CHAPTER I

INTRODUCTION

Because therapeutic range and duration of action of drugs are somewhat important for consideration in drug therapy. Therefore, sustained release products have been widely received a substantial attention in recent years.Sustained release dosage forms are developed for several reasons.The dosage forms are to extend the drug's activity throughout the interval period and the patient compliance increase. In addition the patient taked fewer dose per day and unwanted side effects occur less frequently. They may reduce unwanted toxic effects due to high peak concentrations. Several of drugs in conventional dosage from can be changed to sustained release dosage form to increase efficiency of the drugs. And sustained release dosage froms are important for patient that must be take the drug for a long period of time.

Multiple-unit dosage forms are ones of several sustained release dosage forms. Multiple-unit dosage forms could readily seperate into sustained release units throughout the GI tract after patients'ingestion.

The beneficial characteristic over any other form of sustained release products was obviously reflected by markedly reduced probability in occurance of locally irritating side effects of drug. And the dosage forms had no effect on gastrointestinal transit time.

The core of multiple-unit dosage forms or pellets are manufactured by many techniques. One technique is an extrusion and spheronization process. The pellets produced by the process have spherical particles, very uniform size, low friability, used for automated processes, etc. But the formulations and the conditions employed to prepare pellets are very important for extrusion and spheronization process.

The multiple-unit sustained release dosage forms manufactured by coating the drug contained pellets with GI fluid - insoluble film former would eventually control the drug release through the pore of polymer film by diffusion controlled processes. These film coated multiparticulate pellets could subsequently be filled into capsules or compressed into tablets as suitable.

This present work is to study some factors that had effect on the pellets produced by extrusion and spheronization process, the preparation of drug pellets by this process and the preparation of sustained release pellets by means of the fluidized bed coating technique.

The pellets were prepared by the extrusion and spheronization process using lactose and microcrystalline cellulose (Avicel PH101^{R}) as diluent. This study also investigated the effect of spheronizer speed,spheronization time, binder type,binder concentration and effect of water content.

Ethylcellulose was selected to be a coating polymer. Because it is probably the most widely used water insoluble polymer for film coating. Ethylcellulose is giving a satisfactory control of the drug release pattern as well as inexpensive and easy to prepare into a coating solution.

OBJECTIVES

The objectives of this research were;

1. To study the influence of spheronizer speed, spheronization time, binder type, binder concentration and amount of water on the appearance and physical properties of lactose-Avicel PH101^{R} placebo pellets using extrusion and spheronization process.

2. To prepare terbutaline sulphate pellets using extrusion and spheronization process.

3. To study the influence of amount of ethylcellulose and amount of hydroxypropyl cellulose in the mixture of hydroxypropyl cellulose and ethylcellulose on the terbutaline sulphate release from film coated pellets.

4. To determine the optimal level of ethylcellulose coating which exhibit a satisfactory *in vitro* release pattern.

5. To compare the release profiles of film coated terbutaline sulphate pellets capsule with a commercial product.

Pelletization by Extrusion and Spheronization Technique

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, referred to as pellets. Pellets range in size, typically, between 0.5-1.5 mm (Ghebre-Sellassie, 1989).

Pellets are of great interest to the pharmaceutical industry, especially for controlled-release technology in the delivery of drugs. They have flexibility in dosage form design and development, and improve the safety and efficacy of drugs. And pellets have many advantages over single unit dosage form (Ghebre-Sellassie, 1989).

They include :

a. Pellets offer significant therapeutic advantages over single unit dosage forms.Because they disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering drug bioavailability.

b. Pellets reduce variations in gastric emptying rates and overall transit times.So,intra-and inter-subject variability of plasma profiles are more minimum than single unit dosage forms.

c. High local concentrations of drugs,which may be irritative, can be avoided in pellets dosage forms.

d. Pellets are less susceptible to dose dumping than the reservoir-type, single-unit formulations.

e. Pellets composed of different drug entities can be blended and formulated in a single dosage form.

f. Two or more drugs,that may be incompatible,can be combined in a single dosage form by pellets dosage form.

g. Required release rate of the drug can be prepared by combination of pellets of different release rates.

Although variations in gastrointestinal emptying and transit time reduce in pellets dosage form, there are some factors that effect on gastrointestinal transit time. Some reports which concern with the factors are shown below.

Coupe, Davis and Wilding (1991) found that the gastric emptying of the tablet was less than that of the pellets. The small intestinal transit time of the single unit dosage form was less than that of the multiple units dosage form.

Davis et al. (1984) reported that the transit time of the pellets and tablet formulations were found to be highly dependent on food intake and there was a good correlation between transit times and the calorific value of the meal taken shortly before dosing.

Reilly, Wilson and Hardy (1987) found that the gastric emptying of multiparticulate dosage forms was influenced by the food content in the stomach at the time of dosing. Taking multiparticulate dosage form before a meal resulted in rapid initial gastric emptying which was approximately exponential. Administration of the particles during or

soon after the meal exhibited an approximately linear pattern of gastric emptying.The gastric emptying of sprinkling the particles onto the food was the same as gastric emptying of the particles in capsules.

Price, Davis and Wilding (1991) found that the gastric emptying of single and multiple unit dosage form were uneffected by fiber intake or a vegetarian or omnivorous diet.The small intestinal transit time of both the pellets and the tablet were always found to be slower in the vegetarians than omnivores. There were no large differences in colonic transit between the vegetarians and omnivores. Transit time in each region of the colon was highly variable. High fiber diets were not effect on the transit time.

Sustained release pellets preparations occurred in 1949. Smith Kline & French developed tiny drug pellets that could be load into the capsules. Small sugar particles were used as seed for coating with drug powder and excipient. And in 1964, Smith Kline & French used the other technique for preparing pellets. The technique was spray congealing process in which the drugs were dissolved or dispersed in a liquid material in the molten state to form a slurry, followed by atomization of the slurry into a low-temperature gas chamber until spherical congealed pellets were produced (Ghebre-Sellassie, 1989).

Processes that used to prepare pellets include :

1. Balling is the process in which finely divided particles are converted to spherical particles by continuous rolling or tumbling

motion.

2. Compression is the process in which mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. Infact,pellets produced by compression are nothing but small tablets that are approximately spheroidal in shape.

3. Extrusion and spheronization is the most wildly use process and will discussed in detail later.

4. Powder layering is the process in which involved layering a drug powder and excipients onto nonpareils using syrup as the adhesive solution. The process is the first technique for developing a sustained release dosage form in the coating pan.

5. Solution and suspension layering is the process in which layering a suspension or solution of drug onto a seed material. The process result in pellets that are uniform in size distribution and very good surface morphology.

6. Spray drying is the process in which drugs and excipients in solution or suspension form are sprayed into a hot air stream to generate dry and highly spherical particles.

7. Spray congealing is the process in which a drug is melted, dispersed and dissolved in hot melts of gums,waxes, fatty acid, etc., and is sprayed into an air chamber where the temperature is below the melting points of the formulation components, to provide, under appropriate processing conditions, spherical congealed pellets.

Extrusion and Spheronization Technique

Extrusion and spheronization is the process in which powder raw materials are converted into a plastic mass, using water or other solvents in conjunction with binding agents. This mass is extruded under pressure through a perforated screen. The extrudate is placed in the spheronizer in which extrudates are broken down. They are then rolled into spheres by centrifugal and frictional forces.

Advantages of Pellets Produced by Extrusion and Spheronization Process

Extrusion and spheronization process provide a versatile system for producing spherical particles. Spherical particles produced by extrusion and spheronization method have more good characteristic than spherical or granular particles produced by other methods(Reynolds,1970).

There are :

a. Pellets produced by the process are not required seed core.

b. Pellets produced by the process have spherical particles.

c. Extrusion and spheronization process gives a very uniform size of pellets. Other methods of spheronization produce random sized spheres which have to be carefully classified to obtain uniformity.

d. Pellets produced by the process have extremely low friability resulting in few fines and little associated waste.

e. Hardness measured in terms of compressive force necessary to fracture a particle is greater for pellets produced by the process

than for traditional granulations of similar size and formula.

f. The process is flexible in respect of sphere size which can be produced and is capable of high throughput and easy operation.

g. Spherical particles have good flow characteristic. These improved flow properties may be utilized in automated processes, and all techniques requiring exact metering of solids, as in tableting, capsule filling, powder packaging.

h. The more spherical the particle, the easier it becomes to apply a uniform layer. Thus,if the particle is a smooth sphere,economy in coating material is achieved, as less is required to fill irregularities in the surface.

i. High dose of active ingredients can be used by the process.

j. The application of the process is in the pharmaceutical, food, confectionery, agricultural and chemical products.

Extrusion and Spheronization Equipment

There are two important equipments that used to produce pellets by extrusion and spheronization process. The equipments are extruder and spheronizer. (Hicks and Freese, 1989)

1. Extruder

Extrusion is a method of applying pressure to mass until it flows through an orifice or defined opening.The products are called extrudates. The equipment that used in this method is extruder. Extruders have been grouped into the following general classifications.

1.1 Screw Extruder

Screw extruder utilizes a screw to develop the necessary pressure to force material to flow through uniform opening, producing uniform extrudates. Types of extruder are radial type and axial type (Figure 1). The screw extruder has three major zones that are defined by the principle mechanical operation being performed. Three major zones are feed zone, transport and compression zone and extrusion zone.

Feed zone is the area where material is first introduced into the extruder. It consists of a hopper to channel the flow of material into the chamber where the screws are located.

Transport and compression zone is the area where material is moved by screw from the feed zone into the compression zone. Most extruder manufactures have both single-screw and twin-screw machine designs. The advantages of twin-screw extruder are better transport into the extrusion zone and greater capacity per screw. Some extruders have vents in the compression zone to release the expelled gases from the processing environments.

Extrusion zone is the area where plastic mass is extruded and extrudates were recieved.

Screw design varies in accordance with how much compression is needed.A low pressure extruder may have regularly spaced

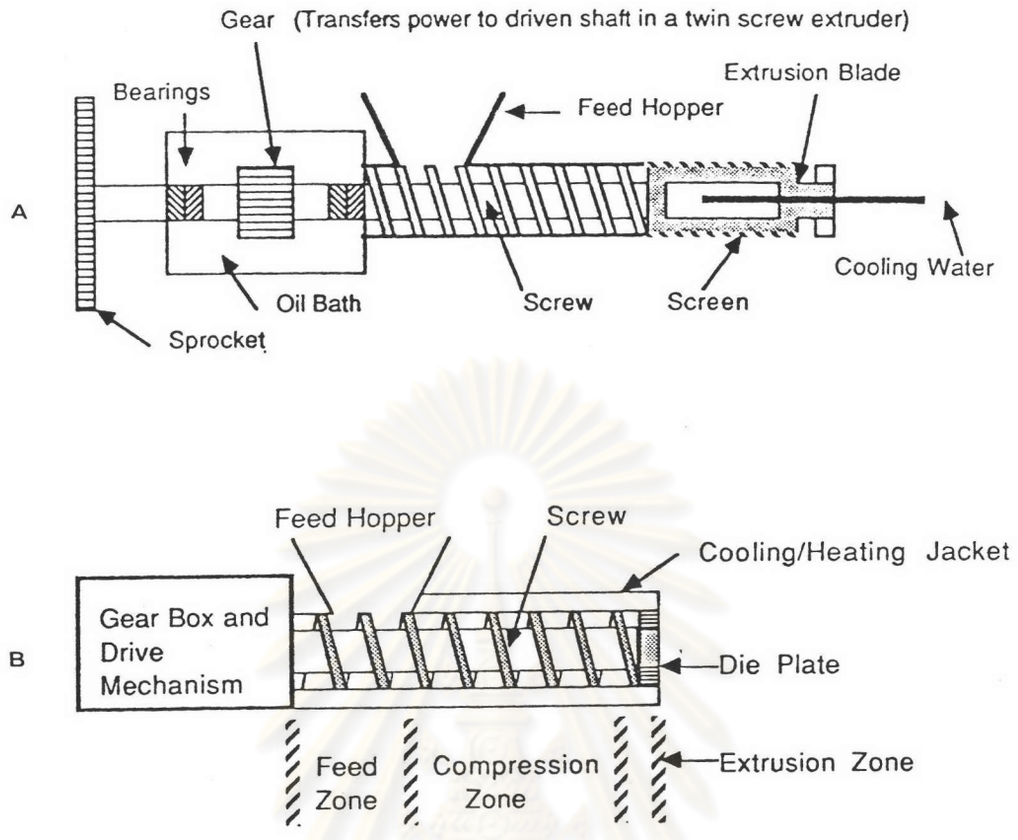


Figure 1 Schematic of screw extruder

A = radial type ; and B = axial type

screw flights which will give some compressions, but the main function of these flights is to transport the material down the barrel of the extruder. A high pressure extruder may have closer screw flights by decrease helix angle. Several types of screw extruders utilize an extrusion blade to create a wiping effect at the die plate. The die openings in the screen or die plate may be of several basic designs. The shape of the opening varies with the application. If a more dense product is needed, a thicker die plate or screen is required to withstand the greater extrusion pressure used.

Screw extruders are the only strictly continuous extrusion devices, since extrudate can exit in a smooth continuous flow.

1.2 Sieve-and Basket-Type Extruders

Sieve-type extruders have a chamber that contains the material to be extruded to plate or screen. Sieve extruders have a rotating or oscillating arm presses the damp material through a sieve or perforated screen. Short or long extrudates depend on the moisture content in the damp material (Figure 2).

Basket-type extruders are similar to sieve-type extruders except that the sieve or screen is part of a vertical cylindrical wall (Figure 2).

The extrudate falls vertically from the sieve plate of a sieve-type extruders, while in a basket-type extruders, extrudate

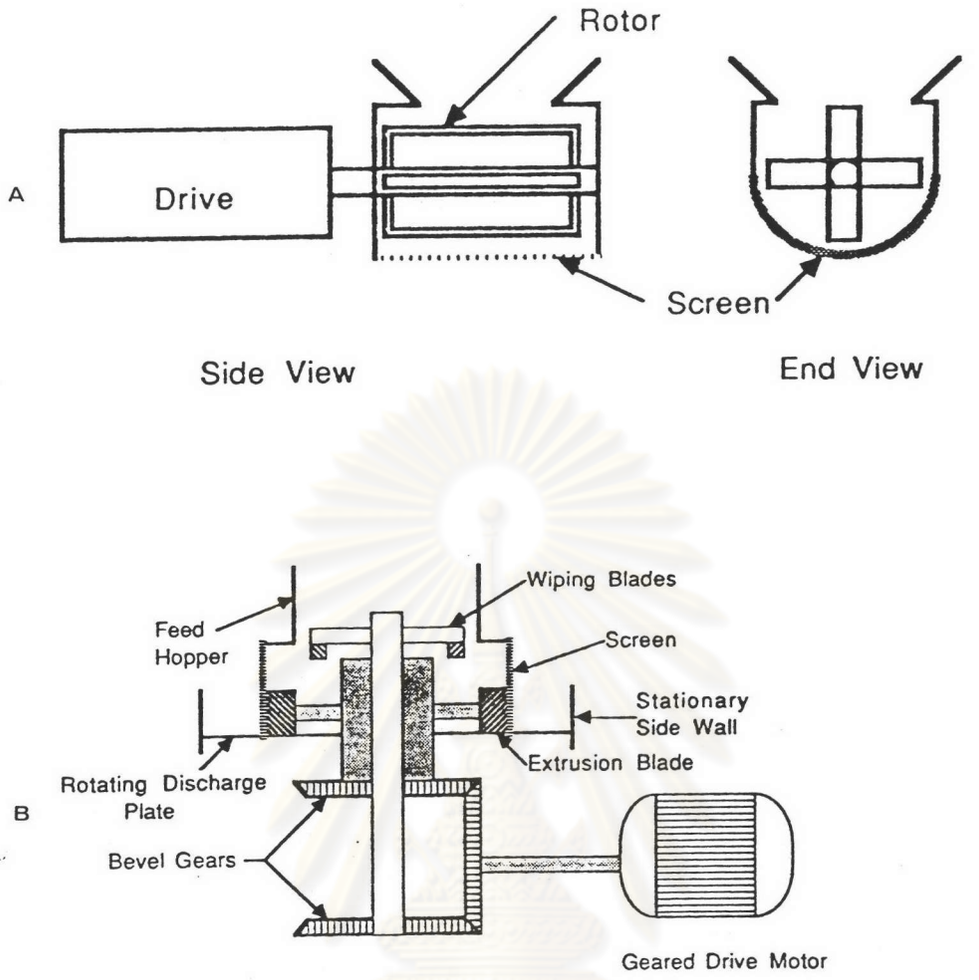


Figure 2 Schematic of sieve - and basket - type extruder

A = sieve type ; and B = basket type

is formed in the horizontal plane as it is forced through the vertical holes.

Sieve-type extruders give the least compaction of the other extruders, and therefore, the number of attractive applications for the extrusion technique is rather limited.Sieve-type extruders are used with moist materials to form granules suitable for feeding to tablet presses.

1.3 Roll Extruder

Roll extruders are known as pellet mills.Roll extruders are operated by feeding material between a roller and a perforated plate or ring die and moist materials are forced through the die. Roll extruders divided into three types (Figure 3).

Type 1: A ring die rotates around one or more rollers installed inside the cylindrical die chamber, each of which rotates on its stationary axis. Multiple rollers can be used to distribute or balance the forces and to increase capacity. All rotating components turn in the same direction. Feed material is introduced onto the inside surface of the ring die and pressed outward by the rollers. The orientation of the perforated cylinder is horizontal, sometimes with a slight inclination to facilitate feeding.

Type 2: One or more rollers are mounted on the outside of the ring die and material is fed from a hopper, occasionally with a

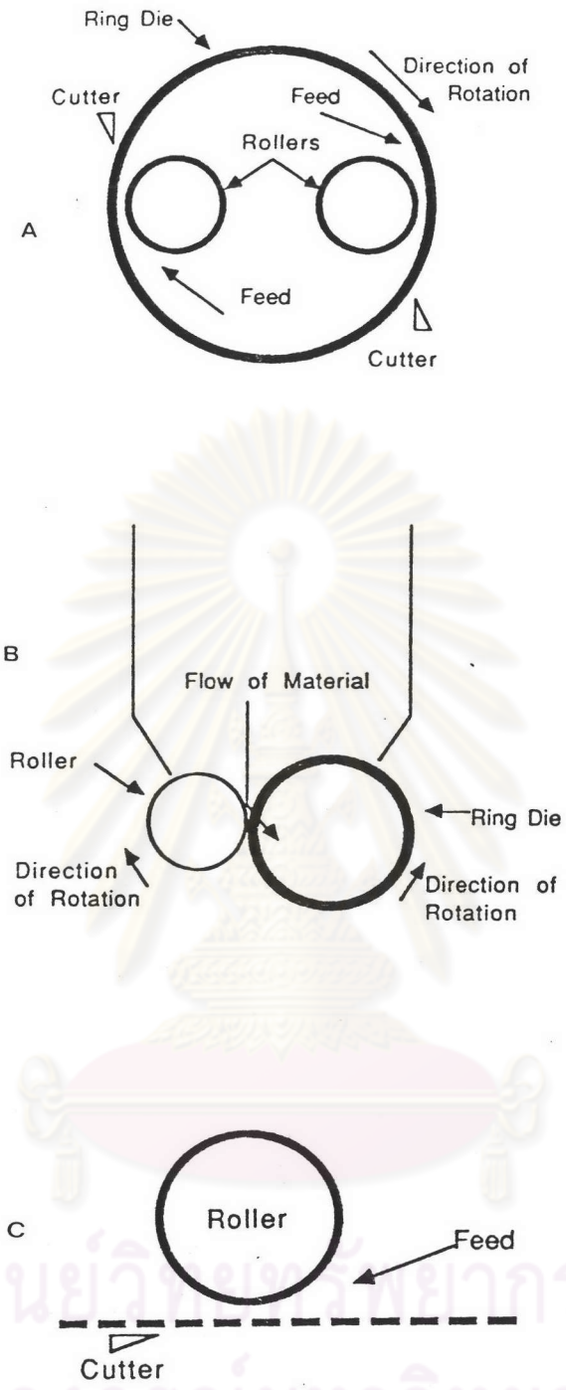


Figure 3 Schematic of roll extruder

A = type I ; and B = type II ; and C = type III

screw, into the region between the roller and the die. Material is extruded into the center of the ring die and flows out one end. The roller and the die move in opposite direction. The orientation of the ring die is horizontal or slightly inclined.

Type 3: Rollers are positioned above and roll along the surface of a flat, stationary die plate. The device resembles a muller with a perforated base, rather than a solid one. Feed material is charged into the top of the chamber and is pressed out the bottom through the die plate.

1.4 Ram Extruder

Ram extruder is the oldest type of extruder. A piston riding inside a cylinderis used to compress material and force it through an orifice on the forward stroke. Each return stroke allowance material to fall into the chamber. The important process variables are the length of the piston stroke, the frequency or period between stoke, the cavity is filled on the backstroke, flow characteristic of the material and configuration of the channel (Figure 4).

2. Spheronizer

Spheronization is a method which begins with damp extrudates. The damp extrudates are broken into uniform lengths almost instantaneously and are gradually transformed into spherical shapes. The products are called pellets. The equipment that used in this process is spheronizer.

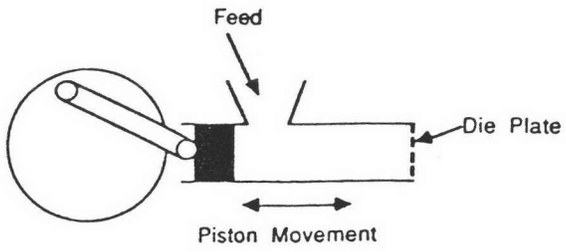


Figure 4 Schematic of ram extruder

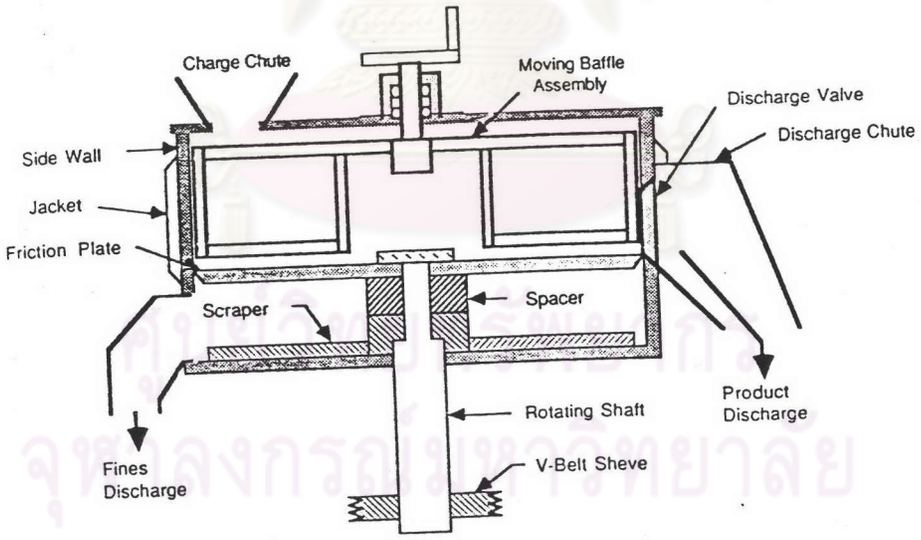


Figure 5 Schematic of spheronizer

Spheronizer consists of a vertical hollow cylinder with a horizontal rotating disk located inside. Extrudate is charged onto the rotating plate and broken into short segments by contact with the friction plate, by collisions between particles, and by collisions with the wall. The most important component is the friction plate which can have a variety of surface textures designed for specific purposes. The most common pattern is cross-hatch design plate which the grooves intersect each other at 90^{o} angles. A possibly more efficient pattern is the radial design plate, which the grooves emanate from the center like spokes of a bicycle wheel.Other plate designs used a ring of teflon or similar material at the outer circumference of the plate to prevent material build up along the outside edge and to increase the upward motion of the particles after they collide with the wall. The proper motion of the moving aggregate of particles should resemble a twisting rope that seem to turn at an angular velocity significantly less than that of the spinning friction plate (Figure 5).

Excipient of Pellet Dosage Form

The excipients used in pellet dosage form are the same as those employed in tablet or capsule formulations.Examples of excipients that are commonly used during the manufacture of pellets are given in Table 1 (Harris and Ghebre-Sellassie, 1989).

1. Filler

Fillers are water soluble or insoluble substances that are

Table 1 Example of commonly used excipient

Filler	Calcium sulfate
	Dibasic calcium phosphate
	Lactose
	Mannitol
	Microcrystalline cellulose
	Starch
	Sucrose
Binder	Gelatin
	Hydroxypropyl cellulose
	Hydroxypropylmethyl cellulose
	Methylcellulose
	Polyvinylpyrrolidone
	Sucrose
	Starch
Lubricant	Calcium stearate
	Glycerin
	Hydrogenated vegatable oil
	Magnesium stearate
	Mineral oil
	Polyethylene glycol
	Propylene glycol
Separating agent	Kaolin
	Talc
	Silicon dioxide
Disintegrant	Alginates
	Croscarmellose sodium
	Crospovidone
pH adjuster	Citrates
	Phosphates
Surfactant	Polysorbates
	Sodium lauryl sulfate
Sheronization enhancer	Microcrystalline cellulose
	Microcrystalline cellulose/sodium carboxymethyl cellulose
Glidant	Colloidal silicon dioxide
	Magnesium stearate
	Starch
	Talc
Release modifier	Ethylcellulose
	Carnauba wax
	Shellac

incorporated into pellet formulations, mainly to add bulk. Some of the fillers used in the pellet formulations are suitable for adding bulk to the finished product, and adding features that facilitate pellet formation. Microcrystalline cellulose is usually used as a filler. Selection of fillers depend on dose,properties of the drug and fillers and manufacturing process.

2. Binder

Binders are adhesive materials that are essential components of pellet formulations to bind powders and maintain integrity. Binders that are added as a solution are more efficient than dry mixing followed by liquid addition. Binders that are dissolved in aqueous solvents are more preferred and commonly used system in pelletization than binder are dissolved in various organic solvents. Since binders differ in their solubility and binding capacity, selection of the best binder for a given pellet formulation is very important. The most factors that have effect on the selection of a binder are the physico-chemical properties of the drug and the manufacturing process. The binders are usually applied in the concentration range of 2-10% w/w. The amount of binder should be optimized so that the pellets are durable and not friable and maintain the other desirable properties of the pellets, such as releasing the drug at the intended rate.

3. Lubricant

Lubricants are substances that are incorporated in pellet

formulations to reduce the coefficient of friction between individual particles or between the particles and the surface of the processing equipment. Lubricants include liquids and solids. Because most liquids have very low film strength, their specific application as lubricants is limited. For extrusion process, the lubricants allows the extrudate to pass through exit the extruder without adhesion to the equipment and prevents the extrudate from sticking to one another.For spheronization process, the lubricants serves to prevent adhesion of the spheres to the wall or friction plate of the spheronizer and to one another. Because excessive lubrication during spheronization can lead to rotation of the plate without movement of the pellets. The amount of lubricant should be determined carefully in order to promote excellent pellet turnover that eventually produces smooth and spherical pellets.

4. Separating agent

Separating agents are materials that adsorb on surfaces and promote the separation of pellets into distinct units during or pelletization process. Separating agents are used in dry form during spheronization to prevent adhesion of the spheres to the friction plated and the cylindrical wall of the spheronizer.

5. Disintegrant

Disintegrants are substance which promote the disruption of solid dosage form such as tablets, pellets granules, capsule plugs, or any other agglomerated materials to regenerate the primary particles

that were originally compacted or agglomerated to produce the dosage form. Disintegrants provide a larger surface area to the dissolving fluid so they enhance the dissolution of the drug. Disintegrants are widely used during compaction (compression and spheronization) which pressure is applied on the formulation to provide very dense pellets. Disintegrants must be very efficient in order to counteract both the effect of the binder and the forces of compaction,if immediate release and rapid dissolution of the active is desired.

6. pH Adjuster

pH adjusters are substances that are incorporated in pellet formulations to influence the microenvironment of drug molecules for a variety of reasons. Buffer systems are added to the core formulation to maintain the pH of the core in a range for drug stability and to enhance the dissolution rates of drugs which solubilities are influence by changes in the pH.

7. Surfactant

Surfactants are substances that are incorporated in pellet formulations to improve wettability and enhance dissolution rates of poorly soluble and hydrophobic drug.Surfactants reduce the strength of the initial bond formed between the primary particles and make the forming pellets friable. As a result, incorporation of surfactants in pellet formulations should be avoided unless it is absolutely essential for the production of pellets that posses specific properties.

8. Spheronization Enhancer

Spheronization enhancers are substances that produce spherical pellets during spheronization process.Spheronization enhancers have plasticity and binding properties that are essential for pellet strength and integrity. During spheronization, extrudates that are rigid, but not plastic, result in the formation of dumbell-shaped pellets or a high proportion of fine relative to spherical pellets. On the other hand, extrudates that are plastic, but not rigid, tend to agglomeration and form excessively large spherical balls.

9. Glidant

Glidants are substances that improve flow properties of the powder and granule by reducing interparticulate friction.Generally, hydrophilic glidants are incorporated to improve the flow of hydrophobic powder, while hydrophobic glidants are more effective for hydrophilic powder.

10. Release Modifier

Release modifiers are substances that provide a multitude of release profiles could be designed.

Steps in Prepared Spherical Granules

There are five steps in prepared spherical granules by extrusion

and spheronization process (Figure 6) (Reynolds, 1970).

1. Dry Mixing

The raw materials that include active ingredients and excipients are mixed in mixers.

2. Wetting

The powder that is wetted by suitable solvent or binding solution results in the formation of a plastic mass for extrusion. The mixture in extrusion must be a little wetter than in moist granulation, and the operation is done, is powerful, kneading-type mixers.

3. Extrusion

The plastic mass is extruded under pressure through the orifice of the perforated screen or die. The cylindrical spagetti-like extrudates are obtained. The diameter of extrudate is limited by size of orifice of the perforated screen or die. Screw extruder is used to produce extrudate more than the other extruder. Axial type and radial type are two types of screw extruder. They consist of the same basic machine but axial type has shorter feed screw, with parallel to the perforated die plate.In radial type,the perforated die plate is radial to the feed screw. Pressure on material using axial type is greater than that using radial type.Axial type give a higher density extrudate than radial type.

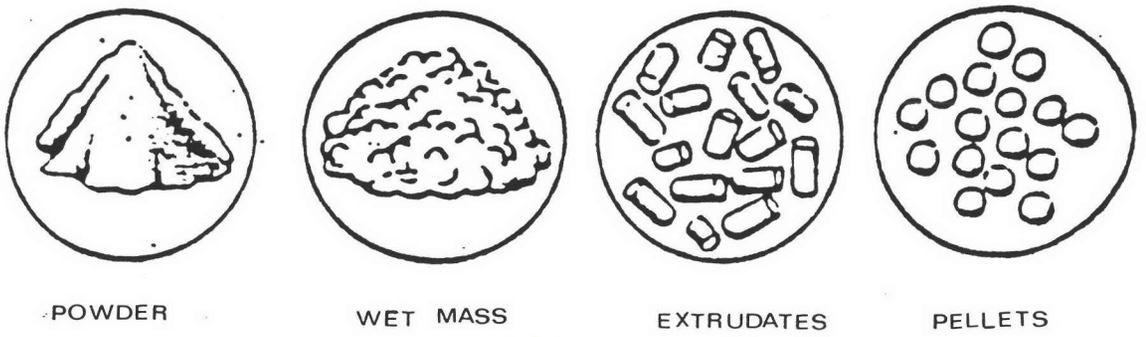


Figure 6 Stages of production from powder to spheres

Figure 7 Shape of moving mass in spheronizer

A = top view ; B = cross-section

4. Spheronization

The extrudates are transformed into spherical particles or spheroids in two phases. Begining of the extrudates are broken into pieces where the length must ideally be equal to the diameter. The latter, the cylindrical pieces are transformed into spheres by the force of friction and centrifugal.

The extrudates are fed onto the revolving spheronizer plate, where it is disposed against the walls in an annular or doughnut-like shape with a quadrant cross section. This doughnut appears to be twisting like a woven rope. This characteristic deposition of the material is due to the transport of the pellets centrifugally to the peripheral of the plate where their residual momentum causes them to rise up the stationary wall and then to fall within or over the mass of pellets as their momentum are dissipated. Accelerating and deaccelerating particles within the mass form a pattern of velocity gradients which result in the rope-like formation (Figure 7).

5. Drying

The last step is that of drying the spherical granules, it is done, as in granulation, in ventilated drying ovens or in fluidized bed system.

Influence of Extrusion and Spheronization Technique on Pellet Properties

Pellet that are produced by extrusion and spheronization technique are better than pellets that are produced by the other techniques. But this technique has many factors that effect on the pellet properties. So it must be carefully consideration about these factors.The factors are devided into processing factors and formulating factors. Processing factors include wetting, extrusion, spheronization and drying. Formulating factors include active ingredient, excipient, liquid granulation and others. There are many reports that concern with effect of many factors on pellet properties.

Woodruff and Nuessle (1972) noticed that spheronizer speed had effect on the granule properties. With the specific base formulation, increased spheronizer speed produced more spherical granules. Granules obtained by extrusion and spheronization process were more uniform,both in shape and particle size distribution,than granules from conventional granulation methods but were less uniform than nonpareil beads.

Jalal, Malinowski and Smith (1972) showed that the spheronizing process resulted in an improved granulation flow rate and narrow particle size distribution as compared to a conventionally processed wet granulation. Pelletizing technique might provide an efficient, reproducible size distribution and minimal amount of fines. Changing of size distribution was occurred with increasing spheronization time. Tablet hardness and disintegration time of tablet prepared by pelletizing techniques were lower than these of tablet prepared by conventional wet

granulation techniques.

Malinowski and Smith (1974) studied about effect of spheronization process variables on selected tablet properties. The process variables had no effect on tablet disintegration time.Increasing extruder screen size resulted in increased tablet hardness, whereas increasing the amount of granulating solvent,the spheronizer speed or the spheronization time resulted in decreased tablet hardness. The dissolution rate was found to decrease as the amount of granulating solvent added were increased.

Malinowski and Smith (1975) studied about effect of process variables on the properties of a granulation.An increased water level decreased the maximum extruder screen temperature whereas an increased extruder speed increased the maximum extruder screen temperature. The maximum product yield would result from a high water content and a low screen size. The maximum flow rate would be obtained at high levels of water content, spheronizer speed and spheronization time. The high values for bulk density would obtained at a high water content, spheronizer speed and spheronization time. A low water content, small screen size and high spheronizer speed would resulted in smaller particles in the final granulation.Lower levels of fines may be obtained at high water content and spheronization time but low screen size and spheronizer speed. An increased water content, spheronizer speed or spheronization time resulted in granulations with a decreased granule friability.

O'Connor and Schwartz (1985) studied about effect of drug, diluent and drug-diluent ratio on properties of pellets. The results showed that Avicel PH101^{R} appeared to be the ideal matrix material for the preparation of pellets containing low dose medicaments. Conversely, Avicel RC581^{R} and Avicel CL611^{R} appeared to be more applicable to the preparation of pellets containing a high dose of drug. Increasing the drug concentration resulted in smaller particles for the pellets prepared with Avicel PH101^{R} and larger particles for those prepared with Avicel RC 581^{R} and Avicel CL611^{R}. The friability appeared to increase with increasing drug concentration. Drug release was found to vary with the drug, the diluent and the drug-diluent ratio. It appeared that the Avicel^{R} had properties that permit spheronization as single component and in binary mixtures of drug and diluent using only purified water as the granulating liquid.

Remon and Schwartz (1987) studied about effect of process variables on granule properties prepared with extrusion and spheronization technique. The results were that increased in quantity of granule solution and sieve size obtained larger granules with reduce friability. Increasing massing time produced granules with reduce friability and more narrow particle size distribution.Fluid bed drier produced smaller and less friable granules than using drying oven.

Chariot, et al.(1987) found that spheronization time and spheronizer speed had effect on yield of granules. Spheronizer load had little effect on the yield but there were strong interactions with spheronizer speed and spheronization time.Extrusion speed had no effect

on the yield.

Ghali, Klinger and Schwartz (1989) found that the solubility of the drug, the grades of microcrystalline cellulose and dissolution medium had effect on drug release from beads. The drug release of more soluble drug was faster than that of less soluble drug. When water was used as the dissolution medium, drug release from Avicel RC581^{R} formulation was slower than that from Avicel PH101^{R} formulation.And dissolution of drug decreased as the Avicel RC581^{R} level increased. If acid was used as the dissolution medium,the drug release was found to be nearly the same from different type and ratio of two grades of microcrystalline cellulose.

Lovgren and Lundberg (1989) found that increased amount of added liquid, increased wet mixing time, increased peripheral velocity and decreased amount of extrudate on the frictional plate had effect on the shape of the pellets by increased of sphericity.But the extruder speed did not seem to influence the degree of roughness.

Zhang, Schwartz and Schnaare (1990)studied about bead properties which were prepared by pan method and extruder/spheronizer method. The results indicated that microcrystalline cellulose beads were successfully produced by both methods, whereas the traditional starch/ sucrose beads could not be processed by the spheronizer.The dissolution of drug from beads made in the pan was faster than the dissolution from beads made by the spheronizer.Drug release from spheronizer beads was described using the pore controlled release mechanism and the

square root of time relationship,but drug release from pan beads did not fit this square root model because they were the disintegrating beads.

Millili and Schwartz (1990) studied about effect of ethanol/ water mixture as a granulating liquid on the physical properties of pellets. The results indicated that a formulation of only micro-crystalline cellulose granulated with 95% ethanol could not be processed into pellets.Neither the same binary mixture nor a formulation of neat microcrystalline cellulose could be processed into pellets when granulated with absolute alcohol. Both of them could be process into pellets when granulated with water. Pellets granulated with water exhibited poor compressibility, whereas the 95% ethanol granulated pellet formulations were reasonably compressible, again indicating a difference in bonding strength. The 95% ethanol formulated pellets immediately and completely disintegrated in the dissolution media resulting in almost complete release. And particle size of the pellets had no effect on dissolution release rate.But the 100% water granulated pellet system remained intact during at least 12 hours of dissolution test resulting in a slower drug release. So the pellets showed a difference in dissolution release rates with varying particle size.

Zhang, et al.(1991)found that an identical coating level, drug release was always faster from pan beads than from spheronizer beads because of the different thickness of the coating, resulting from the different sphere density due to the spheronization method.The critical coating level was found to be inversely proportional to sphere size and sphere density, which may be mathematically predictable. The drug

release mechanism from beads was dependent on the coating level. After the critical coating level,which was a coating level that drug release mechanism becomes completely barrier controlled release of drug that may be described by zero-order kinetics. Pore controlled and barrier controlled mechanisms were involved in drug release from spheronizer beads at the different level of coating. But disintegration, pore controlled and barrier controlled machanisms were involved in drug release from pan beads at the different levels of coating.

Funck, et al. (1991) studied about effect of binder on beads with high drug levels. The results indicated that beads from some formulations were probably arranged in the closest packing and narrow particle size distribution. Beads with binder in the formulation had low friability except the beads containing PVP.The results of dissolution testing showed that beads with carbomer, hydroxypropylcellulose and methylcellulose remained intact but beads with starch, carboxy methyl cellulose, PVP and the control did not.

Hosznos, Langer and Gyarmathy (1992) studied about effect of process variables on size characteristics and moisture content decrease of pellets. They found that extruder speed had not significant effect on size,size distribution characteristics and moisture content decrese characteristics of the produced pellets. The spheronization time had significant effect on yield size of pellets and moisture content decrease both resulting in a decrease. The spheronizer load decreased small size of the pellets. The spheronizer speed and moisture content decreased yielded and small size of pellets. The first interaction of

spheronizer speed and spheronizer load, spheronizer speed and moisture content and spheronizer load and moisture content had significant effects in all cases as well.

Elbers, Bakkenes and Fokkens (1992) found that the best spheres were formed using mixtures with a composition reflected by the ascending part of the plasticity curve directly after this dip. The amount of granulation liquid is related to the amount of Avicel RC 581^{R} in the mixture.

Bianchini, et al. (1992) studied about pellets which contained pH adjuster. The results showed that increasing of spheronizer speeds led to a decrease in the mean particle size of pellets and higher granule density.Increasing the spheronization time was found to produce narrow particle size distribution. The incorporation of the salt, that d-Indobufen release was more rapidly,was found to produce wider particle size distribution but did not influence the densities of the granules. The present of acid and buffer in the pellets to slow the drug release rate, particularly the fumaric acid appeared to be more effective.They found that the ethylcellulose pellets were generally smaller, less uniform, softer and more friable than the acrylic resin pellets. The incorporation of insoluble polymers in the fumaric acid containing formulation determined a further decrease in the release rate.

Doshi and Shrivastawa (1993) studied about effect of moisture content,spheronizer speed and spheronization time on the particle size distribution and sphericity of pellets. They found that extrudate

suitable for spheronization when its moisture content was maintained within a good range. The yield increased with increasing in moisture content. As the spheronizer speed was increased, the quantity of the small size decreased. An increased in spheronization time or higher moisture content improved the degree of spheronization.

Newton, Chow and Jeewa (1993) found that a number of variables could influence the quality of spherical granules prepared by extrusion /spheronization. One variable was the grade and type of commercially available microcrystallins cellulose. Another variable was different bands of the same grade. The same grade was often available from more than one manufacturer, as in the case of Avicel PH101^{R}, Emcocel^{R} and MG100. The moisture content also had effect on the spherical granules prepared by extrusion/spheronization.

Kleinebudde and Lindner (1993) found that the screw speed was an important variable for the steady state mass and the passage time through the extruder. In addition, the water content of the extrudate had the greatest influence on the important extrusion parameters.Higher water contents resulted in smoother masses which lead to lower pressure, lower power consumption and lower temperature. When using a twin screw extruder in a one-step granulation/extrusion process it was the most important to control the water content.

Baert and Remon (1993) studied about influence of amount of granulation fluid on the drug release rate from pellets made by extrusion/spheronization. A slower release rate,increasing in hardness

and density were observed with increasing amount of granulation liquid. A sphere with a smooth surface was obtained by higher amount of granulation liquid.But pellets produced from lower amount of granulation liquid was not round and folding occurred. Possible mechanisms for formation of a cavity during extrusion and spheronization were formed from the plasticine extrudate. The steps followed as : extrudate, rope, drum-bell, sphere with a cavity outside, and sphere.

Hileman, et al. (1993) studied about effect of process variables on high dose pellets development by an extrusion/spheronization process. They found that Avicel^{R} concentration significantly increase the yield in the desirable particle size range and increase density. Spheronizer speed and spheronization time increase density and improve the shape score. But wet massing time, feeder speed and extruder speed did not have significant effects on the fraction of pellets in the desirable particle size range, density and pellets shape.

Batailie, et al. (1993) studied about effect of spheronizer speed and drying conditions on the physico-mechanical properties of Avicel PH101^{R} and lactose granules. The results indicated that increased in spheronizer speed gave decreased in porousness and the average diameter of the pore,smooth surface granules and increased in hardness of the granules. The porousness and the average diameter of the pores of the granules dried by microwave were higher than those of granules dried in an oven. And the granules dried with microwave had more heterogeneous surface condition, with large crevice-cavities compared to those dried in an oven.

Goskonda and Upadrashta (1993) found that Avicel PH101^{R} and chitosan could not produce beads, but Avicel RC591^{R} and chitosan could. When higher viscosity grade of chitosan was used to produce bead, bead sphericity was decreased and surface roughness was increased. The results of various chitosan contents in the formulation were low friability and narrow size distribution. Increasing amounts of chitosan (Seacure^{R}342) slowed the release in acid media but enhanced it in water. When dissolution was conducted using the paddle method in acid media, drug release was faster than using the basket method in acid media.

Ku, et al.(1993) studied about splitplot factorial design which was applied to optimize the levels of process variables for bead manufacture using extrusion/spheronization technique. They found that the yield of desirable size beads was significantly affected by water level, water temperature, extruder speed, spheronizer speed and spheronization time. In addition, the interaction of water level with extruder speed, spheronizer speed with spheronization time were also significant. The optimal processing conditions for the scale-up batches were reproducible.

Goskonda, Hileman and Upadrashta (1994) studied about effect of type and concentration of polymer, type and concentration of acid, drug and plasticizer concentration and spheronization time on physical properties of matrix controlled release beads. They found that polymer type and concentration had effect on dissolution. Eudragit RS 30 D retarded drug release more than Aquacoat ECD-30. Capsule fill weight was expectedly affected by changing drug and polymer concentrations,

acid type and spheronization time. Polymer type, drug and acid concentration had effect on yield of 14/20 mesh beads. Acid type and concentration significantly affect pH. Acid and drug concentration and spheronization time had effect on percent friability.

Pellet Manufacture for Sustained Release

Pellets produced by extrusion and spheronization technique have many advantages over pellets produced by the other techniques. There are two systems for preparing sustained release pellets that are produced by this technique. One system is matrix system using suitable materials such as polymers, lipid excipients. The polymers are such as ethylcellulose, polymethacrylate and the lipid excipients are such as carnuba wax, cutin. The other is membrane system using film coating materials such as ethylcellulose, polymethacrylate. And there are many equipments that are used for film coating process such as sugar coating pan, fluidized bed system, Glatt rotogramulator. But fluidized bed system is a method that would like to used to prepare sustained release pellets.

Pharmaceutical Oral Solid-Dosage Forms of Coated Pellets

A number of oral solid-dosage forms have been produced in the form of coated pellets that can be filled into hard gelatin capsules or compressed into tablets.

Evaluation and Characterization of Pellets

There are many methods that used to evaluate pellets such as particle size distribution, surface area, porosity, density, hardness and friability (Mehta, 1989).

1. Particle Size Distribution

It is essential that particle size distribution should be as narrow as possible because :

a. A narrow particle size distribution will ensure minimum variation in coating thickness throughout the batch of pellets and uniform performance of pellets within a batch.

b. During capsule filling operations or the compression of pellets into tablets, segregation may occur if the particle size distribution is too wide, leading to variations in the content uniformity.

c. A narrow particle size distribution facilitates blending process if blending of different types of pellets or different batches of pellets is required.

Particle size distribution is determined by :

1. Sieving

Sieving is the most widely used method for measuring

particle size distribution of pellets, because it is inexpensive, simple and rapid, with little variation among operators. The disadvantages of sieve analysis include blending of screens and inability of sieves to detect variations in the shape of particles.

2. Microscopy

Microscopy is a direct method for determining particle size distribution of pellets, Two types of microscopy are optical microscopy and scanning electron microscope. Both types of microscopic techniques provide valuable information, such as presence of aggregates which may not be detected by sieve analysis. But they are tedious, since a large number of particles need to be measured individually in order to create a size frequency distribution plot. And considerable variation among the generated data is possible among operators.

2. Surface Area

Surface area is a important factor because it has effect on the release rate of pellets. Because the thickness of the film applied to pellets in a substained release type dosage form dictates the rate at which drug is released from the coated pellets, the reproducibility of the surface area to be covered from batch to batch can be required.Three methods of measuring surface area of pellets are mathematical calculation, gas adsorption and air permeability.

3. Porosity

Porosity of pellets can affect the capillarity action of the dissolved drug and, consequently, influence the rate of release of drugs from the pellets. It also affects film deposition and formation during coating. The porosity can be determined by scanning electron microscopy or mercury porosimetry.

4. Density

Density should be not variation because :

a. Most pellets are filled into hard gelatin capsules volumetrically,using automated capsule filling machines. If the density of pellets vary significantly from batch to batch, the potency of the finished capsule will also vary.

b. Any significant variation in the density of pellets will affect the batch size determinations in the coating equipment.

c. If mixing of different types of pellets or different batches of pellets in necessary prior to filling them into capsules or prior to tableting, it is advisable and may be necessary not only to have similar densities but also reproducible density from batch to batch.

Tapped density is indicative of the packing properties of particles and is greatly influenced by the diameter of spherical seeds or pellets. It can be measured by using an automated tapper.

True density indicates the extent of densification or compactness of sustances and is influenced by the diameter of spherical

pellets ot a lesser extent. It can be determined by an air comparison pycnometer or by solvent displacement method.

5. Hardness and Friability

It is necessary to determine hardness and friability of pellets. Because hardness and friability of pellets can withstand handling, shipping, storage, and other processing such as coating. Hardness and friability measurements for pellets may not be determined accurately. Because instruments such as the Kahl pellet hardness tester provide relative hardness values, and a friabilator may be employed for generating the friability index.

Sustained Release Pellet Using Coating Techniquein Air Suspension System

Coating of pharmaceutical solid dosage forms provide into two types. There are sugar coating and film coating (Porter and Bruno,1990).

Film coating is quite a complex process that draws on technologies associated with polymer chemistry, industrial adhesives and paints and chemical engineering. Film coating can be simplified to represent one that involves the application of thin polymer based coatings to an appropriate substrate such as tablets, beads, granules.

Film coating process has many reasons such as:

a. Improved qualities of the product

b. Masking of unpleasant taste and odor

c. Enabling the product to be more easily swallowed by the patient.

d. Facilitating handling, particularly in high speed filling or packaging lines.

e. Improving product stability

f. Modifying drug release characteristic such as enteric coating and sustained release coating.

Film Coating Technique for Sustained Release

Film coating technique can be effectively used to sustained the release of the active ingredient from a pharmaceutical solid dosage form. This technique provide into film coating formulation and film coating equipment.

Film Coating Formulation

The essential components of a typical film coating formulation are polymer, plasticizer and solvent.

Polymer or film former is the major ingredient in the coating formulation. The characteristics of a polymer that are important in helping to decide its suitability in a particular coating formulation are solubility characteristics, coating solution viscosity,permeability characteristics and mechanical properties. Common polymers used in film coating formulations for sustained release for example are ethyl-

cellulose, polymethacrylate, etc.

Plasticizer is necessary for film coating formulation. Plasticizer reduces the bonds and increases the distances between the polymer chains. In providing more space for the polymer molecules to move around, the resultant mass is softer and more easily deformable. The effects of these changes is to reduce the tensile strength of the coating and reduce the elastic modulus (increase elasticity) of the coating. Typical plasticizers used in film coating formulation are glycerin, propylene glycol, polyethylene glycols, triacetin, acetylated monoglycerides, citrate esters or mineral oil.

Solvent is important for film coating formulation. Typical solvents that have been used in film coating formulation are alcohols, ketones, esters, chlorinated hydrocarbons or water.

For sustained release dosage form, tablets and multiparticulates are used as substrates. Multiparticulates have minimization of risk of dose dumping. Multiparticulates are such as drug-loaded beads, granules, crystals, powder.

Film Coating Equipment

Film coating equipments are sugar coating pan, Glatt roto-granulator and fluid bed system. However, fluid bed equipment is suitable for sustained release coating.

Fluidized bed system is a bed of solid particles with a stream of air or gas passing upward through the particles at a rate great enough to set them in motion. The bed is like a liquid which creates the potential for improved mixing. The surface area of fluidized particles is large, which improves heat transfer, reduces process time. and imparts reproducible operating parameters. Therefore, the primary factor influencing a fluidized-bed process is airflow (Parikh, 1991).

There are many types of fluidized bed which concern with airflow (Figure 8) such as :

An expanded bed is formed when the gas or airflow rate increases and particles move apart.

A slugging bed is a fluid bed in which air bubbles occupy entire cross sections of the vessel and divide the bed into layers.

A boiling bed is a fluid bed in which the air or gas bubbles are approximately the same size as the solid particles.

A channeling bed is a fluid bed in which the air or gas forms channel in the bed through which most of the air passes.

A spouting bed is a fluid bed in which the air forms a single opening through which some particles flow and fall to the outside. A spouting bed principle is successfully implemented for coating in Wurster's process.

An aggregative or bubbling fluidized bed is occurred at higher airflow rate, agitation becomes more violent, the movement of solids becomes more vigorous and not expand much beyond volume of the bed at minimum fluidization.

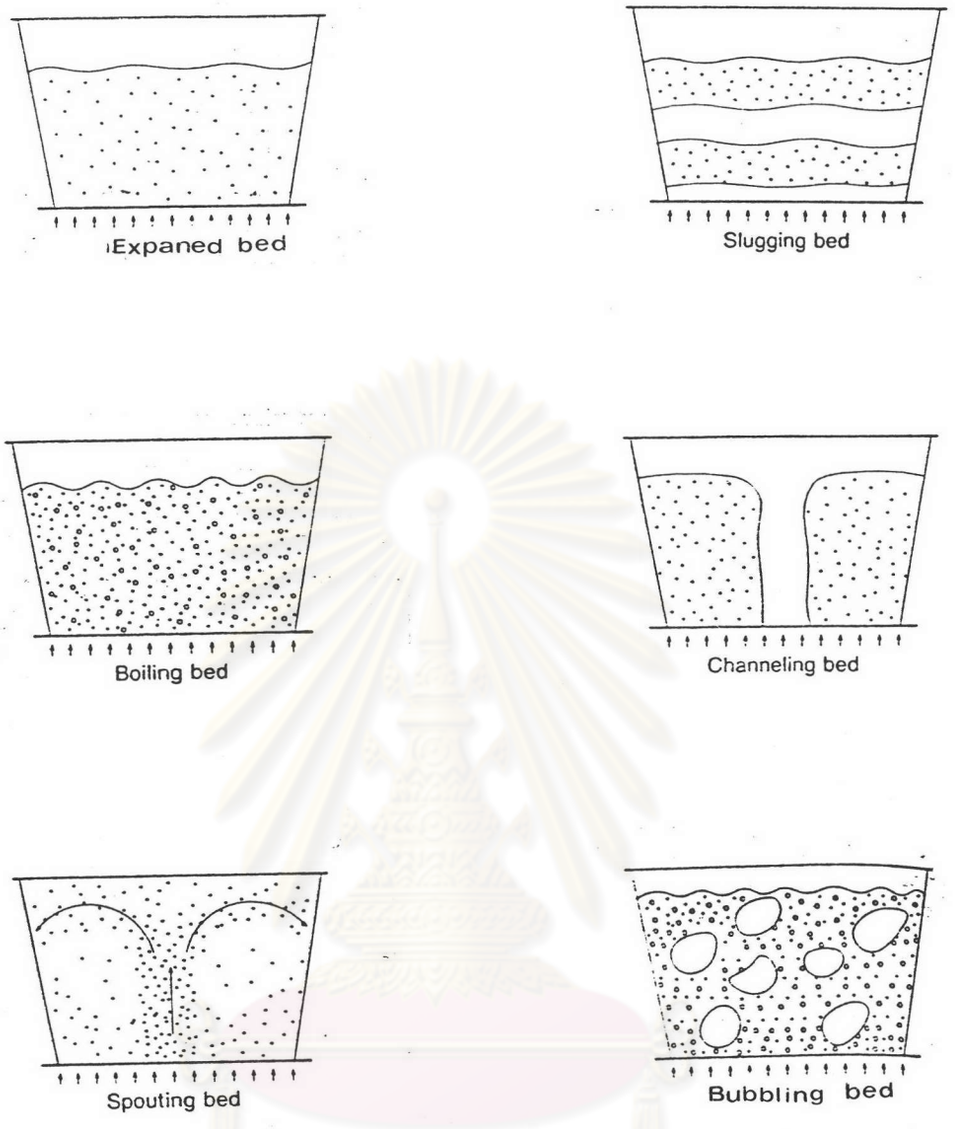


Figure 8 Types of airflow of fluidized bed

Airflow in fluidized bed passes through distributor plate. The distributor plate are many types which are identified by their percentage of open area. So an operator can selects a plate with optimum lift properties in each product.

As the process air enters the fluid bed unit's air handling system, it can be heated, humidified, dehumidified or filtered. Because the quality of airflow is an important factor to have good product.

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. Coatings can be applied to fluidized particles by a variety of techniques, including spraying from the top, from the bottom, or tangentially. The choice of spraying method in fluid-bed processing is based on a consideration of finished product performance requirements and projected product volumes. (Jones,1988)

Top Spraying Method

Top spraying method is conventional method. It has been used for more than a decade for coating. It evolved from the fluidized bed dryers commercialized more than 30 years ago. Top spraying coater is shown in Figure 9. The substrate is placed in the product container(A), which is typically an unbaffled, inverts, truncated cone with a fine

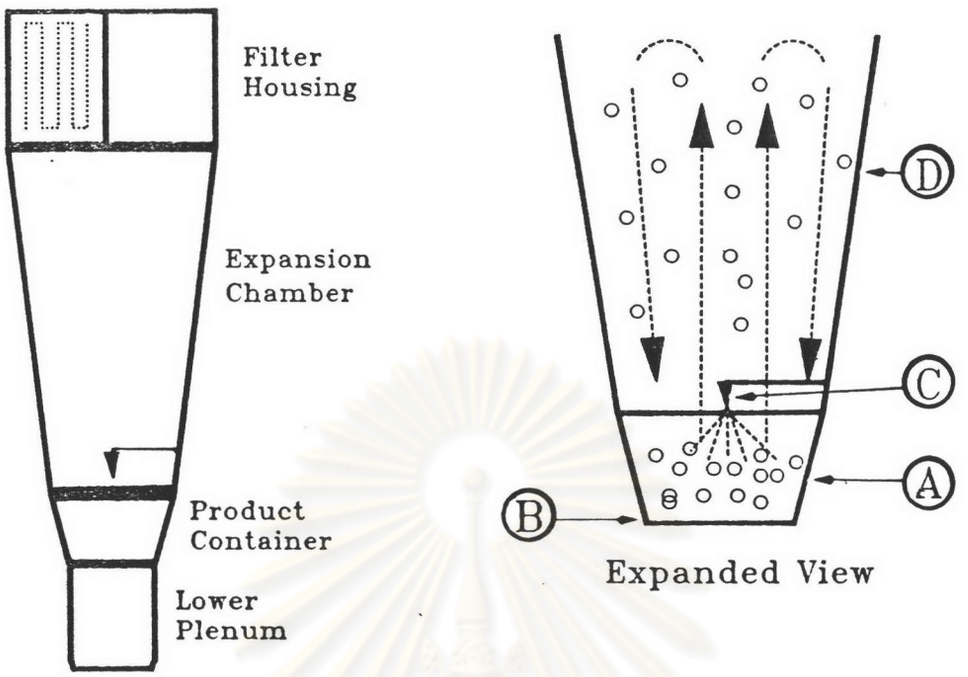


Figure 9 Top spraying of fluidized bed

retention screen and an air or gas distribution plate (B) at its base. Preconditioned air is drawn through the distribution plate (B) and into the product. As the volume of air is increased, the bed no longer remains static but becomes fluidized in the air stream. The particles are accelerated from the product container pass the nozzle (C), which sprays the coating liquid countercurrently onto the randomly fluidized particles. The coated particles travel through this coating "Zone"into the expansion chamber (D), which is wider in diameter than the base of the product container, this results in a decreasing air velocity that allows deceleration of the particles to below entrainment velocity.The particles fall back into the product container and continue cycling throughout the duration of the process.

Microscopic examination of particles coated by this method appears shiny and transparent(in the absence of colorants).Nevertheless, a sizable amount of coating is performed in this method because this method provides greater capacity and has simplicity of its design.This method can be used to achieve the properties such as taste masking, enteric release, isolator or barrier films. This method should not be used for applying films for sustained release when precise reproducibility is required and for applying films from organic solvents for enteric release.

The most significant characteristic of the top spraying method is that nozzle sprays countercurrently or down, into the fluidizing particles. The fluidization pattern is random and unrestricted. As a result, controlling the distance the droplets travel before contacting

the substrate is impossible. The surface of a pellet coated is imperfect and the core will dissolve. rapidly when placed in water.

Bottom Spraying Method

Bottom spraying method or Wurster coating system is available for coating process. The components of the system are illustrated in Figure 10. The coating chamber (A) is an unbaffled cylinder that contains another cylinder half its diameter known as a partition (B). At the base of the coating chamber is a fine screen and an air distribution (orifice) plate (C). In the center of the plate, a nozzle (D)is positioned to spray upwardly. The holes in the plate in the area beneath the partition are larger in diameter than those outside, Air passes through the plate at a high volume and velocity and pneumatically transports particles vertically through the partition and coating zone. The coated particles exit the partition and begin to decelerate in the expansion chamber(E). When the air velocity is such that the particles can no longer be entrained, they drop into the area between the partition and the wall of the coating chamber known as the down bed. The air volume in the down bed depends on the size and number of holes in the orifice plate in the area outside of the partition. This air volume should be enough only to enhance downward motion, keeping the down bed in near weightless suspension. The horizontal transportation of particles toward the coating zone,which completes the coating cycle, is accomplished by the proper selection of the distance between the base of the partition and the air distribution plate (known as partition height).Particles are recycled through the coating zone in a matter of

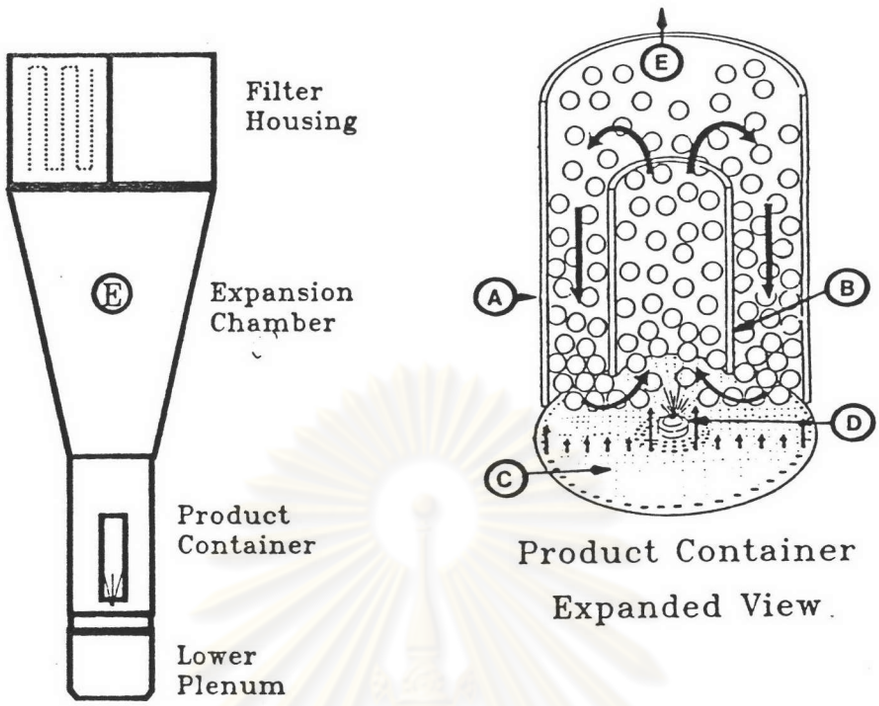


Figure 10 Bottom spraying of fluidized bed (Wurster coating system)

seconds, as the conventional, top spraying technique, but by contrast, the fluidization pattern is much more controlled in the Wurster system.

Bottom spraying method can be used for coating process better than top spraying method. This method can be used for applying films for sustained release when precise reproducibility is required and for applying films from both water and organic solvents.

Bottom spraying method is also affected by the air distribution plate configuration and the partition height.The finer are the particles to be coated, the smaller the open area in the down bed section of the orifice plate and the tighter the gap between partition and orifice plate.

Tangential Spraying Method

Tangential spraying method or rotary fluid bed equipment is used for granulating and coating process.Tangential spraying method is shown in Figure 11. The product container consists of an unbuffled cylindrical chamber (A) with a solid, variable-speed disc (B) at its disc.The disc and chamber are constructed such that during the process a gap(C) exists at the perimeter of the disc through which preconditioned air is drawn. During fluidization, three forces combine to provide a pattern best described as a spiraling helix. Centrifugal force causes the product to move toward the wall of the chamber,air velocity through the gap provides acceleration upward, and gravity cascades the product inward and toward the disc once again. Beneath the surface of the

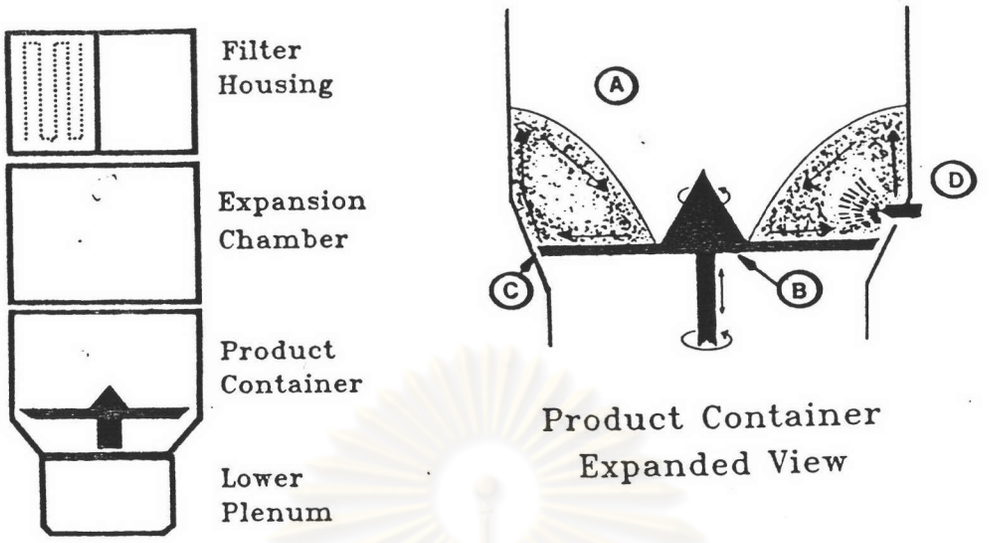


Figure 11 Tangential spraying of fluidized bed (rotary fluidized bed)

rapidly tumbling bed, a nozzle (D) is positioned to spray the coating liquid tangentially to and concurrently with the flow of particles.The particle cycling time of this technique is very rapid,hence, the films are uniform in thickness.

Tangential spraying method is being used to produce high dose pellets by applying a layer of drug particles to some type of seed material. The controlled release coating can subsequently be applied. This method has been used with organic solvents and water based coating.

The process variables of the tangential spraying method involved disc slit width, disc configuration and disc speed. The velocity of the fluidization air through the slit controls the rate at which the bed tumbles or spirals. Typically, this velocity is as high as possible without seriously distorting the fluidization pattern. In solution or suspension layering, the slit is usually wide; velocity is achieved by using a high air volume to maximize drying capacity and,to an extent, spray application rate. When spraying a binder solution and dosing powder, the slit is usually narrow and the air volume and temperature much lower. The disc may be configured with a variety of surfaces from simple antislide baffles to a multipyramid type of waffle plate. In layering and coating, the disc should be smooth. In addition to enhance particle motion, the disc speed may affect the spray application rate. Spray rate is limited by the tackiness of the coating material and can be elevated by increasing the velocity of the particles through the coating zone. Again,caution must be exercised to avoid excessive radial velocity, which may result in core fracture.

The velocity is determined empirically and will vary with different formulations.

The three fluidized bed process offer different advantages and disadvantages as shown in Table 2.

The successful scale-up of any process to pilot-or production-sized equipment depends greatly on the existence of an effective laboratory development program. It may be necessary to alter a less significant variable in order to produce the desired results. If the product in its final form performed well when processed under a broad range of conditions in the laboratory, the conditions that offered the shortest process time should be used for full-scale production.

Previous Researchers Studied about Preparation of Sustained Release Pellets Dosage Form by Film Coating Technique

Sakellariou, Rowe and White (1986) studied about polymer/polymer interactions in blends of ethylcellulose with hydroxypropyl methyl-cellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and polyethylene glycol 6000 using torsional braid pendulum. The authors found that all the film former were incompatible with ethylcellulose exhibiting phase separation.

Ragnarsson and Johanasson (1988) found that the release rate from barrier coated cores is directly proportional to the surface area of the material. When reducing the particle diameter to half of its

Table 2 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 possible Not recommended for friable products

original value, the amount of coating solution has to be doubled to obtain the same film thickness. When reducing the particle diameter to half of its original value, four times more coating solution is need to maintain the release rate per gram of coated cores.

Wesdyk, et al.(1990) reported that smaller beads had greater surface area per unit mass than the larger beads, and release rate of drug from smaller beads was faster than that from the larger beads.The larger or heavier beads received more thickness film than the smaller or lighter beads because of difference in the fluidization patterns and velocities of the various size beads.

Li, et al.(1990) studied about improving the dissolution rate profile. They found that an ethylcellulose dispersion plasticized using dibuthyl sebacate could be used for the manufacture of controlled release products. The incorporation of water soluble materials into the dispersion increased the in vitro release rate of drug from film coated granules. The permeation rate through the film depended on the type and the amount of additives.

Hossain and Ayres (1990) found that more effective coats were obtained when airflow through the chamber was increased by removing an air-diffusing base plate. Coat integrity improved with increasing temperature. Small nozzle openings provided coating that produced slower drug release and films with fewer surface imperfections. Triethyl citrate was most efficient in producing slower release, followed by the combination of triethyl citrate and dibuthyl sebacate, and dibuthyl

sebacate was least efficient.

Gilligan and Po (1991) found that the ratio of ethylcellulose to hydroxypropyl methylcellulose had a major influence on drug release rate.The pseudolatex coat of the pellets did not fully coalesce in the begining.But in later,coalescence proceeds to produce a more continuous polymer film resulting in a decrease in drug release rate. Additional, drying of the pellets at higher temperature promoted further gradual coalescence and thus further decreased the drug release rate from the pellets.

Zhang, Schwartz and Schnaare (1991) found that at low levels of coating, drug release data can be described by a square root of time relationship. The break in the pseudo-lag time as a function of the coating level curve indicated a mechanism change. The explanation of this break is that longer times are required for water to penetrate a complete film and comparatively short times are needed for water to enter pass the pores an incomplete coating.

Munday and Fassihi (1991) studied about effect of stress storage conditions on drug release rate from film coated mini-tablets. The mini-tablets were film coated with polymers such as ethylcellulose with PEG 1540, ethylcellulose with Eudragit L^R and Eudragit RL^R. Dissolution was significantly impeded to a degree directly proportional to temperature, but the effect of relative humidity appeared insignificant.

Ragnarsson, et al. (1992) studied about influence of drug

solubility and particle size on in-vitro release characteristics of membrane coated pellet formulation. The results indicated that the particle size and drug solubility were important for the release properties of the pellets. The drug solubility influenced on drug release profile because of the different in concentration gradients over the membrane as osmotic effect.But diffusion is the main effect.

Sheen, et al. (1992) found that the increased coating level decreased drug release rate from film coated pellets. In addition a water soluble polymer, hydroxypropyl methylcellulose was added to Surelease^{R} in an attempt to create pores in the coating and increased in the drug release rates. The results of short term stability studies showed no significant changes in dissolution rate, possibly due to the complete curing of Surelease^{R} coating during the coating process.

Yuen, Deshmukh and Newton (1993) studied about multiparticulate sustained release theophylline formulation.The release rate was related inversely to the thickness of the film, suggesting that the film was controlling the release process. Comparing the additives used,PEG 4000 and MC 400 appeared to be more effective and satisfactory in enhancing the film permeability than used sodium chloride, acacia, PEG 400 and MC 15. However, the addition of PEG 4000 into the polymer dispersion yielded a tacky mixture which caused agglomeration of the pellets during coating.The rate of drug release is unaffected by pH and stability of release during storage can be achieved by additional thermal treatment of the coat.

Bianchini, et al.(1993) found that the release of d-Indobufen was obtained by modifying both the core composition and the film composition characteristics. Eudragit^{R} coating seemed to be more suitable to reduce drug release rate than ethylcellulose coating,this may be due to ethylcellulose coating showed higher pore size than Eudragit^{R} coating. When added PEG 6000 into Eudragit^{R} increased in release rate was observed because of it also induced pore formation.

Chetty and Dangor (1994) studied about effect of various formulations on controlled release pellets. The rate of release was a function of film thickness and composition of the membrane.The release rate decreased as the film thickness increased. The release rate increased as the increased hydroxypropyl methylcellulose level to replaceethylcellulose.Drug release was more rapid in batches where the plasticizer such as dibuthyl phthalate or polyethylene glycol was employed into Eudragit RS^{R} coating membrane. But there was a greater degree of pellet agglomeration in these batches because of the increased tackiness of the coating solutions. Lubricants or anti-adherents are solid inclusions which decrease the tackiness of coating solutions and which may also have an inhibitory effect on the rate of drug release due to the hydrophobic nature of these substances.

<u>Terbutaline Sulphate</u>

Terbutaline sulphate is a synthetic sympathomimetic amine which is similar to isoproterenol and metaproterenol in chemical structure and in pharmacologic action. It is used as a bronchodilator in the

treatment of bronchial asthma (Ahuja and Ashman, 1990).

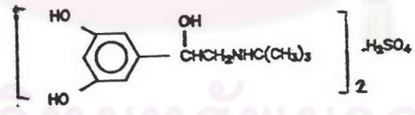
Terbutaline sulphate has been described by the following chemical names :

(i) 5- [2-[(1,1-Dimethylethyl) amino]-1-hydroxyethyl]-1,3- benzenediol sulphate (2:1 salt)

(ii) α-[tert-Butylamino) methyl]-3,5- dihydroxybenzyl alcohol sulphate (2:1 salt)

(iii) 1-(3,5-dihydroxyphenyl)-2-(tert-butylamino)-ethanol sulphate (2:1 salt)

Its empirical formula is $C_{24}H_{40}N_2O_{10}S$ and a molecular weight of 548.658. Its structural formula is



Terbutaline sulphate is an odorless or with a faint odor of acetic acid, white to gray-white crystalline powder. It is freely soluble in water (more than 20 mg per ml) and slightly soluble in ethanol (about 1.2 mg per ml).

The solution at 0.1 mg per ml of 0.1 N hydrochloric acid shows maximum absorption at 276 nm with E 1%-1 cm of about 0.6745.

Terbutaline sulphate is a stable compound under normal storage conditions. No change in chromatographic impurities was detected after three years storage at room temperature.Terbutaline sulphate is stable in solution with a pH 1-7 and is sensitive to excessive heat.

Terbutaline sulphate stimulates beta-adrenergic receptors of the sympathetic nervous system and has little or no effect on alpha-adrenergic receptors. The main effect of terbutaline sulphate is relaxation of smooth muscles of the bronchial tree and the peripheral vascular. Terbutaline sulphate does not appear to cause changes in arterial oxygen tension.

Pharmacokinetics study reveals that terbutaline sulphate has a biological half-life of 3.6 hours, and is usually administered three times daily, thus pharmacokinetic datas are necessary in developing a sustained-release preparation with an extened clinical effect. Ruiz, Saks and Sprockel (1990) found that sustained release for terbutaline sulphate was successfully obtained by microencapsulation with cellulose acetate butyrate and ethylcellulose using an emulsion-solvent evaporation technique.