curves.

A typical stress-strain data curve is shown in Figure 13. Along the linear portion has relation between stress and strain. The elongation is directly proportional to the applied stress, following Hooke's law is given in equation 8.

$$\sigma = E \times \varepsilon \quad (8)$$

Where δ, $\mathcal{E}$ and E represent tensile stress, strain and Young's modulus, respectively.

Tensile strength, ultimate strength or breaking stress is the maximum stress applied to a point at which the film specimen breaks. Tensile strength can be computed from the applied load at rupture divided by the cross sectional area of fractured film. The determination of tensile strength alone is not very useful in predicting mechanical performance of the films, however higher values of tensile strength of the films are desirable for abrasion resistance.

Strain or elongation ($\mathcal{E}$) is a measure of the ductility of the film. Strain is deformation of materials after applied stress. Strain in tension is called elongation. It is the increase in length relative to the original length. Elongation is dimensionless because it is expressed as a fraction of the original length. It can also be expressed as a percentage.

Young's modulus or Modulus of elasticity (E) is the most basic and structurally important of all mechanical properties and is a measure of stiffness and rigidity of the film. It is calculated as applied stress divided by the corresponding strain in the region of linear elastic deformation (slope). The greater slope of the curve, the higher the elastic modulus. The high value of the elastic modulus indicates the stiffness and the

strength of film and more stress will be required to produce a given amount of deformation (O'Donnell and MacGinity, 1997).

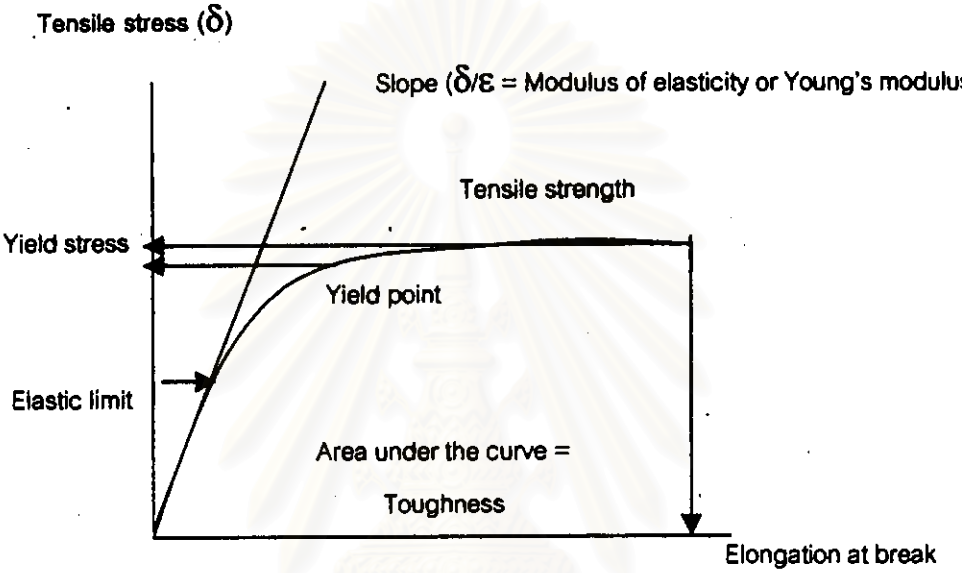

Figure 13. Typical stress-strain curve.

Elastic limit is the maximum stress, which may be developed during a simple tension test that does not cause the permanent or residual deformation when the load is entirely removed. The region of stress-strain curve extending from the origin to the elastic limit is called the elastic range, and the region extending from the elastic limit to the point of rupture is called the plastic range.

Yield point is the point that there is an increase in strain with no increase in stress.. Stress at this point called yield stress. When the applied stresses exceed yield stress the specimen exhibits plasticity, becoming ductile and flowing or creeping under nearly constant stress, resembling a highly viscous liquid and the sample undergoes permanent elongation.

Area under the stress-strain curve is a function of work done in breaking the film specimen and is representative of the film toughness. The sample that has more area under the stress-strain curve also has more hardness and toughness.

Mechanisms of release from coated pellets.

The major mechanism by which the drug is released from a pellet dosage form will naturally depend on the type of coating and the method by which it is applied. An important determinant of kinetics of release is the solubility behavior of the coating material under GI conditions. Behavior may be wildly classified according to three general types: (1) the coating is insoluble under all physiologically relevant conditions, (2) the solubility changes dramatically at some point of GI tract, and (3) the coating is slowly erodible under GI conditions.

Pellets coated with a polymer not soluble under GI conditions

The purpose of coating pellets with an insoluble polymer is to retard the rate of drug release, so that blood levels are sustained over a prolonged period. The most commonly used materials are the insoluble ethers of cellulose, such as ethylcellulose. These may be applied from organic solution or from an aqueous dispersion. The method

of application and processing conditions may influence the porosity of the coating and consequently the release mechanism. Cellulose esters such as acetates and butyrates can also be applied to produce insoluble films. Some methylacrylate polyesters, such as Eudragit S, which are insoluble over the pH range 1 to 7.5, may also be considered as coatings that are essentially insoluble under GI conditions. There are several possible mechanisms by which release from pellet dosage forms coated with GI-insoluble polymers my occur:

A. Solution/Diffusion through the continuous plasticized polymer phase

This mechanism assumes that the polymer forms a continuous phase in which the plasticizer and other additives are homogeneously dispersed. The diffusion of a solute molecule within an amorphous polymer phase is an activated process involving the cooperative movements of the penetrant (drug) and the polymer chain segments around it. In effect, thermal fluctuations of chain segments allow sufficient local separation of adjacent chains to permit the passage of a penetrant, then hindered molecular diffusion occurs. Another, less likely mechanism of release is the movement of the drug on the polymer chains, known as configurational diffusion.

The release rate for such a model can be described by:

$$J = \frac{Pm}{h} \times (Cs - Cb) \qquad (9)$$

Where J is the flux (release rate per unit surface area of coating), C_s and C_b are the concentration of drug at the drug-coating interface and the bulk, respectively,

and h is the coating thickness. The permeability coefficient (Pm) of the coating polymer can be written as

$$Pm = \frac{D \times V \times k}{\tau \times \beta} \qquad (10)$$

Where D is the molecular diffusivity of the drug, k the distribution coefficient of the drug between the polymer membrane and fluid in the core (imbibed water), V the volume fraction of the chain openings, β a chain immobilization factor, and τ the tortuosity factor.

The solution/diffusion mechanism has been demonstrated for many polymer films prepared from organic solvents, which tend to form complete films. In general, it will be dominant only in those cases where the film is continuous (lacks pores) and flexible, and where the drug has a high affinity for the polymer relative to water.

B. Solution/diffusion through plasticizer channels

When the plasticizer is not uniformly distributed in the coating polymer, and when the plasticizer content is high, the plasticizer could conceivably take the form of continuous phase in the form of patched channels. If the solubility of the drug in the plasticizer is higher than that in water, it is possible that the drug would be preferentially transported through such plasticizer channels.

The release rate for this model can be described by equation 9, but with the permeability coefficient, Pp represented as,

$$Pp = \frac{(Dp \times Vp \times kp)}{\tau_p} \qquad (11)$$

In this case, kp is the distribution coefficient of the drug between plasticizer and the core fluid (imbibed water), τ_p the tortuosity of the plasticizer channels and Vp the volume fraction of plasticizer channels.

B. Diffusion through aqueous pores

In this model, the coating is not homogeneous and continuous, but punctuated with pores. These pores fill with solution when the dosage form comes in contact with an aqueous medium, and thereby facilitate the diffusion of the drug. This mechanism is more likely to be operative for coatings formed from aqueous dispersions of pseudolatexes than when the coating is applied from an organic solvent. During the coating and curing processes, the pseudolatex particles often do not fuse completely, thereby creating pores in the coating. These pores may be on the order of 1 μm. The transport mechanism in these pores can range from pure molecular diffusion to convection, depending on the pore size. For diffusion through aqueous pores, the permeability coefficient, Pa , is given by

$$Pa = \frac{Da \times Va}{\tau_a} \qquad (12)$$

Where Da is the aqueous diffusivity of the drug, Va the volume fraction of the aqueous channels. And τ_a the tortuosity of the aqueous channels. The partition coefficient, K, will be unity, as there is no partitioning between the channels and the aqueous environment in the bulk.

This mechanism is often accompanied by other mechanisms. The most usual combination is diffusion through the continuous polymer phase in parallel with diffusion through aqueous channels. Assuming that two mechanisms operate independently, the resultant permeability is given by equation 13.

$$Pt = Pm + Pa = \frac{D \times V \times k}{\tau \times \beta} + \frac{Da \times Va}{\tau_a} \qquad (13)$$

Where *Pm* and *Pa* are the permeabilities in the polymer and the aqueous phase respectively.

C. Osmotically driven release

When the coating is porous, there is also the possibility of release being driven by an osmotic pressure difference between the core materials and the release environment. Sources of osmotic pressure in the core formulation include low molecular weight excipients and the drug. For the drug to contribute significantly to the osmotic pressure, it should be highly water soluble, be low molecular weight, and be present in a substantial dose (capable of achieving saturation concentration in the core).

When pellets come into contact with an aqueous environment, water is imbibed through the coating, creating a solution in the core. The excipients and/or drug dissolve in the imbibed water, generating the interior osmotic pressure. The osmotic pressure difference between the core and the external medium then provides the driving force for efflux through pores in the coating. The release for this process can be described by equation 14.

$$J = \frac{Lp}{h} \times (\sigma \times \Delta\pi - \Delta P) \times (Ci - Cm) \qquad (14)$$

Where Lp is the filtration coefficient, σ the reflection coefficient of the coating, $\Delta\pi$ the osmotic pressure difference across the coating, ΔP the hydrostatic pressure difference and Ci and Cm are the interior and media drug concentrations, respectively.

The choice of core material will influence the degree of osmotic pressure generated. Because of their high sugar content, use of Nu-Pareil seeds is more likely to result in osmotically driven release than are granules in which the drug is spheronized with high-molecular-weight materials such as Avicel®. The usual method to check for osmotically driven release is to add various amount of urea to the dissolution media and observe whether the release rate is inhibited. Sodium chloride is less preferable, as in this case both osmotic pressure and ionic strength effects can contribute to changes in the release profile. One should also check that the drug solubility is not affected by the presence of large concentrations of the osmotic agent used.

Model drug

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). It has generally been indicated for the treatment of angina and hypertension. Diltiazem hydrochloride is a potent dilator of coronary arteries and has been shown to increase exercise tolerance in man. It is available for dosing as immediate release tablets and as extended or sustained release capsules.

The chemical structure of diltiazem hydrochloride is given in Figure 14. The molecular formula and molecular weight of diltiazem hydrochloride are respectively, $C_{22}H_{26}N_2O_4S \bullet HCl$ and 450.98 g/mole. Diltiazem hydrochloride is also described under the following chemical names.

(1) (2S-cis)-3-(acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxy-phenyl)-1,5-benzothia-zepin-4(5H)-onemonohydrochloride.

(2) (+)-cis-3-(acetyloxy))-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-onemonohydrochloride

(3) (+)-5-[2-(dimethylamino)ethyl]-cis-2,3-dihydro-3-hydroxy-2- (p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate(ester) monohydrochloride.

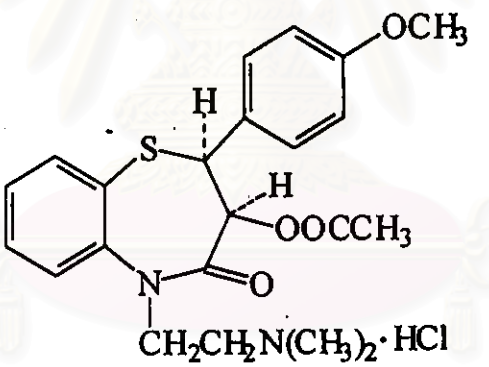

Figure 14. Chemical structure of Diltiazem hydrochloride.

Diltiazem hydrochloride is a white to off-white crystalline powder. It is odorless and has a bitter taste. The melting point of diltiazem hydrochloride is about 210 °C (207.5 °C -212 °C) with decomposition at higher temperatures. Its solubility in a variety

of solvents is presented in Table 3. Solubilities are indicated in terms of current USP definitions.

Table 3. Solubility of Diltiazem hydrochloride at 25 °C.

Solvent	Solubility
Chloroform	Freely soluble
Formic acid	Freely soluble
Methanol	Freely soluble
Water	Freely soluble
Dehydrated alcohol	Sparingly soluble
Benzene	Practically insoluble
Ether	Insoluble

The pH of a saturated aqueous solution of diltiazem hydrochloride in water is 3.0. A 1.0% w/w solution of drug in water has a pH of 4.2. A pH of 4.7 $\pm$ 0.3 has been reported for a 1.0% w/v solution of diltiazem hydrochloride in water (Mazzo, Obetz and Shuster,.1994).

In the solid state, diltiazem hydrochloride is found to be highly stable. Storage of the drug substance under conditions of room temperature and 33% or 79% relative humidity for 57 days did not have any deleterious effect on its physical and chemical properties. Storage of diltiazem at 40 °C /75% relative humidity in dark for 3 weeks did not affect its stability, when exposure to UV light under the same conditions did not affect its chemical stability and only slightly affect its physical stability. This was manifested by only a slight yellowish change in its colour (Suleiman et al., 1989).

Diltiazem undergoes hydrolysis to desacetyl diltiazem in aqueous buffer solutions pH 1-7. Diltiazem is most stable at pH 5.

Diltiazem hydrochloride belongs to the benzodiazepine class of compounds. It was originally developed and introduced by laboratories of Tanabe Seiyaku Co., LTD in Japan. Since the introduction of diltiazem hydrochloride in pharmaceutical formulations, it has gained wide acceptance as an anti-anginal and anti-hypertensive agent. It was observed to dilate peripheral arteries and arterioles. The drug increases myocardial oxygen supply by relieving coronary artery spasm and reduces myocardial oxygen demand by decreasing heart rate and reducing overload.

The drug is rapidly and almost completely absorbed from the digestive tract. It reaches peak plasma levels within one hour after administration of drug in gelatin capsules. Oral formulations on the market are sustained-release preparations providing peak plasma levels three to four hours after administration. Diltiazem is extensively metabolized after oral dosing by first-pass metabolism. As a result, the bioavailability is about 40% of the administered dose. The drug undergoes several biotransformations including deacetylation, oxidative O- and N-demethylations, and conjugation of the phenolic metabolites. Of the metabolites only the primary metabolite, deacetyldiltiazem is pharmacologically active. Deacetyldiltiazem has about 40% to 50% of potency of the parent compound (Cocolas, 1998).

Polymer membrane

Ethylcellulose is an inert, hydrophobic polymer that become widely use in pharmaceutical film coating, especially when it is necessary to produce a modified-release dosage form. Ethylcellulose is an ethyl ether of cellulose, a long chain polymer consisting of anhydroglucose units joined together by acetal linkages. Each anhydroglucose unit has three replaceable hydroxyl groups which are substituted to the extent of 2.25-2.60 ethoxyl (OC_2H_5) groups per unit, equivalent to an ethoxyl content of 44-51%. The structure formula of ethylcellulose is shown in Figure 15.

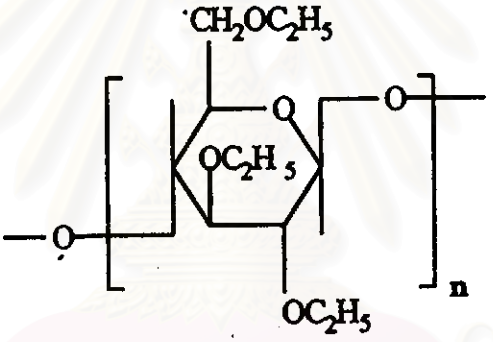

Figure 15. Structural formula of ethylcellulose.

It can be seen that each anhydroglucose unit (of cellulose) has three reactive hydroxy groups that can be ethoxylated, and consequently is said to have a degree of substitution (D.S.) of 3.0. In practice, the D.S. may vary, depending on end use of the polymer.

Ethylcellulose is soluble in a wide variety of solvents, thus making it easier to use when solution application is desirable. Among the useful solvents are the esters, aromatic hydrocarbons, alcohols, ketones, and chlorinated solvents. Ethylcellulose is most soluble in solvents that have nearly the same cohesive energy density or solubility

parameter as the material itself. The solubility parameter ranges vary with degree of substitution (D.S.). Ethylcellulose that contains less than 46.5 % of ethoxyl groups is freely soluble in chloroform, methyl acetate, tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol and toluene.

Solutions of ethylcellulose in aromatic hydrocarbons are highly viscous; consequently, solutions of low concentrations are practical when these solvents are used individually. On the other hand, solvents like ethanol and methanol yield solutions having lower viscosity; however, film properties are too poor for practical purposes. The mixtures of aromatic hydrocarbons with ethanol or methanol yield solutions having a lower viscosity than is obtainable with either solvent type when used alone. Furthermore, this mixed solvent system also deposit films having good strength. The lower molecular weight aliphatic esters and ketones yield ethylcellulose solutions of relatively low viscosities and form films of good strength and extensibility. However, it is preferable, in most cases, to use these solvents with a small proportion of one of the lower viscosities obtainable from such mixtures.

Glass transition temperature is the temperature at which a film strip laid on a heated metal bar begins to soften. It is important fundamental property, since it gives an indication of the tackiness likely to be encountered with film coatings. The high glass transition temperature of ethylcellulose about 130-133 $^{\circ}$C make it ideal polymers.

Ethylcellulose alone yields very tough films of excellent tensile strength, flexibility and elongation characteristics; yet such film lack suppleness. Also ethylcellulose alone softens and flows at too high temperature to be practical in

applications requiring good thermoplasticity. Therefore, plasticizers are added to ethylcellulose to obtain the proper degree of suppleness, to lower the softening point, and to improve thermoplasticity.

Ethylcellulose is the most stable of the cellulose derivatives. It is resistant to alkalis, both dilute and concentrated, but is sensitive to acids. It takes up very little water from moist air or during immersion, and this evaporates readily leaving ethylcellulose unchanged. Light, visible or ultraviolet, had no discoloring action on ethylcellulose. Application of heat up to its softening point has little effect on ethylcellulose (Gurvinder et al., 1995).

Plasticizer

Triethyl citrate (TEC) and other citrate esters are used as plasticizers for coating applications. Its chemical names were known as follow;

(1) 2-Hydroxy-1, 2, 3-propanetricarboxylic acid

(2) Triethyl ester

The structural formula is presented in Figure 16.

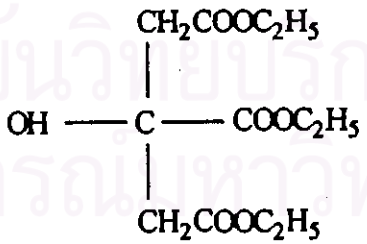

Figure 16. Structural formula of triethyl citrate (Wade and Weller, 1994).

Chemical formula and molecular weight of triethyl citrate is $C_{12}H_{20}O_7$ and 276.29 respectively. Triethyl citrate occurs as a bitter tasting, odorless, practically colorless, oily liquid and has boiling point at 288°C, density is 1.135-1.139. It is soluble 1 in 125 of peanut oil, 1 in 15 of water (about 6.5g/100ml). Miscible with ethanol (95%) and ether. Triethyl citrate and other citrate esters are stable if stored in a well-closed container in a cool, dry place.

Diethyl Phthalate is clear, colorless, oily liquid. It is practically odorless, or with a slight aromatic odor. It is bitter, disagreeable in taste. It is produced by esterification of phthalic anhydride (Wade and Weller, 1994).

The chemical names of diethyl phthalate is 1,2-Benzenedicarboxylic acid, diethyl ester or Ethyl-O-benzene-1,2-dicarboxylate which have empirical formula and molecular weight is $C_{12}H_4O_4$ and 222.24, respectively. The structural formula is shown in the Figure 17.

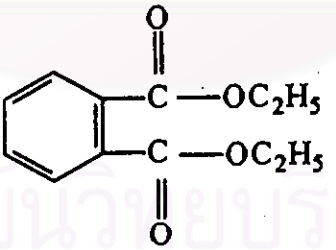

Figure 17. Structural formula of diethyl phthalate.

Diethyl phthalate has a boiling point of 295 °C. It can miscible with ethyl alcohol (95%), ether, and soluble in many other organic solvents but insoluble in water. The specific gravity of it is 1.232 at 14 °C. It is stable to light and high temperatures. However, when exposed to heat or flame, there is slight danger of fire since diethyl

phthalate can react with oxidizing materials. It should be stored in tight containers in a cool location. Diethyl phthalate can be used as a plasticizer for film coatings on tablets, beads and granules at concentrations of 10-30 %.

Castor Oil is the fixed oil obtained by cold expression from the seeds of *Ricinus communis* and contains 80 % ricinoleic acid triglyceride (Figure 18). It is a clear, almost colourless or slightly yellow, viscid liquid; odour, very slight and characteristic; taste at first bland, but afterwards slightly acrid.

$$CH_3(CH_2)_5CH(OH)CH_2-CH=CH(CH_2)_7COOH$$

Figure 18. Ricinoleic acid (Smolinkske, 1992).

Castor oil can soluble in 2.5 parts of ethyl alcohol (96%) and in ether, slightly soluble in petroleum spirit, miscible in all proportions with absolute ethanol and with glacial acetic acid.