Chapter 1

General Background

Introduction

Sustained release dosage forms are developed for a variety of reasons such as avoiding patient compliance problems, reducing unexpected toxic effects due to high peak concentration, and improving efficiency in treatment because of less fluctuations in drug level. Characteristics accommodated for developing the sustained release dosage form are decreasing dosage frequency and maintaining concentration blood level. Sustained release drug preparations are especially recommend when the drug has a relatively short half-life. Also, they are advisable when steady plasma drug level needs to be achieved in desired therapeutic effects due to its narrow therapeutic range.

Propranolol hydrochloride is an example which consists of both properties. It is almost completely absorbed after oral administration. Peak plasma concentration is achieved at approximately two hours in fasting patient with narrow therapeutic range at constant condition in plasma at 20-50 μg/ml. It is about 85-95 % bound to plasma proteins but it has short plasma half-life of 3-4 hours (Evan, 1973) and rapid hepatic metabolism after administration, therefore; it needs 3-4 times by oral regimen. Consequently, propranolol hydrochloride has been made in sustained release preparation in order to attain those advantage as described.

Two main approaches utilized in the production design of oral sustained-release dosage forms are (a) an introduction of a physical barrier preventing contact between the drug and the fluid of the digestive system, the effects of which are to reduce the rate of diffusion or leaching out of the drug from the dosage form, (b) an addition of

selected interactants to the formulation, such as ion-exchange resins or complexants, which form weak chemical bonds with the drug (Friedman and Donbrow, 1978).

Film coating is one of accepted methods of prolongation of drug release from pellets (Friedman, Donbrow and Samvelov, 1979). The coating material may be soluble or insoluble in fluid of the digestive system. In the case of soluble coating materials, the dosage form may include a variety of pellets or cores with different coat thickness. The release rate in such a system may be controlled by the dissolution of the coat or the diffusion of the drug through the coat or both process. However, with insoluble coating materials, the release process will be controlled solely by the diffusion of drug through the film coat and the rate limiting step is penetration of the drug not controlled by coating layer. Examples of the most common insoluble polymer candidates are methacrylate ester copolymer (Eudragit®RL, Eudragit®RS, and Eudragit®NE), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and ethylcellulose.

Wellknown sustained release capsules of propranolol hydrochloride have been marketed in the names of Inderal®LA80 and Inderal®LA160 which composed of 80 and 160 mg of the drug, respectively. These products are multiple unit type dosage form and the coated pellets are encapsulated in hard gelatin capsules. The membrane barrier for the pellet coating to control the release rate of the drug is found to be ethylcellulose polymer.

This study is also concerned with preparation of sustained release propranolol hydrochloride preparations of multiple unit type. The core pellets which contains propranolol hydrochloride were prepared by using oscillating granulator and spheronizer and the pellets were then coated with the polymer membrane by means of fluidized bed coating technique.

In this study, the mixtures of ammonio methacrylate copolymer and ethylcellulose in various ratios were used as a film to control the release of drug.

Two types of ammonio methacrylate copolymer were employed to combine with ethylcellulose polymer, Eudragit®RS100 (low permeability, ammonio methacrylate copolymer type A) and Eudragit®RL100 (high permeability, ammonio methacrylate copolymer type B).

The effect of the ratios of ethylcellulose and Eudragit®at various coating levels on the release of the drug was investigated. Following release studies, the coated pellet of various formulations which holds the suitable release rate were selected and combined to formulate sustained release propranolol hydrochloride capsules of 24 hours type that can meet the USP specification for a release testing of propranolol hydrochloride extended release capsule.

Objectives of the Study

1. To prepare propranolol hydrochloride pellets using extrusion and spheronization technique.

2. To study the optimum condition in coating the pellets with the mixture of ammonio methacrylate copolymer and ethylcellulose by fluidized bed coating technique.

3. To study drug release characteristics of propranolol hydrochloride pellets coated with the mixture of ammonio methacrylate copolymer and ethylcellulose.

4. To study mechanism and drug release pattern of the propranolol hydrochloride pellets.

5. To develop the 24-hours sustained release propranolol hydrochloride to comply with the USP specification in terms of the release behaviors.

Literature Review

1. Propranolol Hydrochloride

1.1 Physico-Chemical Properties

Chemical name : (±)-1-Isopropylamino-3-(1-naphthyloxy)propan-2-ol hydrochloride

Empirical formula: $C_{16}H_{21}NO_2 \cdot HCl$

Structural formula :

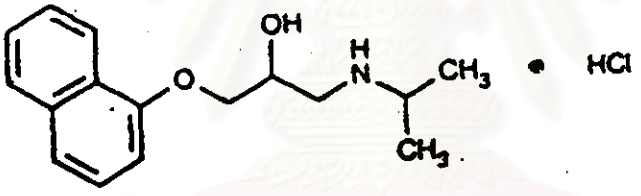

Figure 1 Chemical structure of propanolol hydrochloride.

Molecular weight : 295.80

Description : White or off-white, odorless or almost odorless, crystalline powder with bitter taste.

Solubility : 1 in 20 of water and of alcohol, slightly soluble in chloroform and practically insoluble in ether.

Stability : propranolol hydrochloride preparations should be protected from light and stored at room temperature (approximately 25°C) in well-closed containers.

Propranolol hydrochloride is a nonselective β-adrenergic blocking agent which can inhibit responses to adrenergic stimuli by competitively blocking at the β-adrenergic receptors within myocardium, bronchial and vascular smooth muscle.

Propranolol hydrochloride is almost completely absorbed from a GI tract and appears in plasma within 30 minutes, and peak plasma concentrations are reached about 60-90 minutes after oral administration.

Propranolol hydrochloride is widely distributed into body tissues including lungs, liver, kidney, heart and readily crosses the blood-brain barrier or placenta. The apparent volume of distribution at steady state widely varies in proportion to the fraction of unbound drug in whole blood. Propranolol hydrochloride is more than 90% bound to plasma proteins over a wide range of blood concentrations. Both free and protein-bound drug are metabolized. Increased plasma protein binding of the drug increases its metabolism and decreases its volume of distribution, resulting in a shorter terminal half-life.

Propranolol hydrochloride is almost completely metabolized in the liver and at least 8 metabolites have been identified in urine. Only 1-4 % of an oral dose of drug appears in feces as unchanged drug and metabolites.

Elimination of propranolol hydrochloride appears to follow first-order kinetics and seems to be independent of plasma concentration or the dose administered, at least with oral doses of 160-320 mg/day.

In recent years, a number of drug entities has been developed into sustained release products, propranolol hydrochloride is one of the drug candidate prepared in such dosage forms.

In order to modify propranolol hydrochloride controlled release system, several alternatives have been applied. Because of the least complicated approach to

manufacture, the matrix tablet and pellets seems to be the popular delivery systems. A few investigations have been reported on the design and manufacture of propranolol hydrochloride in matrix tablet and pellet dosage form, which are:

Jayaswal et al. (1980) studied Propranolol hydrochloride matrix tablets and coated matrix tablet using Eudragit®RL/RS in two forms; powder and granule as matrix materials and film former.

Ford et al. (1985) studied propranolol hydrochloride matrix tablet, using various viscosity grade hydroxypropyl-methylcellulose (HPMC) as matrix materials.

Ganga et al. (1992) studied the drug release of the hydrophillic matrix tablets containing different ratio of Na-CMC and HPMC.

Hosny et al. (1994) prepared and evaluate the controlled release characteristics of propranolol hydrochloride beads. Eudragit®RS100 was used as release controlling materials and beeswax was used as overcoating. The beads were characterized for their particle size distribution, drug loading efficiency and their dissolution behavior in 0.1 N HCl. The result showed that the coating level of the polymer, particle size of the beads and overcoating with beeswax play a major role in determining the release rate of the drug from coated beads.

Bodmeier and Paeratakul (1990) prepared film containing propranolol hydrochloride by dissolving the drug in the aqueous colloidal polymer dispersion of Eudragit®RS30D and study function of drug content, plasticizer content method of film preparation and storage humidity. The result showed that the addition of the more hydrophilic Eudragit®RL30D increased the permeability of the films. The amount of water-soluble plasticizer, triethyl citrate added had a pronounced effect on drug release. The release was rapid at low and high plasticizer concentration because of incomplete coalescence of latex and leaching of the plasticizer.

2. Materials Used in Coating Formulations

In this investigation, the coated systems consist of Eudragit®RL100 or Eudragit® RS100 and ethylcellulose as coating polymers. In this action, the organic solvent systems are employed by using mixture of acetone and isopropyl alcohol to prepare coating solutions. Dibutyl phthalate was selected to be the plasticizer of the coating materials. By changing polymeric mixture types, polymer ratios, and coating levels, the characteristics of drug release would be affected. Brief descriptions of the materials used in the experiment are delineated in the following sections.

2.1 Film Formers

2.1.1 Ethylcellulose

Physico-Chemical Properties

Chemical name : **Cellulose ethyl ether**

Empirical formula : **Ethylcellulose is an ethyl ether of cellulose , a long chain polymer consisting of anhydroglucose unit joined together by acetyl linkages. Each anhydroglucose unit has three replacable hydroxyl groups which are substituted to the extent of 2.25-2.60 ethoxyl groups per unit, equivalent to an ethoxyl content of 44-51 %.**

Structural formula :

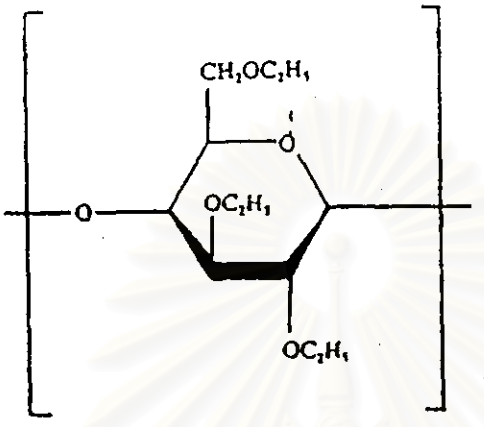

Figure 2 Chemical structure of ethylcellulose.

Description :Ethylcellulose is a tasteless, free flowing, white to light tan colored powder.

Solubility :Practically insoluble in glycerin, propylene glycol and water. Ethylcellulose that contains less than 46.5 % of ethoxyl groups is freely soluble in chloroform, methyl acetate, tetrahydrofuran, and in mixture of aromatic hydrocarbons with ethanol (95 %). Ethylcellulose that contains not less than 46.5 % of ethoxyl group is freely soluble in chloroform, ethanol (95 %), ethyl acetate, methanol and toluene. Solubility of ethylcellulose in presented in Table 1.

Stability :Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrate, and to salt solutions, although it is more sensitive to acidic materials than cellulose esters.

Table 1 Solubility of ethylcellulose in various solvents (Wade and Weller, 1994).

Solvent	solubility (mg/ml)	
	A	B
ethanol at 25° C	53	15
ethanol at 37° C	66	25
hexane at 25 °C	< 2	< 2
hexane at 37 °C	< 6	< 6
propylene at 25° C	25	25
propylene at 37° C	25	25
water at 25°C	< 1	10
water at 37° C	< 1	10

Supplier : A. Hercules LTD.
B. Dow chemical CO.

With magnificent characteristics of ethylcellulose in film coating system, many experiments then come cross. Many applications are applied to control drug delivery systems. Many utilizations involve with the mixture of ethylcellulose. Some outstanding implementations are as followed:

Porter (1989) reviewed and described the characteristics of ethylcellulose film coating system. Ethylcellulose has properties that make it very suitable to be used as the main film former in film coatings that are applied for controlled-release purpose. Both organic-solvent-based and aqueous film-coating methodologies can be employed.

Biswanath et al. (1990) developed micropellet dosage form using ethylcellulose as a polymer with a view to achieve a controlled release oral drug delivery system for theophylline. The result showed that in vitro release of theophylline from micropellets having different drug-polymer ratios and different sizes followed both first-order release and diffusion controlled release processes by differential rate treatment. It was found that the overall release, infact, followed diffusion controlled process.

Hema and Sanghavi (1994) formulated pindolol into a controlled drug delivery system. Drug pellets were prepared by extrusion-spheronization technique. These were coated with different retarding polymer, namely ethylcellulose and Eudragit® RS100. The effect of different variables such as coating level has been studied.

Ozturk et al. (1990) have shown in their studies the possible mechanism of phenylpropanolamine release from pellets coated with an ethylcellulose-base film. Nonetheless, a mathematical expression in conclusion for such system showed that the release from drug-contained pellets coated with ethylcellulose based film appeared to be a combination of osmotically driven release and diffusion through the polymer and aqueous pores.

Sarisuta and Sirithunyalug (1988) studied sustained release indomethacin granules by mean of the air suspension coated technique. Indomethacin granules were coated with film of ethylcellulose-glyceryl monostearate mixture at various percent by weight of coat. They found the relationship between the coating weight and first order release rate constant.

Friedman and Danbrow (1979) studied the preparation of sustained release granules coated by means of the fluidized bed coater. Salicylic acid and caffeine were selected as model drugs, while ethylcellulose with polyethylene glycol were representative of coating materials. The results shown that the instrument has been successfully used for producing sustained release products by coating granules of model drug with ethylcellulose.

Li et al. (1990) coated theophylline granules by mixture of ethylcellulose and dibutyl sebacate with Wurster coating column. Various additives were incorporated into the film coating mixture. The result showed that the incorporation of water soluble materials into the dispersion could increase the in vitro release of theophylline from the coated granules.

2.1.2 Eudragit®RL100, RS100

Physico-Chemical Properties

Chemical name : ammonio methacrylate copolymer type A, B

Empirical formula : Eudragit®RL and RS are copolymers synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth) acrylic acid esters is 1:20 with Eudragit®RL and 1:40 with Eudragit®RS.

Structural formula :

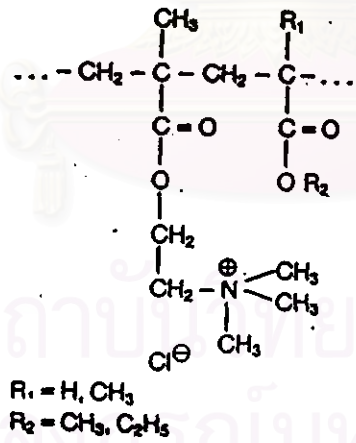

Figure 3 Chemical structure of Eudragit®RL and RS.

Molecular weight :150000

Description : Eudragit®RL and RS are tasteless, colorless, transparent, brittle granules, amine-like odor.

Solubility : 1g of dry substance dissolves in isopropyl alcohol containing small amounts of water or in acetone, ethyl acetate and methylene chloride to give clear to slightly opalescent solutions. Solubility of Eudragit® RL and RS are presented in Table 2.

Stability : Store at a temperature not exceeding 30°C. Keep solutions in well-closed containers and protect solid substances from damp.

Table 2 Solubility of polymethacrylates in organic solvents (Klaus, 1994).

Solvent	Ammonio methacrylate copolymers	
	RL100	RS100
water	SW	SW
methanol	+	+
ethanol	(+)	(+)
isopropranol	(+)	(+)
acetone	+	+
dichloromethane	+	+
ethyl acetate	+	+
mixture{isopropanol-acetone 60:40}	+	+

+ , soluble up to 10% or more

(+) , soluble at lower concentration

SW, swelling

- , insoluble

Eudragit®RL100/RS100 are copolymers synthesized from acrylic and methacrylic acid esters with hydrophillic quaternary ammonium groups as functional units in the polymer chain. They can be used without other release-controlling exipients as a permeable membranes. The permeability depends directly on the content of the hydrophilic units (trimethylammonioethyl methacrylate chloride). Eudragit®RL100 contains 10 % w/w of this unit, resulting in very permeable film that tend to disintegrate quickly in water; therefore, this type is used for fast disintegrating cores. On the other hand, Eudragit®RS100 contains only 5 % w/w hydrophillic units and exhibits very low permeability. With increasing film thickness up to about 100 μm, the release rate can be dropped down to very low rates, to give sustained release over 24 hour or even more.

Because of the outstanding characteristic of Eudragit®RL and Eudragit®RS, many utilization have been presented. Many applications are applied to the controlled drug delivery system. By changing polymer types, polymer ratio, coating level, and pH range, the characteristics to the drug release will be affected. Such. implementations are followed:

Bianchini, et al. (1993) prepared a multiple units dosage form in order to control the release of α-Indobrufen. The system consists of cores containing the active substance coated with a diffusive film. Polymer chosen for the film formulation were ethylcellulose and copolymers of acrylic ester with differing permeability characteristics. Film composition and thickness are reconfirmed as parameters that extremely influence drug release profile.

Chang, et al. (1989) prepared theophylline pellets coated with Eudragit®RL and RS in a fluidized bed. The effect of polymer type and coating level, plasticizer concentration, and pH of the dissolution medium on drug release Eudragit®RS films retarded theophylline release over a wide pH range. Release of the drug was found to

be a function of the polymer coating level, plasticizer concentration and dependent on pH of the dissolution medium.

2.2 Plasticizer

Dibutyl Phthalate

Physico-Chemical Properties

Chemical name : 1, 2-benzenedicarboxylic acid dibutyl ester

Empirical formula : $C_{16}H_{22}O_4$

Structural formula :

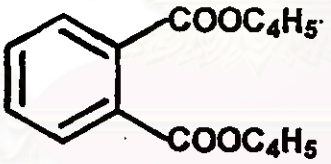

Figure 4 Chemical structure of dibutyl phthalate.

Description : A clear, colorless or faintly colored oily liquid.

Solubility :Very soluble in acetone, benzene, ethanol (95 %) and ether ; soluble 1 in 2500 of water.

Stability :Dibutyl phthalate is stable when stored in a well-closed container, in a cool, dry place.

By concerning on plasticizer, the various amount of plasticizer influences the permeability of the film. These characteristics lead to numerous experiments on applications of the plasticization of Eudragit® and dibutyl phthalate, which are as followed:

Schmidt and Niemann (1993) studied dissolution profile of theophylline pellets coated with Eudragit®RS 30D in a miniature fluid bed pan coater called Miniwid and plasticized with varying amounts of dibutyl phthalate, polyethylene glycol 6000, and triethyl citrate. The result showed that at a coating level of 4 %, a sustained- release profile was obtained from the dispersion plasticized with TEC or DBP. By reducing the amount of plasticizer from 20 % to 10 %, films with higher permeability were obtained.

Sinko and Amidon (1988) studied the plasticization of Eudragit®S100 with polyethylene glycol 200 and dibutyl phthalate. This study focused on the plasticization-induced changes in the rate of mechanical response. Results indicated that at a constant temperature, the addition of plasticizer changes the time scale of response by shifting the spectronegatively within the experimental time.

Hutchings and Sakn (1994) studied six potential plasticizers for ethylcellulose (EC) pseudolatex coating system (Aquacoat). Three levels (25, 30 and 35 %) of plasticizer were evaluated to study the influence of these additives on the release of a model compound, propranolol hydrochloride, from pellets in two different media, dilute HCl and phosphate buffer pH 7.4. The result showed that the release rate decreased when larger amounts of plasticizer were incorporated into the coating.

3. Pelletization Technology (Ghebre, 1989)

Pelletization is an agglomeration process that produces small, free flowing, spherical or semi-spherical units from fine powders or granules of bulk drug and

exipients, refereed to pellets. The classification of pelletization process was shown in Figure 5.

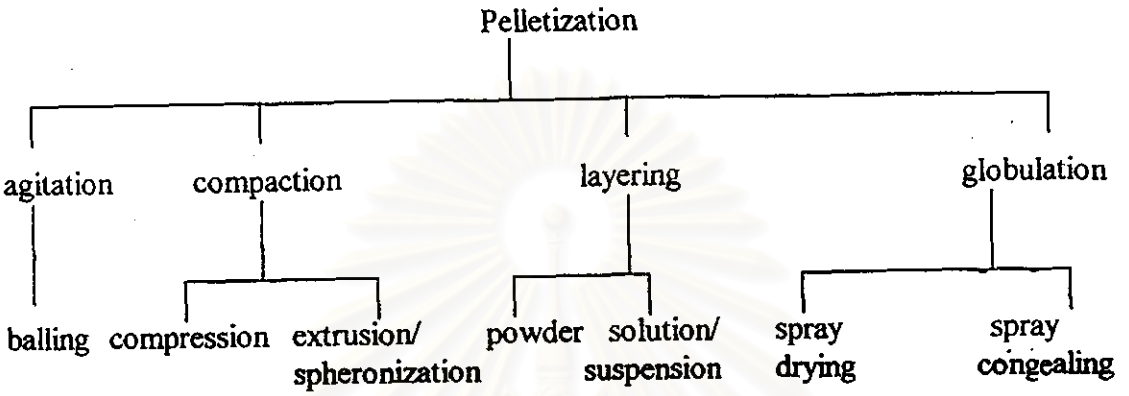

Figure 5 Classification of pelletization process.

The most widely used process in pharmaceutical industry is spheronization which can be processed by several techniques ; Glatt retrogranulation, spheronization (marumerization), CF granulation, and conventional sugar coating pan. The extrusion of moist material following by rounding on a rapidly rotating, roughened plate is known as spheronization. Spheronization technique is suitable for use with a wide range of drug contents , from 0.5 % to the upper limit depending on drug properties. This technique may be the only practical way of achieving pellets with a very high drug content.

With a typical manufacturing process is followed. The drug and any necessary exipients are dry mixed. Liquid, usually either water, and alcohol/water mixture, or a binding solution, is to form a wet mass similar in consistency to that prepared when wet massing a tablet granulation. The mass is then extruded using a suitable extruder and the extrudate is transferred to the spheronizer. The spheronizer consists of a plate, usually "9-36" in diameter, which rotates in range of 100-1000 rpm speed. The surface of the plate is roughened, usually with a regular pattern. Figure 6 is represented the schematic of simple extrusion-spheronization process.

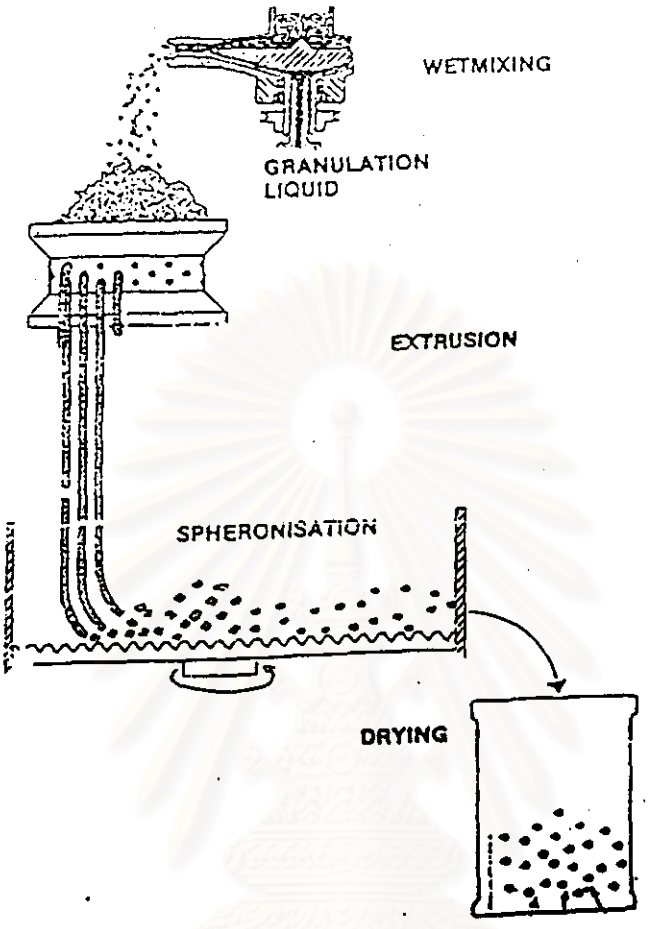

Figure 6 Schematic representation of simple extrusion-spheronization process.

The liquid content of the wet mass prior to extrusion is highly critical. If a formula is successful, then the product should be uniform pellets approximately diameter of the holds in the extruder plate used. If the mixture is too dry, the excessive quantity of fines may be produced. This can be seen as a band of fines on the top of material rotating within the spheronizer. On the other hand, if the mixture is too wet, it will adhere to the spheronizer plate and aggregation will occur as material transferred from pellet to pellet via the plate.

The material which is not sufficiently plastic may tend to form "rugby ball" which never round into sphere are stable, i.e. do not change on prolonged spheronization. Over-wetted batches tend to form a satisfactory product very quickly (14-30 sec. spheronization) which then aggregates uncontrollably. A stable

production formula must achieve a balance between these two extremes. The duration of the spheronization is usually 2-10 minutes.

The limitations of spheronization lie in a minimum concentration of extrusion aids required to produce a satisfactory product; which in turn limit the maximum drug concentration. The physicochemical properties of the bulk drug such as, very highly soluble, extreme particle size or moisture sensitive, may not be possible to spheronize at all, particularly at high drug levels. Two approaches to get round this problems are changing of the composition of the binding liquid, and using the alternative extrusion aids. Also, modification of drug particle size to produce a better extrudate may be possible.

4. Pellets Coating Technology (Mentha and Jones, 1985)

Coating equipment has derived from two basic principles such as traditional pan coaters and fluidized bed machine. In this study, it was concentrated only on the fluidize bed machines. The fluidized bed is well known for its drying efficiency, as it has been used for drying and granulating for many years. It has a ability to apply virtually to any type of coating system (solution, suspension, emulsion, latex and hot melt) to a wide range of particle sizes coating, with various techniques such as top spray, bottom spray, and tangentially.

4.1 Top Spray Coater

A top spray coater was developed from conventional fluidize bed dryer for coating pharmaceutical dosage forms. The spray nozzle equipped in the fluidized powder bed was shown in Figure 7. The coating suspension was sprayed downward onto the substrate as it was randomly fluidized by air from air distribution plate below the coating chamber. The films from top spray process gains smoothness and continuity of coating surface over pellets coated in a conventional or perforated pan due to its greater drying efficiency of the fluidized bed technique.

However the top-spray coating always have imperfections of films in a finished product. Although the spray nozzle immersed in the fluidized pellets, the fluidized pattern was still disorganized. As a result, droplets travel random distances before impinging on the substrate. Coating solution was sprayed downward against the heated air stream, counter-current style, which generated viscosity changed as the solids content of the droplet increases with high evaporation rate of solvent used and spray dried occurs. Since a top spray film always involves imperfections, this method is nowadays primary used for barrier (protective) coating, but less for controlled release films.

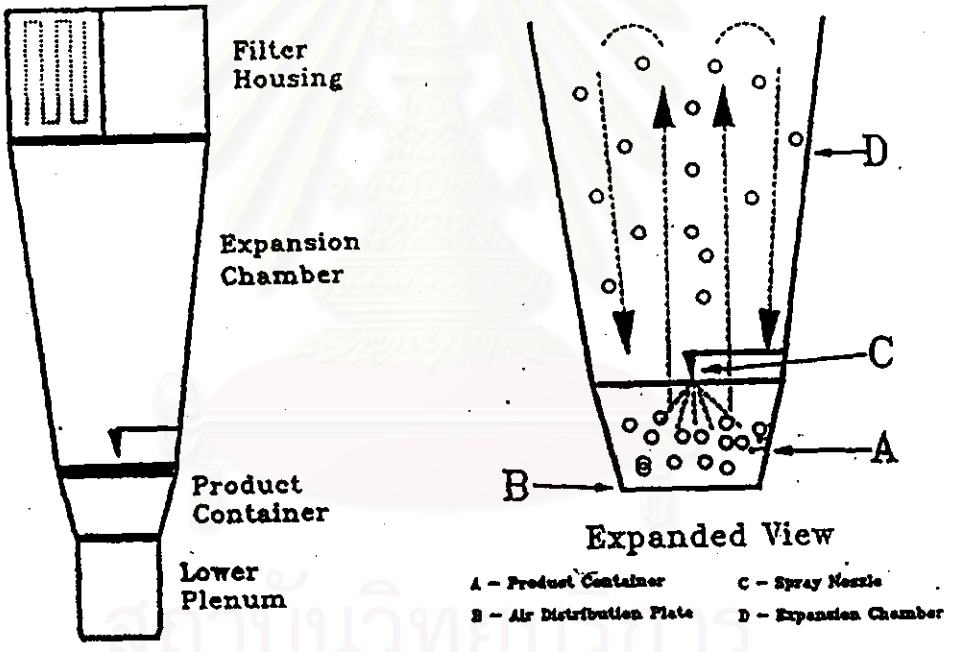

Figure 7 Top spray coater.

4.2 Wurster (bottom) spray coater

Another type of fluidized-bed coating process was introduced by Wurster. The spray nozzles was equipped at the bottom of coating chamber as in Figure 8. This system is currently widely used for film coating of particles, pellets and tablets.

The fluidization pattern is much more controlled in Wurster system which affects by air distribution plate and partition height in coating chamber as shown in Figure 8. The coating solution is applied concurrently from the bottom at the same time and same direction as the product motion and process air flow.

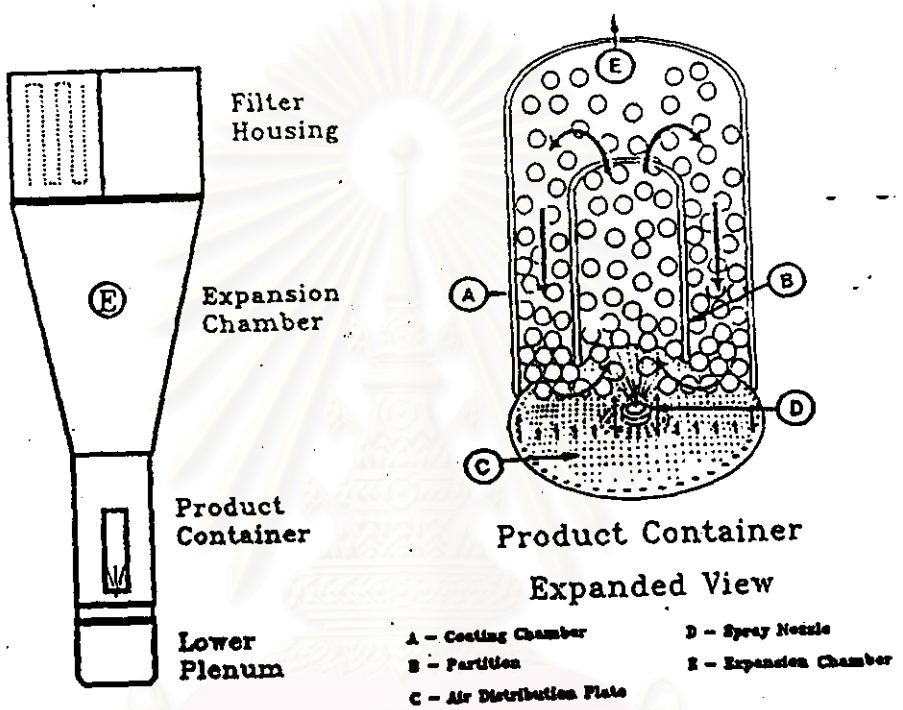

Figure 8 Wurster (bottom) spray coater (from Glatt air technique, Inc., 1987).

Wurster bottom spray coater organizes the pellets to be close to the spray nozzle, an arrangement prevents any appreciable change in ratio of solid to liquid in the coating suspension. Consequently, the film forming droplets can spread onto the product at the lowest possible viscosity.

Drying of the film occurs after particles have left the partition and enter the conical expansion chamber, where the product velocity is decreasing and the particles are separated from each other to allow efficient heat exchange and hardening of the film. The dried particles are then returned in regular intervals into the spray area to take up the next film layer. This allows each layer of coating to dry more completely before pellets are recycled to receive further coating. The thickness of the coating in such cases is easily to control as well as to reproduce. Consequently, drug release

rates can also be controlled. The physical quality of this coating appears to be superior than another type of equipment that mention before and appears to provide ideal for coating in controlled release formulation (Mentha and Jones; 1985).

The Wurster bottom spray process is gaining more and more popularity, also because of the easy reproducibility of the process conditions, uniform product quality and morphology batch by batch.

4.3 Tangential Spray Coater

For tangential spray or rotary fluidized bed coating, three forces are combined to provide a pattern best described as a helix. Centrifugal force generates by the rotating disc causes the product to move toward the wall of the chamber (Figure 9), air velocity through the gap provides acceleration upward, and gravity cascades the products inward and toward the disc once again. The coating suspension is sprayed tangentially in the same direction, concurrently, as the movement of the pellets in chamber, similar to those of the coating applied using the Wurster bottom spray method. Film applied using the rotor tangential spray system are high in quality, similar to those found using the Wurster process. However, the process is more susceptible to adhesion of particles to upper wall of the product container owing to static electricity; hence, coating of smaller and lighter particles is difficult, especially with organic solvents (Jones, 1990).

Additionally, the higher kinetically energy produced by the centrifugal forces of the fast rotating disc makes the rotor more suitable for the film coating of powders and tablets. The process also has more mechanical stress than other methods thus it is discouraged for use with friable substrates.

Mentha and Jones, 1985 reported that top spray method may be unacceptable for producing a reproducible sustained release coating. Whereas Wurster bottom spray and tangential spray coating provide smooth, continuous film of polymer.

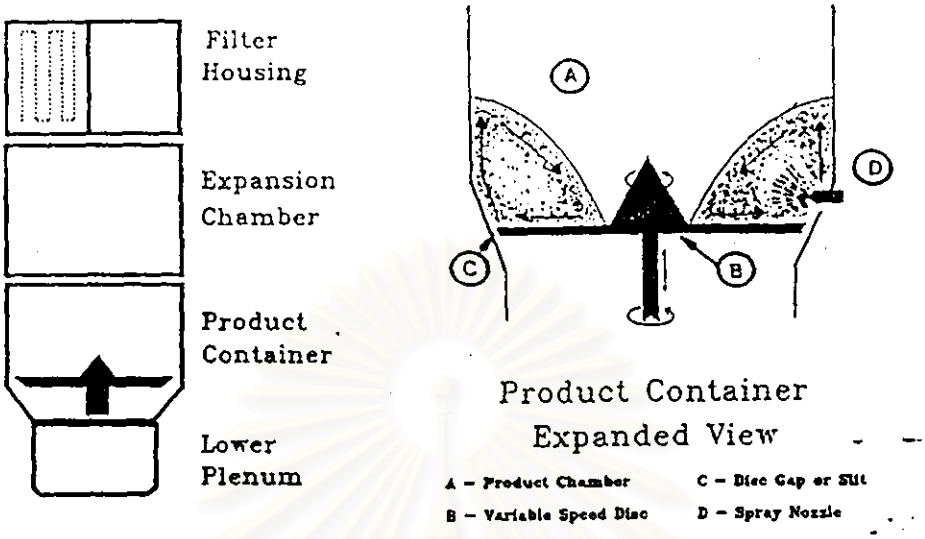

Figure 9 Tangential spray coater.

The evaluation and advantages and disadvantages of each of these fluidize bed techniques have been summarized in Table 3.

Table 3 Comparison of three fluidized-bed coating process.

Processing method	Advantage	Disadvantage
A. Top spray coating (granular mode)	Large batch sizes Simple to set up Easy access to nozzle	Limited applications
B. Bottom spray (Wurster)	Moderate batch sizes Uniform and reproducible film characteristics Widest application range	Tedious to set up Impossible to access nozzle during process Tallest fluid bed machine for fine particle coating
C. Tangential spray (Rotary mode)	Simple to set up Nozzle access during process Higher spray rate Shortest machine	Mechanical stress on product