# Chapter I

# General Background

## Introduction

Sustained release dosage forms are developed for a variety of reasons such as they may reduce unwanted toxic effects due to high peak concentrations. It is also likely that patient compliance will increase when the patient has to take fewer doses per day and when unwanted side-effects occur less frequently. Sustained release drug preparations are especially recommended when the drug has a relatively short half_life and needs steady plasma drug levels to achieve desired therapeutic effects.

Theophylline meets both of these specifications: its half-life is approximately 4-9 hrs and the therapeutic range is 10-20 ug/ml.(Joknman, Schoenmaker, Grimeberg and Zeeuw, 1981). Conventional theophylline dosage forms require drug intake every 6 hr. Such a schedule may result in low trough level in the morning resulting in a symptom breakthrough in most asthma patients. The use of properly designed sustained release preparations may eliminate this problem. On this rationale, several drug manufacturers have introduced sustained release theophylline preparations in recent years.

The two main approaches utilized (Friedman and Donbrow, 1978) in the design of sustained release products are (a) the 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) the addition of selected interactants to the formulation, such as ion-exchange resins or complexants, which form weak chemical bonds with the drug.

The present work is concernd with the first type of product which in practice may be produced using widely different technology. The main ones are based on 1) coating techniques and 2)embedding the drug in a wax or polymer matrix. (Friedman and Donbrow, 1978)

Film coating is one of the accepted methods of prolongation of drug release from granules ( Friedman, Donbrow and Samuelov, 1979). The coating material may be soluble or insoluble in the fluid of the digestive system. In the case of soluble coating materials, the dosage form may include a variety of granules or cores having 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 processes. However, with insoluble coating materials, the release process will be controlled solely by the diffusion through the film coat and the rate limiting step is penetration of the coating

layer not controlled by drug dissolution rate.

A new research product of Boehringer Ingelheim KG., Theophylline granular SR 12, was introduced commercially. It is theophylline granule with a sustained release coating and release rate determined in vitro for a period of 12 hours (=SR12). This product which is a granulated theophylline with controlled release properties is obtained by coating with various grade of Eudragit acrylic resin. The aqueous dispersion is applied by pan coating or fluidized bed processing.

This present work was a study of the preparation of sustained release granules by means of the fluidized bed coating technique.

The core granules were prepared by the wet method using PVP K30 as a binder. Previous study(Eerikainen and Lindqvist,1991) reported that fillers in granules significantly affectd drug release behaviors. This study also investigated the effects of fillers such as microcrystalline cellulose (Avicel PH101®), corn starch, dibasic calcium phosphate (Emcompress®) and lactose.

Ethylcellusose was selected to be a coating polymer since it is probably the most widely used water insoluble polymer for film coating; giving a satisfactory control of the drug release pattern as well as inexpensive

and easy to prepare into a coating solution(Porter,1989).

## Objectives

On the basis of the rationale mentioned above, the objectives of this research are

1. To study the influence of various filler excipients on the theophylline release from theophylline granule coated with varying amount of ethylcellulose by fluidized bed coater.

2. To determine the optimal level of ethylcellulose coating and type of filler excipient which would exhibit a satisfactory in vitro release pattern.

3. To prepare theophylline sustained release tablets using coated granules technique.

4. To compare the releases profiles of tablets prepared from coated granules with a commercial product.

Literature Reviews

## 1. Sustained Release Dosage Forms

Such products are designed to produce sustained blood concentrations of drugs at minimum effective levels for prolonged periods, that is, at least two to three times longer than those obtained with regular dosage forms, such as capsules and tablets.

### 1.1 Drug Available in Sustained Release Form

Drugs with long biological half_lives or requiring large doses should not be formulated as prolonged action products. Drugs used for chronic conditions, with medium-duration half_lives, in small doses are much better candidates for such formulations.

The number of drug substances that are currently available in sustained release dosage form is illustrated in Table 1 (Welling, 1983)

Theophylline is one of the drug candidates prepared in sustained release dosage forms. The use of properly designed sustained release preparations can offer several advantages. The main advantage is reduction in fluctuations of theophylline serum concentrations, which could result in continuous protection of the patient

against attacks of bronchospasm.

Table 1 Some Substances Available in Sustained Release Form (Welling 1983)

Vitamins, Minerals, and Hormones

Ascorbic acid
Iron preparations
Methyltestosterone
Nicotinic acid
Potassium
Pyridoxine
Vitamin combinations

Diuretic and Cardiovascular Drugs

Acetazolamide
Ethaverine HCl
Isosorbide dinitrate
Nicotinyl alcohol
Nitroglycerin
Papaverine HCl
Pentaerythritol tetranitrate
Procainamide
Quinidine gluconate and sulfate
Reserpine

CNS Drugs

Amphetamine sulfate
Aspirin
Caffeine
Chlorpromazine
Dextroamphetamine sulfate
Diazepam
Diethylpropion HCl
Fluphenazine
Indomethacin
Lithium
Meprobamate
Methamphetamine HCl
Orphenadrine citrate
Pentobarbital
Pentylenetetrazole
Perphenazine
Phenmetrazine HCl
Phenobarbital
Phentermine HCl
Phenylpropanolamine HCl
Prochlorperazine

Respiratory Agents

Aminophylline
Brompheniramine maleate
Carbinoxamine maleate
Chlorpheniramine maleate
Combination, antitussive
Combination, expectorant
Combination, upper respiratory
Dexchlorpheniramine maleate
Dimethindene maleate
Diphenylpraline HCl
Dyphylline
Phenylpropanolamine HCl
Pseudoephedrine HCl and sulfate
Theophylline
Trimeprazine
Tripelennamine HCl
Xanthine combinations

Antimicrobial

Tetracycline

Gastrointestinal Drugs

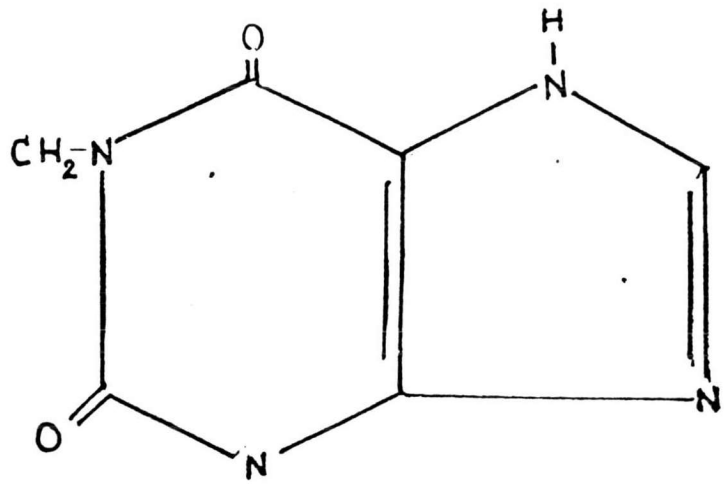
Belladonna alkaloids
Hexocyclium methylsulfate
l-Hyoscyamine sulfate
Isopropamide iodide
Prochlorperazine maleate
Tridihexethyl chloride

Other

Pyridostigmine bromide

Theophylline, 1H-Purine-2,6-dione,3,7-dihydro-1,3-dimethyl-mono or anhydrous;1,3-dimethylxanthine, is a dimethyl xanthine. Its structural formular is given in Figure 1 along with its molecular weight (Cohen, 1975). It is white, odorless, crystalline powder with a bitter taste. Its saturated aqueous solution is neutral or slightly acid to litmus. The solubilities are 8.3 mg/ml in water, 12.5 mg/ml in ethanol, 11.6 mg/ml in chloroform, and freely soluble in solutions of alkali hydroxides and ammonia. It melts at about 269°C-274°C. Theophylline is stable in air. Its solutions are generally quite stable over the entire pH range.

Absorption is delayed by the presence of food in the gastrointestinal tract. The time required to reach peak plasma level varies with the route and formulation used; following oral administration of capsules or uncoated tablets, peak plasma level are reaches in 1 to 2 hours (Gennaro et al, 1990). Theophylline plasma or serum of about 10 to 20 μg/ml are usually needed to produce optimum bronchodilator response. Adverse reactions to theophylline often occur when plasma levels exceed 20 μg/ml and becomes progressively more severe at higher serum concentrations. Tachycardia, in the absence of hypoxia, fever, or administrtion of sympathomimetic drugs, may be an indication of theophylline toxicity. Anorexia, nausea and occasional vomiting, diarrhea, insomnia, irritability, restlessness, and headache




Molecular weight = 180.17(anhydrous)

= 198.18(monohydrous)

Figure 1 Chemical Structure of Theophylline

commonly occur(Gennaro et al, 1990).

The first modern sustained release theophylline, Aerolate®, was marketed by Fleming and Co. in 1972-73 (Shangraw, 1988).The product-Aerolate® is still marketed today and is composed of enteric coated beads designed to simply bypass the stomach. Shortly thereafter, another small company, Dooner, introduced the first truly sustained release theophylline product under the name Slophylline Gyrocaps®.

In 1977, Key Pharmaceuticals, Inc. introduced Theodur® and promoted it on pharmacokinetic principles zero order release. Theodur® is one of the most complicated products in terms of both formulation and method of manufacture. It is a combination of coated beads embedded in a slowly disintegrating matrix. The theophylline was coated onto sugar beads which were then enclosed in various coatings of lipid material (glyceryl monosterate, cetyl alcohol, beeswax) and/or an acid polymer cellulose acetate phthalate. The beads were then compressed into slowly disintegrating waxy type matrix tablet containing additional drug. It has relatively uniform release pattern over a 12-18 hours period of time (Shangraw,1988).

## 1.2 Technology to Achieve Oral Sustained Release Form

Various technology have been used by pharmarceutical company to achieve sustained therapy with oral dosage forms:(Swarbrick and Boylan, 1988)

A. Coated Granules: Varying thickness of a waxy coating are applied to granules of drug. Such coatings are designed to erode, disintegrate, or emulsify at varying rates, depending upon their respective thickness. Such granules can be encapsulated in hard or soft gelatin capsules or may be formulated into compressed tablets.

B. Leaching from Inert Carrier: In this case, the drug is granulated with inert plastic resins and water soluble, nontherapeutic compounds that channel aqueous, GI fluids into the core tablet to leach the drug at a constant sustained rate. Thus, the tablet does not disintegrate, and after the drug leached, the porous "empty" resinous core is excreted.

C. Eroding Core Tablets: In this type, the sustaining drug portion is formulated as a non disintegrating waxy core tablet from which the drug is slowly released to achieve sustained blood levels. An initial dose portion can be included in a compression coating or pan-coating portion of the tablet.

D. Ion-Exchange Resins: Cationic or Anion exchange resins have been used to complex with suitable drugs. Such drug-resin granules can be encapsulated. Upon oral administration, the drug is displaced (exchanged) from the resin at appropriate rates by various ions of the GI fluids

Recently, these drug-resin complexes have been encapsulated or coated with appropiate polymer. Such coating effectively mask unplesant, resinous taste. This has allowed incorporation of such coated granules in viscous, syrup vehicles for oral, liquid dosing as, for example, cough syrups.

E. Other Complexation: Certain compounds (e.q.,tannic acid, galacturonic acid) have been used to complex with various drugs. The resulting compound is then formulated into tablets. Upon oral administration, such complexes release the drug gradually and uniformly to the GI fluids.

F. Diffusion through Appropriate Polymer: Drug granules can be microencapsulated with selected polymeric materials that are not water soluble but that allow water passage and ultimate diffusion of drug solution to the GI tract. Such coated granules then can be compressed into tablets or encapsulated in gelatin shells.

G. Osmotic Pressure Drug Release: Core tablets of drugs can be coated with polymers that allow water into the core (semipermeable). The water dissolves the drug. The resulting solution cannot pass through this "membrane" coating in this cases. Thus, a significant osmotic pressure develops within the tablet (if the dose of drug and the resultant osmotic pressure is small, other nontherapeutic, osmotic pressure-building compounds can be included). Each such tablet has a tiny hole cut through the coating into the core by laser technology. The osmotic pressure then causes the drug solution to be forced through the opening at a sustained (zero-order) rate.

Sustained therapy also has been achieved in recent years by other than oral routes. Thus,the osmotic pressure technology has been adapted for release form tiny discs (Ocusert®) placed under the lower eyelids for ophthalmic disorders such as glaucoma. Wise like, sustained release through appropriate membranes, from semisolid matrices or from tiny, microencapsulated beads that are incorporated into the adhesive components of plastic "bandage" strips, has been used to achieve prolonged therapy through percutaneous absorption by adaptation into medicated dermal patches

Products that are representative of well established and also some more novel categories are

summarized in Table 2 (Welling, 1983). This list will increase further as more novel dosage forms are introduced

## 2. Film Coating Equipment

Current coating equipment has derived from two basic principles: The traditional pan coaters and the fluidized beds. The main advantage of the pan type coaters is that they can carry out both sugar coating and film coating even in large batch size. The disadvantages are poor control of the product flow pattern and low drying capacity.

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 recieved increased interest owing to its ability to apply virtually to 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 spray from the top, from the bottom or tangentially.

### 2.1 Top Spray Method.

The conventional top spray method shown in Figure 2 has been used for more than a decade for coating. It evolved from the fluidized bed drugs

Table 2 Some Categories of Oral Controlled Release Dosage Forms (Welling, 1983)

| Category | Product | Active Ingredient |
|---|---|---|
| 1. Slow erosion with initial fast release dose | Tedral SA | Theophylline, ephedrine HCl, phenobarbital |
| 2. Erosion core only | Tenuate Dospan | Diethylpropion HCl |
| 3. Repeat action tablets | Chlor-Trimeton Repetabs | Pseudoephedrine sulfate, chlorpheniramine maleate |
| 4. Pellets in capsules | Combid Spansule | Isopropamide iodide, Prochlorperazine maleate |
| 5. Pellets in tablets | Theo-dur | Theophylline |
| 6. Leaching | Desbutal Gradumet | Methamphetamine HCl, pentobarbital sodium |
| 7. Ion-exchange resins | Biphetamine | Amphetamine, dextroamphetamine |
| 8. Complexation | Rynatan | Chlorpheniramine, phenylephrine, and pyrilamine tannates |
| 9. Microencapsulation | Nitrospan | Nitroglycerin |
| 10. Flotation-diffusion | Valrelease | Diazepam |
| 11. Osmotic pressure | Osmosin[1] | Indomethacin |

[1] U.K. market.

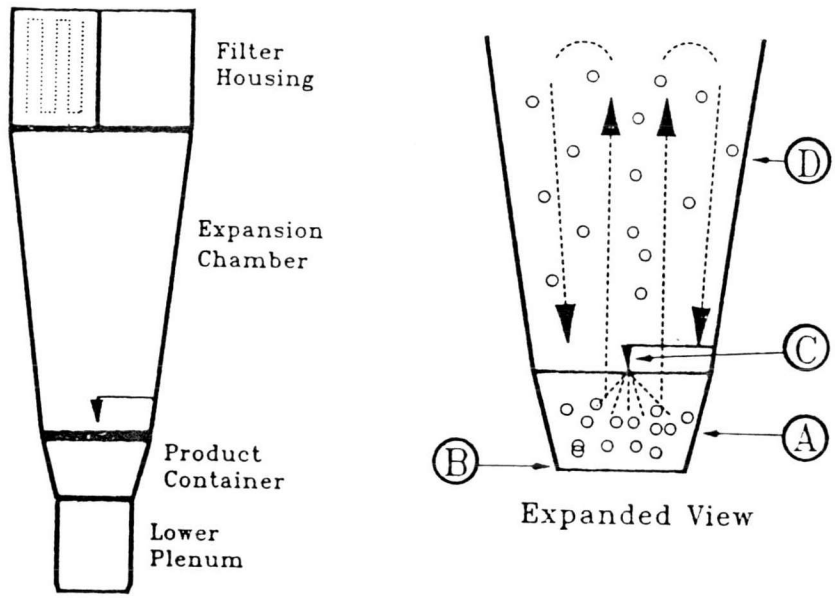



**Figure 2** Top Spray Coater:(A)Product Container; (B)Air Distribution Plate; (C)Spray Nozzle; (D) Expansion Chamber (Swarbrick and Boylan, 1988.

commercialized more than 30 years ago (Swarbrick and Boylan,1988).

The substrate is placed in the product containner(A), which is typically an unbaffled, inverted, truncated cone with a fine 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 system

The particles are accelerated from the product container part 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 result in a decreasing air velocity that allows decelaration of the particles to below entrainment velocity. The particles fall back into the product contianer and continue cycling throughout the duration of the process.

## 2.2 Bottom-Spary Coating (Wurster Process)

The Wurster process,Fig 3, was invented by Dr. Dale Wurster(Swarbrick and Boylan, 1988), then at the University of Wisconsin, This technique is significantly different form those discussed previously.

The Wurster machine employs a cylindrical product container with a perforated plate. Inside the container is a second cylinder (coating partition), which is raised slighthy above the perforated plate. Centered in the plate below this partition is a spray nozzle used to dispense the coating solution. The perforated plate is

designed with large holes in the area under the coating partition and smaller holes in the remainder of the plate, except for one ring of large holes at the perimeter. This design allows the substrate particles to be pneumatically transported upward through the coating partition, and downward outside this partition. Material passing through the coating partition receives a layer of coating material, dries in the expansion chamber, and falls back in a semifluidized state. Material circulates rapidly in this fasion and receives a layer of coating on each pass through the coating partition.

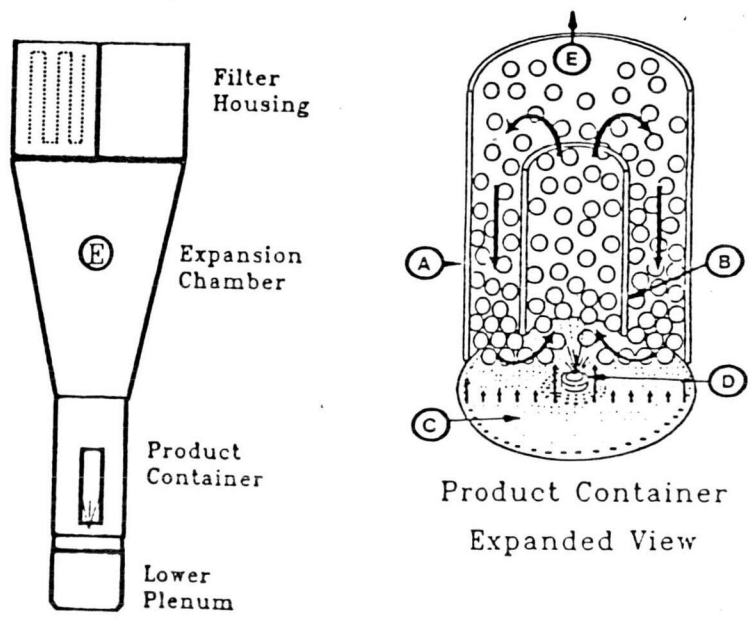



Figure 3 Wurster Bottom Spray Coater:(A) Coating Chamber; (B) Partition ; (C) Air Distribution Plate; (D) Spray Nozzle ;(E) Expantion Chamber (Swarbrick and Boylan, 1988)

The qualitative characterstics of the Wurster coater process, Figure 4, are described below (Yum and Eckenhoff, 1981).

Regions 1 and 2

Solid particles are sucked from region 1 into region 2 because of a pressure differential that exists between the two regions: The pressure in region 2 ($P_2$) is normally lower than that at region 1 ($P_1$).

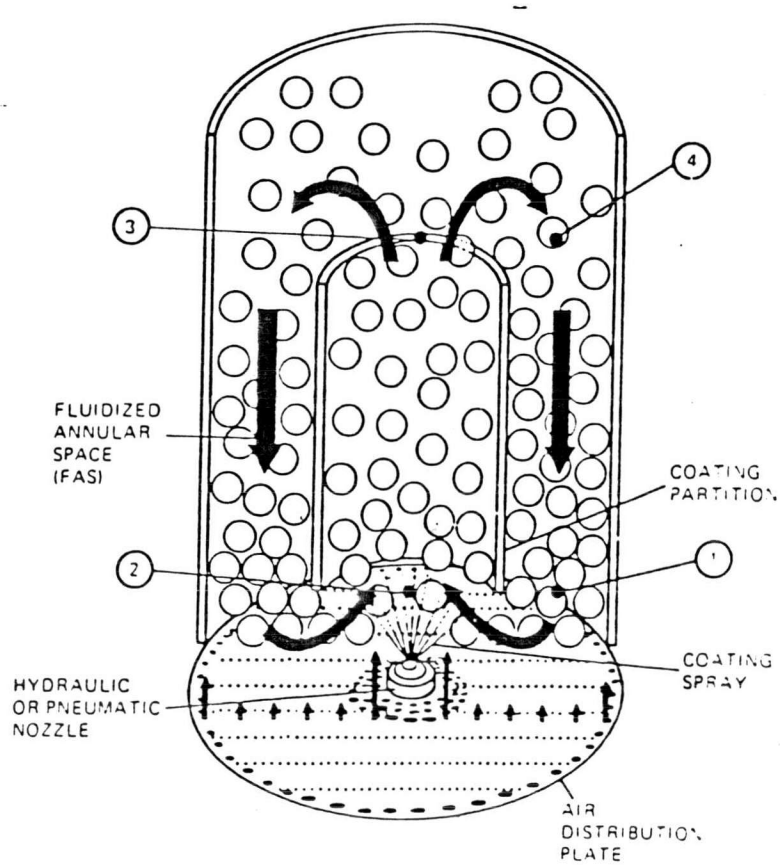



Figure 4 Diagram of the Wurster Coating Chamber.
(Yum and Eckenhoff, 1981)

Reverse flow of air will occur, however, if $P_2$ is greater than $P_1$. This situation, which may create a sluggish flow of particles in both coating partition and fluidized annular space (FAS), occurs when the equipment is operated with too large a gap between the bottom of the partition and the air distribution plate for a given particle size, bulk density and air flow-rate.

## Rigions 2 and 3 (Coating Partition)

The phenomena occuring between regions 2 and 3, the coating partition, are analagous to those of a vertical pneumatic conveyor. The total air flow is the sum of the air injected through the spray nozzle, the air by passing from region 1 to 2, and the air supplied through the openings of the air distribution plate directly under the coating partition. Concurrent with the conveying action, liquid spray is generated from the nozzle and deposited onto the solid particles. Evaporation of volatile solvents in the liquid that is deposited on the solid particle surfaces starts in the coating partition. Particle-particle and particle-partition interactions may lead to attrition of solid particles. The effects of collisions may vary, depending on the magnitude of kinetic energy of the particles, the specific surfaces area of the solid particles, the specific loading, properties of the coating material deposited on the particle surfaces, and geometric factors of the solid particles.

Regions 3 and 4 (Expansion Chamber)

The velocity of air flow begins to decrease in region 3. Between regions 3 and 4 called the expansion chamber. The air velocity decreases below that necessary to support solid particles. When the air velocity becomes less than the supporting velocity of the particles in the expansion chamber, the particles fall into region 4. Convective drying of the solvent from the wet coating continues in the expansion chamber. Particle-particle and particle-wall interactions once again can lead to attrition in this region. Again, the effects of collisions depend on the several factors listed previously.

**Regions 4 and 1 (Fluidized Annular Space)**

The solid particles in this region descend, thereby forming a downward-moving fluidized bed. At steady state, the rate at which the solid particles recirculated through region 4 to region 1 is the same as that of the solid conveying rate in the coating partition or the feeding rate from region 1 to region 2.

Significant evaporation of the solvent in the wet coating on the solid particles occurs between regions 4 and 1, Though the rate of drying depends on voidage, air flow rate, particle geometry, and other transport properties, such as fluid density, viscosity and diffusivity of solvent

through coating.

## 2.3 Tangential Spray (Rotary Fluidized Bed Coating)

A relatively new approch to coating is referred to as tangential coater (Fig 5)(Swarbrick and Boylan, 1988). Originally conceived for high-density fluid bed granulation, this technique is being used to produce high dose pellets by applying a layer of drug particles to some type of material. The controlled release coating can subsequently be applied.

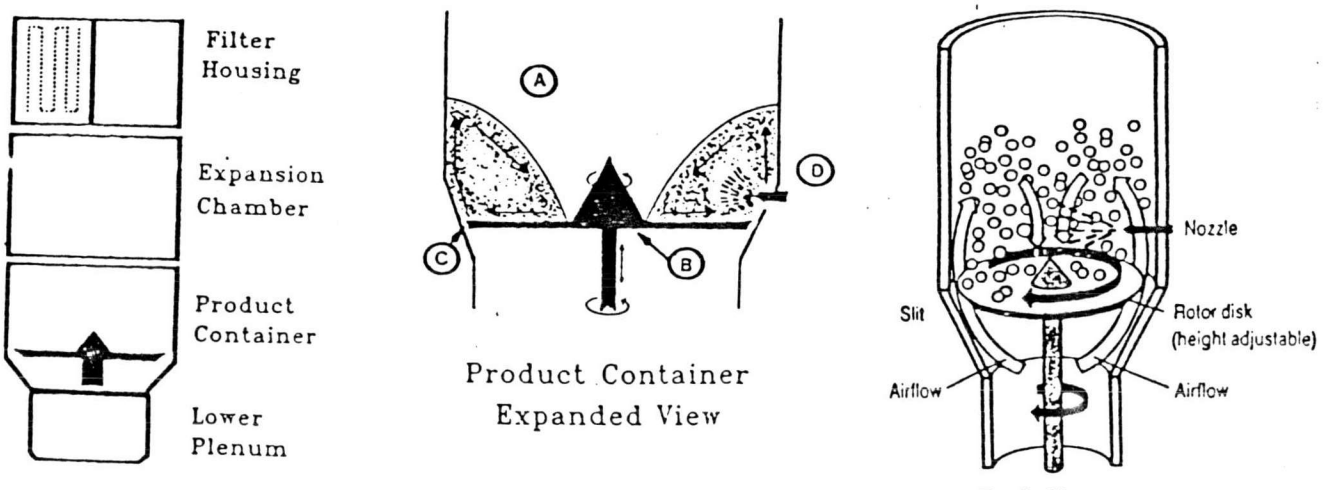



Figure 5 Rotor Tangential Spray Coater : (A) Product Chamber ; (B) Variable-speed Disc; (C) Disc Gap or Slit; (D) Spray Nozzle (Swarbrick and Boylan, 1988)

The product container consists of an unbaffled cylindrical chamber (A) with a solid, variable-speed disc (B) at its base. 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 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.

The three fluidized bed process offer different advantages and disadvantages, as shown in Table 3(Metha, 1988), and consequently the performance requirement of the finished product must be considered when selecting a coating process for a particular product.

Many advantages of fluidized bed coating method over the pan-coating technique were stated(Friedman and Donbrow, 1978): a) Irregular particles may be coated directly. b)Loss of material is minimal. c) The process could be automated such that learning the "art" of coating

is not required. d) It saves time and labor.

Table 3 Characteristics of Three Fluidized Bed Coating Process (Metha, 1988).

| 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<br>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<br>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<br>Hotmelt coating possible<br>Not recommended for friable products |

It is possible to encapsulate the small particles by means of this technique which could be applied not only to spherical micro-tablets and pellets with a diameter of 0.5-3 mm, but also to compact granules with finer and more irregular-shaped particles under 0.5 mm in diameter with no particle agglomeration at optimal operating conditions (Lehmann and Dreher, 1979).

## 3. Coating Materials

Various coating materials are applied to powdered particles, granules and compressed tablets for several reasons: protect components from atmospheric conditions; mask unplesant tastes; prevent contact with irritation or potentially allergic compounds; separate reactive ingredients; control site of drug release (enteric coating); delay or prolong absorption of drug components; improve appearance; change the physical surface characteristics of the ingredients (surface modification).

The film former is the major ingredient in a coating formulation. The polymer can be divided into essentially two classes: 1) aqueous soluble polymers and 2) water insoluble or pH dependent soluble polymers (Swarbrick and Boylan, 1988).

The most commonly used aqueous-soluble polymers consist primarily of:

Acrylate copolymers: Eudragit E® (cationic copolymer based on dimethylaminoethyl methacrylate and other neutral methacrylic acid esters)

Cellulosic polymer: Carboxymethyl cellulose
Sodium, USP
Hydroxypropylcelllulose, NF
Hydroxypropyl-methylcullulose, USP
Methylcellulose, USP
Methyl hydroxyethyl cellulose

Polyethylene glycol, NF

Povidone, USP

Hydroxypropyl methylcellulose has most of the desired properties. It is water soluble and stable in the presence of heat, light, air and moisture, and its films are flexible, tolerate the presence of colorants and other additives, and are resistant to abrasion.

The water insoluble polymers are used when an enteric coating or a special controlled release delivery system is desired. Some of the most common insoluble polymer candidates are:

Methacrylic acid copolymer, NF: Eduragit L and S® (anionic copolymers based on methacrylic acid and methacrylic acid methyl ester)

Cellulose acetate phthalate, NF(CAP)

Hydroxypropyl methylcellulose phthalate, NF

Polyvinyl acetate phthalate, NF

Ethylcellulose, NF

The phthalate ester derivatives are used as enteric coating polymers. Cellulose acetate phthalate (CAP) was the major enteric polymer for many years, but its films were brittle and they did not dissolved below pH 6.8.

The enteric polymers, hydroxypropyl methylcellulose phthalate and polyvinyl acetate phthalate, are available in different grades that dissolve at lower PH values about 5.5 and 5.0. In addition, the polymer are chemically more stable and form better films than CAP.

The two most common hydroxypropyl methylcellulose phthalates are referred to as HP-50 and HP-55, corresponding to pH values of 5.0 and 5.5 at which the polymers dissolve.

The acrylic resins Eudragit L® and Eudraget S®. provide films that are resistant to gastric fluid, and they are soluble at PH 6 and pH 7.

The ethylcellulose has been accepted as a non toxic pharmaceutical agent and proved to be useful as a binder in tablet and film coating material for tablet and drug particles. It is free-flowing white to light-tan

powder which is tasteless and odorless. Aqueous ethyl cellulose suspensions are neutral to litmus. It is completely insoluble in water and gastrointestinal fluids. The polymer is soluble in a wide range of organic solvents such as ethyl acetate, ethylene dichloride, benzene, toluene, xylene, butyl acetate, acetone, methanol, ethanol, carbon tetrachloride etc. It forms film with a refractive index of 1.47. The polymer is also quite stable under most environment conditions. Moreover, the release of drug from granules coated with ethylcellulose film is not dependent on pH of the extraction medium. There fore, ethylcellulose was extensively used either alone or in combination with water soluble polymers in coating drug granules or tablets for the purpose of controlling drug release in manufacture of sustained release dosage forms by many workers(Fassihi and Munday, 1988; Li, Metha, Buehler, Grim and Harwood, 1990; Friedman and Donbrow, 1978; Eerikainen and Lindqvist, 1991; Sarisuta and Sirithunyalug, 1988; Friendman, Donbrow and Samuelor, 1979).

Many workers studied preparation of sustained release dosage forms by means of the fluidized bed coated techniques:

Nicotinic acid (niacin) was prepared as sustained release pellets by polymer coated techniques (Sheen, Sabol, Alcorn and Feld, 1992). Fluid bed coating

machine with a Wurster column was used to apply Surelease® dispersion to the niacin pellets. According to scanning electron microscope examination, the surface of the coated pellets appears smooth and continuous, possibly due to the complete curing of Surelease® coating during the coating process. The test showed the release of niacin was able to be controlled by a level of Surelease® coating.

Eerikaner and Lendqvist (1991) investigated the release of indomethacin from polymer coated granules. The result showed that permeability of the film was modified by incorporating varying amount of hydroxypropyl-methylcellulose. The ratio of ethylcellulose and hydroxypropyl methylcellulose affected the release of indomethacin from film coated granule using a fluidized bed technique irrespective of the filler in the granules.

The investigation of Sarisuta and Sirithunyalug (1988) also studied sustained release indomethacin granules by means 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 the first order release rate constant.

Friedman and Danbrow(1978) 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 material. The results showed that the instrument has been succesfully used producing sustained release products by coating granules of model drug with ethylcellulose.

Theophylline was also prepared as sustained release granules by fluidized bed coater. But they were studied only for the effect of additives used in coating solution to theophylline release:

Li, Mehta , Bueher, Grim and Harwood (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 ethylcellulose dispersion could be used for the manufacture of controlled release product. The incorporation of water soluble materials into the dispersion could increase the in vitro release of theophylline from the coated granules.

Eudragit® E30D was utilized in conjunction with talcum and xanthan gum to coat the theophylline granules via a Wurster coating column (Li, Jhawar, Metha , Harwood and Grim, 1989). The release profile of theophylline from the coated granule was found to be dependent on the ratio of the additives to the resin used in the coating

suspension as well as on the coating level applied to the final product.

All of details above suggest that the fluidized bed coating technique is appropriate for preparation of sustained release dosage form by way of coating small particles or granules.