CHAPTER I

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 μg/ml. (Joknman, Schoen-maker, Grimeberg and Zeevw, 1981). Conventional theophylline dosage forms require drug intake every 6 hrs. Such a schedule may result in low trough level in the moring 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 concerned with the first type of product which in practice may be produced using coating technique (Friedman and Donbrow, 1978).

Film coating is one of the accepted methods of prolongation of drug release from granules (Friedman, Donbrow and Samvelov, 1979). The coating material may be soluble or insoluble in the fluid of the digestive system. Some of the most common insoluble polymer candidates are methacrylate ester copolymer (Eudragit® RL and RS, Eudragit® NE), cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, ethylcellulose

Surelease® (Ethylcellulose aqueous dispersion) and Eudragit® NE 30 D [Poly (ethylacrylate methylmethacrylate) aqueous dispersion] are selected to be a film coating since the both aqueous polymeric dispersion had sustained release action characteristic and were continuously dispersed in water. While initial emphasis was places on using organic solvent-based solution of these polymer, more recent introduction of aqueous polymeric dispersion of ethylcellulose and poly(ethylacrylate methylmethacrylate) have attracted a lot of interest for save environment. The principal means of drug release of these polymers is diffusion through the polymeric membrane. This is initiated by flaws (dislocations) caused by stress cracked segments of low mechanical strength, or through pores resulting from localised incomplete coalescence during the initial stages of film formation. Osmotic pressure can also contribute to diffusion in some cases. The rate of release is controlled by the degree of porosity, tortuosity, geometry and thickness of film. (James, 1989)

In pharmaceutical production, fluidization methods are utilized in stages of drying, granulation and coating. As a coating technique, its main advantages over the pan coating method are as follows : (a) irregular particles may be coated directly, (b) loss of material is small, (c) the process may be automated and does not require learning the "art" of coating, (d) it is very rapid. The coating morphology and dissolution characteristics of the finished product can be effected by the variables of the fluid bed process such as (Jones, 1985) : the processing time, atomization air pressure, fluidization air temperature, fluidization air volume.

Study various sizes and various coating levels of granules significantly affect drug release behaviors. The release of drug from smaller granules is faster than from the larger granules and the rate of drug release is related inversely to the thickness or the coating levels of the coat, suggesting that the film and the particle size are controlling the release process. Similar effect was found by Li, Feld and Kowarski, 1991.

The present work is a study of the preparation of sustained release granules by means of the fluidized bed coating techniques are also investigated the effect of various coating levels of aqueous polymer dispersion coated on theophylline granules and various particle sizes of granules on release rate profile of drug.

OBJECTIVES

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

1. To prepare sustained release granules of theophylline by coating with poly(ethylacrylate methylmethacrylate) or ethylcellulose aqueous dispersion.

2. To study the suitable conditions of the coated theophylline granules by fluidized bed technique.

3. To determine the optimal level of poly(ethylacrylate methylmethacrylate) and ethylcellulose aqueous dispersion coating which would exhibit a satisfactory in vitro release pattern.

4. To study the influence of various particle size on the theophylline release from theophylline granules

5. To study the physiochemical properties of coated theophylline granules and the preparation of capsule containing coated theophylline granules.

Literature Reviews

The objective of developing a modified-release dosage form for oral administration is to control the release of the therapeutic agent and thus control drug absorption from the gastrointestinal tract.

Modified-release dosage forms are unique in that they attempt to stabilize the availability of the drug for absorption from one dose administration to the next , thereby providing a more stable plasma level profile , one characterized by fewer peaks and valleys than the profiles of conventional dosage forms. Release rate reproducibility within a given batch and between batches is critical for the manufacturer and the patient. The manufacturer must abide by rigid specifications set for the product and will lose profits if a batch fails to meet these specifications and cannot be reworked. The patient loses the therapeutic benefits of the specialized dosage form if the product fails (James, 1989).

The terms , controlled release and sustained release are not new to many of us working in various disciplines of pharmaceutical research and development.

Controlled-release drug administration means not only prolonged duration of drug delivery , as in sustained-release and prolonged release , but also implies predictability and reproducibility of drug release kinetics.

Technology to Achieve Oral Sustained Release

Various technology have been used by pharmaceutical 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-release dosage forms employs polymeric coatings or matrix materials and a class of colloidal or near colloidal aqueous polymer dispersions as rate limiting film membranes (James, 1989). These dispersions or aqueous

polymer emulsions may be prepared by emulsion polymerization contain small polymer particles averaging about 0.1-0.3 μm in diameter, but the precursor monomers are limited to those that are polymerizable in an aqueous medium in the presence of free radical initiators. Polymer emulsions from monomers not so polymerizable are prepared by emulsifying the previously polymerized monomers by means of any of a number of general types of emulsification procedures.

A multiple-unit type of dosage form such as pelllets or granules, compared to single-unit type such as tablets, is less influenced by variations in the gastric emptying rate and overall gastrointestinal transit time and therefore has more reproducible absorption behavior. The advantages of multiple-unit dosage form product over single-unit dosage forms have been demonstrated by several workers.

The coating of particulates such as powders, granules, pellets and tablets to produce controlled-release dosage form is becoming increasingly popular, mainly as a result of recent advances in fluidized-bed process (Donbrow and Friedman, 1978).

Theophylline in Sustained Release

Sustained release dosage forms are of great interest for the formulation of an oral drug containing an active ingredient with short half-life in plasma and narrow therapeutic range. They offer a way to reduce the number of administration. In recent years, many drug entities has been developed into sustained release products. 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.

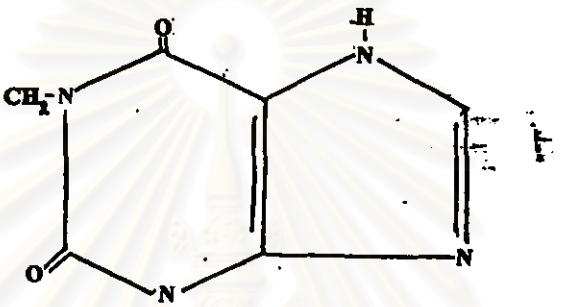
Anhydrous theophylline, Its structure formular is given in Figure 1 along with its molecular weight (Cohen, 1975). It is white, odorless, crystalline powder with a bitter taste. Its saturated aqueous solution is neutral or slightly acid to litmus. The solubilities are 8.3 mg/ml in water, 12.5 mg/ml in ethanol , 11.6 mg/ml in chloroform, and freely soluble in solutions of alkali hydroxides, ammonia and mineral acids. 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 administration of sympathomimetic drugs, may be an indication of theophylline toxicity. Anorexia, neusea and occasional vomiting, diarrhea, insomnia, irritability, restlessness, and headache 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 by pass the stomach. Shortly thereafter, another small company, Dooner, introduced the first truely sustained release theophylline product under the name Slophylline Gyrocaps®.



Molecular weight = 180.17 (anhydrous)

= 198.18 (monohydrous)

Figure 1 Chemical Structure of Theophylline

Materials Used in Coating Formulations

Surelease® (Ethylcellulose aqueous dispersion)

Surelease® is an off-white opaque liquid dispersion of colloidal ethylcellulose with plasticiser. The plasticiser is already incorporated within the polymer during the unique manufacturing process. It has the characteristic odour of ammonia. It is the most technologically advanced system available for controlled release membrane coatings and matrix applications. It can also be used as a functional polymer in barrier for taste masking and moisture protection. Its structure formula is given in Figure 2

Surelease® has a solids content of 25% with a nominal particle size of 0.2 microns. Its pH is 9.5-11.5 and a specific gravity of 1.00-1.05.

Surelease® is a stable dispersion but should not be stored above 30^0C and should be protected from freezing. Partly consumed containers should be thoroughly stirred before use.

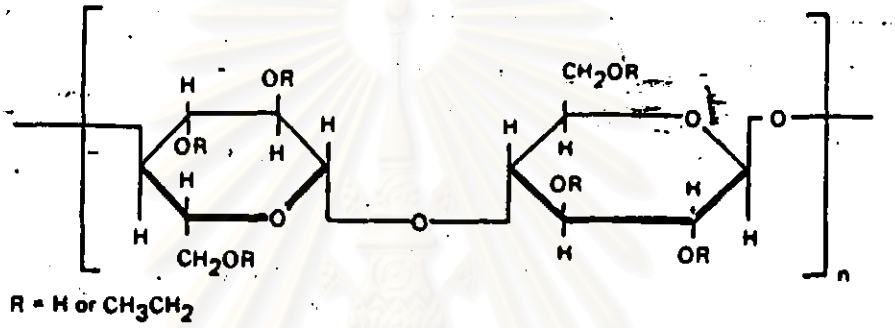


Figure 2 Structural formula of Surelease®
(ethoxy content 48-49.5 %)

Surelease® is Composed of the Following Ingredients

Ethylcellulose : This has a long history of use in the pharmaceutical industry as a sustained-release polymer. It forms a relatively impermeable barrier. Due to its water insolubility, it has been finely dispersed in the Surelease system.

Dibutyl sebacate and oleic acid : These ingredients are the plasticizers for the Surelease system. In the manufacturing process they are incorporated within the dispersed polymer particles to achieve a consistent and effective plasticizer level.

Ammoniated water : Ammonia is used to stabilize the dispersed polymer and as the vehicle for the system. It imparts a characteristic ammonia odor to the product.

Fumed silica : This ingredient is added to facilitate the application of Surelease; it is an antiadherent.

Advantages of Surelease®

1. Totally aqueous system
2. Consistent, uniform drug release confirmed by stability testing
3. Easy adjustment of release profile
4. Successful results possible at low weight gains
5. Film coalescence occurs during the coating process
6. Drug release relatively insensitive to pH
7. Reproducible release rates though scale up
8. Ease of preparation and coating
9. Plasticiser incorporated with polymer during a unique manufacturing process

Surelease® Applications

a) Controlled release coatings
b) Compressed membrane coated beads
c) Matrix granulations for controlled release
d) Taste masking
e) Barrier-Sealant coating

Beyond its use as an advanced permeable membrane coating for multi-particulates Surelease® has been found to give reproducible profiles when coated beads are compressed into tablets or when used as a wet granulation binder.

Coalescence Theory of Surelease®

The mechanism of film formation from an aqueous system is quite different from that resulting from a solvent based solution. The discrete Surelease® particles arriving on the surface of the substrate are drawn together by capillary forces generated as the water evaporates.

The boundary between adjacent Surelease® particles is breached as a result of viscous flow arising from the remaining energy in the polymer chains, enabling diffusion through the free volume left by the evaporating water.

The extent of coalescense depends on the degree of viscous flow achieved, which is dependent upon effective plasticisation fo the polymer. The integral nature of the plasticiser in Surelease® permits full coalescense of the film to occur during the coating process under standard conditions.

Drug Release of Surelease®

Beyond structural irregularities in the membrane related to the substrate or specific defects arising from formulation modifications or processing conditions, the principal means of drug release is diffusion through the Surelease® membrane. This is initiated by flaws (dislocations) caused by stress

cracked segments of low mechanical strength, or through pores resulting from localised incomplete coalescence during the initial stages of film formation.

The nature of the drug is also important, particularly its solubility or specific chemical affinities.

Osmotic pressure can also contribute to diffusion in some cases. The rate of release is controlled by the degree of porosity, tortuosity, geometry and thickness of film and can further be modified by the use of fillers or additives. Typically, easily hydrated, swelling or water soluble components are added.

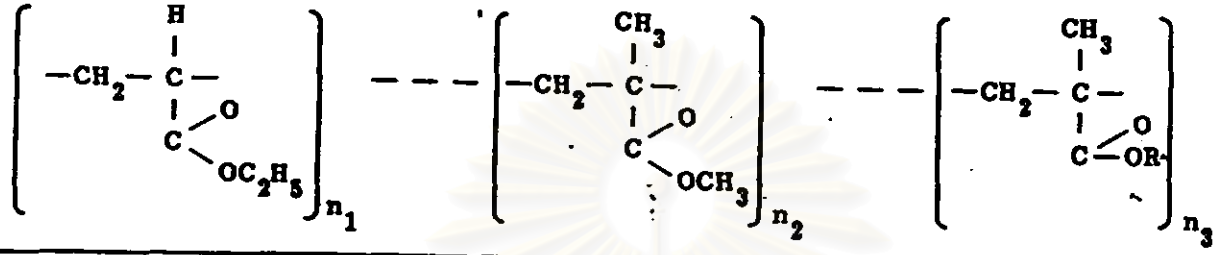
As Surelease® is a totally preformulated system, initial studies will allow rapid optimization of release profiles to meet performance requirements with minimum adjustment of process or formulation parameters.

Surelease® is a ready prepared dispersion, it is easy to use. To facilitate spraying it is recommended that the total solids content of the formulation be diluted to 15% using purified water and gently stirred for 15 minutes using a low shear mixer. Vigorous mixing should be avoided. It is imperative that the final suspension be continuously agitated throughout the coating process. Surelease® is easy to spray in various types of equipment under standard coating conditions. Fluid bed coating is the usual technique employed for the coating of small particles, althrough side-vented pans are extensively used.

Eudragit® NE 30D (Poly (ethylacrylate methylmethacrylate) Aqueous Dispersion)

Eudragit ®NE 30D is a neutral poly (meth) acrylate which consists of emulsion polymers of ethylacrylate and methylmethacrylate, including such products as poly (EA-MMA) 2:1. Its structure formular is given in Figure 3. It is described in the Federal Register under "Food Additives" as safe for use as a food-contact surface for articles intended for packaging and holding food, including heating of prepared food. The molecular weight is around 800,000. The latex contains 30% solids including some emulsifier. The polymer Eudragit® NE 30D is not commercially available as a solid. A sticky powder that tends to form lumps can be prepared by freeze - drying. The polymer has no functional groups and is practically neutral. Therefore the films are insoluble in water and in aqueous buffer solutions over the entire physiological pH range but will swell in water and give permeable membranes. The permeability is independent of the pH. Eudragit® NE 30D meets the requirements of solubility tests given in the Federal Register:Exposed to water at 212^0 F for 30 min and also to n-heptane at 120^0F for 30 mins , it will yield total chloroform-soluble extractables not to exceed 0.5 mg/in^2. The total amount of residual monomers in the latex is less than 0.1% of solid material. It is used mainly for sustained-release and transdermal drug formulations. The MFT (minimal film forming temperature) is around 5^0C , and a soft, flexible film is formed at room temperature without any plasticizer. Normally no reactions or absorptive effects are observed when the polymer comes in direct contact with drug substances , so it is a very useful material for embedding drugs, for granulation processes, and also for protective coatings. Changes in pH do not alter the properties of the polymer, and the latex is not very sensitive to the incorporation of drugs or excipients.

Methacrylate ester copolymers



Scientific name	$n_1:n_2:n_3$	MW	Behavior in digestive juices	Eudragit type	Marketed form
Poly(ethylacrylate. methylmethacrylate)	2:1	800,000	Insoluble films of medium permeability	NE 30 D	30% aqueous dispersion
Poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride R: $CH_2—CH_2—N^+(CH_3)_3Cl^-$	1:2:0.2	150,000	Insoluble films of high permeability	RL 30 D	30% aqueous dispersion
				RL 100	Granules
Poly(ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride) R: $CH_2—CH_2—N^+(CH_3)_3Cl^-$	1:2:0.1	150,000	Insoluble films of low permeability	RS 30 D	30% aqueous dispersion
				RS 100	Granules

Figure 3 Structural Formula of Methacrylate Ester Copolymers

The pigment-binding capacity of the polymer is very high, so that up to 2-3 parts by weight of additives can be incorporated into 1 part by weight of dry polymer without affecting the film properties. The latex is compatible with talc, titanium dioxide, color lakes, iron oxide pigments, and magnesium stearate, when these additives are suspened in water before mixing with the latex. Optimal stability is in the pH range of 7-8.5, but the latex can also be acidified if necessary by adding dilute acid slowly under moderate stirring. As stabilizing agents, neutral surfactants such as polysorbitans and polyoxyethylenealkylphenyl ethers can be used. Carbowaxes can be added as glossing agents, but higher amounts of low molecular weight carbowaxes can cause undersired plasticizing effects. Many solid additives are useful as lubricants or glidants to reduce the stickiness of the polymer during the film forming process and during storage, so a minimum of approximately 25% of such additives calculated on dry polymer basis should be used in any formulation.

To increase the permeability of film layers or to increase the disintegration tendency of matrix structures of drug formulation, several water-soluble or water-swellable substances can be added, such as sucrose, lactose and other saccharides, starch, micronized cellulose, poly (vinyl pyrrolidone), poly (vinyl alcohol) and carbowaxes. Water-soluble cellulose ethers have limited compatability; they stimulate slow agglomeration and coagulation within several hours or days. Cab-o-sil is effective as an additive to prevent sticking of small coated particles during storage, especially at elevated temperatures and high humidity. The hardness of Eudragit ®NE 30D depends on the content of methyl methacrylate and ethylacrylate. As moreethylacrylate and less methylmethacrylate is used, softer polymers result. Eudragit ® NE 30

D forms soft, soft flexible films even below room temperature and does not need any plasticizer for processing.

Film-Forming Mechanisms of Eudragit® NE 30D

Polymer dispersions exhibit a special film-forming mechanism. During the first stage of the drying process, when water eraporates, the lalex particles are layered together to form a dense mass of spheres. During further evaporation, the latex particles flow together provided the polymer substance is soft enough. This process is called coalescence. In this stage the rest of the water is squeezed out of the system, and a practically homogeneous, water-insoluble film is formed.

One driving force of the film-forming process is the profit of surface tension energy, but obviously the capillary forces developing in the channels between the small latex particles in a dense mass play a more important role. It can be calculated using the Laplace equation for pressure, P=2y/r,where y is the interfacial tension between water and air and r is the radius of the latex particles or the curvature of the aqueous meniscus. Both mechanisms were assumed by Bindschaedler et al. to be valid also in film-coating processes. When the radius of the latex particles in the range of 1,000 nm is reduced by one magnitude to 100 nm, the capillary forces increase tenfold. This means that fine particulate dispersions show much better film formation.

Film formation is disturbed when the latex is applied to a porous surface where the water can penetrate into the underlying surface. In this case, the time to build up the capillary forces is shortened and their effectiveness is reduced. This is even more critical as the coating temperature approaches the MFT.

The space between the latex particles in the dense sphere package is only 26% of the whole volume. So the shinkage of the coating layer during film formation is low compared with the drying process of films from polymer solutions, where gelation occurs when 40-60% of solvents are still present.

Stability and Compatibility of Eudragit^{R} NE 30D

Sedimentation of the very small latex particles does not occur because the process is over compensated by Brownian movement and thermal convection. But, in practice, most dispersions, even if they are of good quality, contain some amounts of coarse particles that will form a faint sediment after a few months. If particles are larger than 1 μm, a sediment can be observed after only a few hours. Film formation is scarcely affected as long as particles are not larger than about 5 μm and the amount of sediment is less than about 1% of solid polymer.

Cab-0-Sil M-5

Synonyms : colloidal silica, fumed silica, silicon dioxide fumed, syloid, light anhydrous silicic acid, silicic anhydride functional ; Categor : suspending and/or viscosity increasing aget, glidant and/or anticaking agentant ;Flow conditioning agent: tablet disintegrant; Empirical Formula : S_iO_2 Molecular weight : 60.08 ; Description : submicroscopic, light, loose, bluish-white, odorless, tasteless, non-gritty, amorphous powder

Density : 220 g/l

Compacted bulk : 50-120 g/l

Flowability : 35.52%

Moisture content : 3.8%

Particle size : 7-16 nm

Solubility : Insoluble in purified water; forms a colloidal dispersion ; soluble in hot solutions of alkali hydroxide ; Insoluble in acids, except hydrofluoric ; Insoluble in organic solvents.

Stability and Storage Conditions for Cab-0-Sil M-5

Colloidal silicon dioxide is hygroscopic, but absorbs large quantities of water without liquefying. Store in well-closed container.

Incompatibilities of Cab-0-Sil M-5

The use of silicon dioxide as an excipient may have clinical consequences only for diethylstilbestrol preparations

Safety

Prolonged inhalation of the dust can cause fibrosis of the lung (silicosis). However, no such incidence has been reported. Intraperitoneal and subcutaneous applications may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should not be administered parenterally.

Handling Precautions

Protect the mouth and eyes from dust and avoid excessive inhalation. The working area should be well ventilated. Risk of ignition is minimized by electrical grounding of equipment

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 suger 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 received 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.

Top Spray Method

The conventional top spray method shown in Figure 4 has been used for more than a decade for coating. It evolved from the fluidized bed drugs commercialized more than 30 years ago (Swarbrick and Boylan, 1988).

The substrate is placed in the product container (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

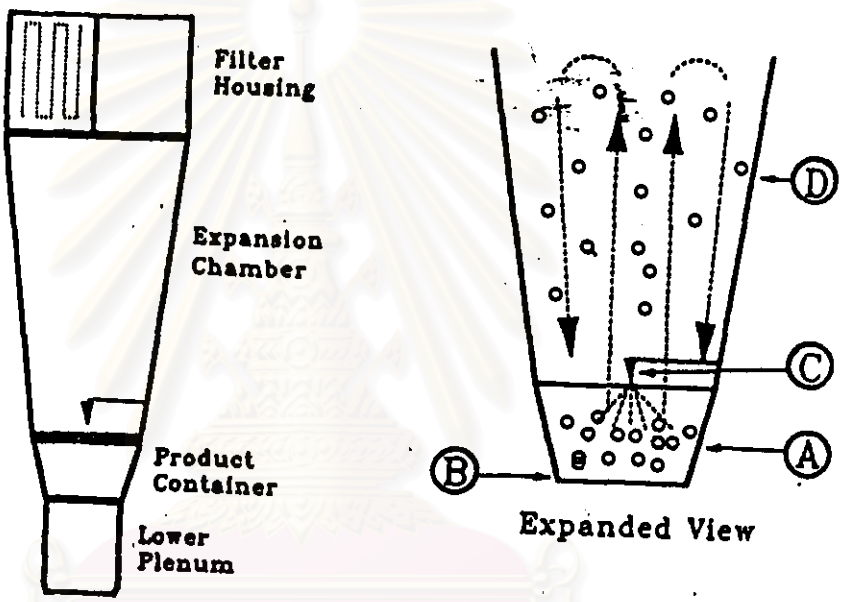


Figure 4 Top Spray Coater : (A) Product Container : (B) Air Distribution Plate; (C) Spray Nozzle; (D) Expansion Chamber (Swarbrick and Boylan, 1988)

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 deceleration of the particles to below entrainment velacity. The particles fall back into the product container and continue cycling throughout the duration of the process.

Bottom-Spray Coating (Wurster Process)

The Wurster process, Fig 5, 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 disperse 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.

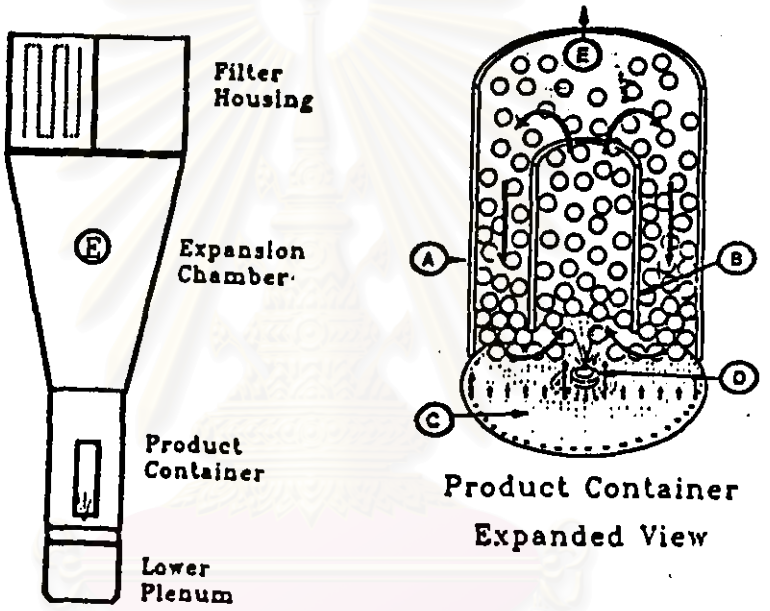


Figure 5 Wurster Bottom spray Coater : (A) Coating Chamber ;
(B) Partition ; (C) Air Distribution Plate ;
(D) Spray Nozzle ; (E) Expantion Chamber
(Swarbrick and Boylan, 1988)

Tangential spray (Rotary Fluidized Bed Coating)

A relatively new approach to coating is referred to as tangential coater (Fig 6) (Swarbrick and Boylan, 1988). Originallly 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.

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 1 (Metha, 1988) and consequently the performance requirement of the finished product must be considered when selecting a coating process for a particular product.

Fluidized bed 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 0.5-1mm, but also to compact granules with finer and

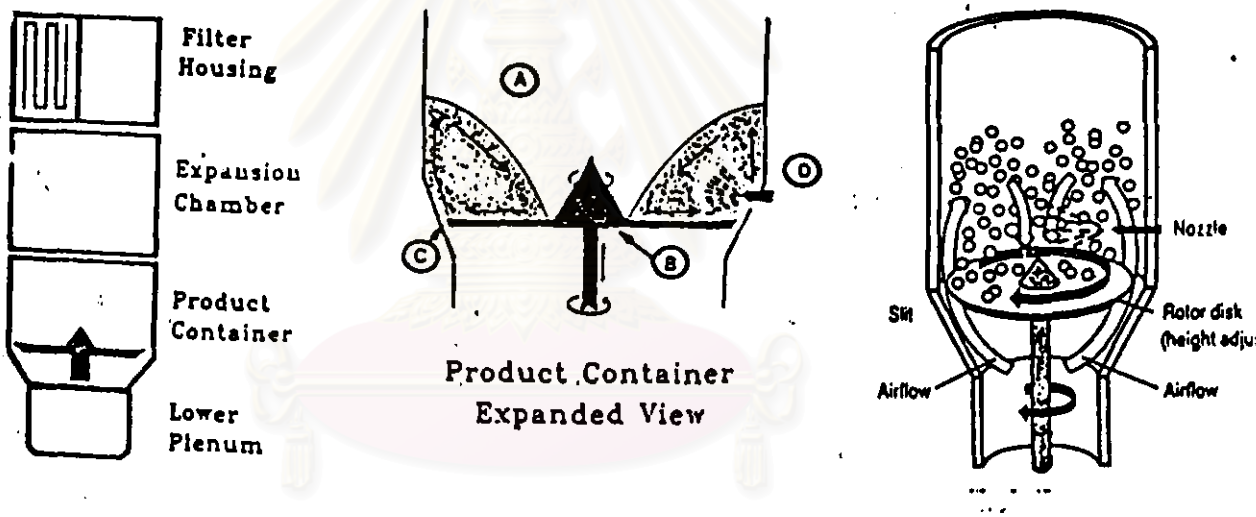


Figure 6 Rotor Tangential Spray Coater : (A) Product Chamber ; (B) Variable-speed Disc; (C) Disc Gap or Slit ; (D) Spray Nozzle (Swarbrick and Boylan, 1988)

Table 1 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
Bottom-spary coating (Wurster)	Accommodates moderate batch sizes, produces unifor 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, entericrelease, 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 possibel Not recommended for friable products

more irregular-shaped particles under 0.5 mm in diameter with no particle agglomeration at optimal operating conditions (Lehmann and Dreher, 1979).

Each approach has its advantages and disadvantages, depending on :

- Batch size of product being coated
- Functionality of the final coating
- Type of coating formulation being applied (eg. solutions, polymeric dispersions, hot melts)
- Flexibility with regard to the variety of types of coating that need to be applied in one piece of equipment.

The coating efficiency of the apparatus was examined on the basis of the following criteria : a) non - blockage of the spray nozzle

b) non - aggregation of the beads

c) homogeneity of the coating in each batch of beads

d) identify of coating in repeated batchs

The coating morphology and dissolution characteristics can be effected by the variables of the fluid bed process such as:

1. Spray Rate

The primary objective of particle coating is to envelope each particle with sufficient coating material to achieve the desired functions. To accomplish this, the size of the coating droplets must be kept small relative to the size of the particle that is to be coated. The liquid spray rate affected the degree of wetting and droplet size. Although increasing the liquid spray rate

increases the droplets size, this also allow for a reduction in the processing time that is necessary.

The spray rate factor also will be determined by the size of the particle of the substance, the viscosity and nature of the liquid to be sprayed, and the temperature of the product.

Although it is possible to reduce the processing time by increasing the spray rate to its maximum level which does not cause agglomeration.

In addition, the atomizing air pressure that is selected might determine the spray rate in term of the size of the droplets.

2. Atomization Air Pressure

The majority of the nozzles that are used in fluid-bed processer are binary. That is, the liquid is supplied at a low pressure and it atomized into droplets by air. As mentioned previously, it is necessary to minimize agglomeration and to provide uniform film characteristics. In general, the higher the atomization air pressure, the smaller the size of the droplets at any given spray rate.

Atomization pressure affects the spraying pattern and droplet size. Excessive high atomization pressure may result in the loss of coating materials and breakage or attrition of the substrates. Excessive low atomization pressure may overwet the core and cause side wall bonding.

3 . Inlet - Air Temperature

The fluidization air temperature is a key variable in the coating process. A low fluidization air temperature might lead to a problem commonly known as the weather effect. In a coating process that uses one or more organic solvents to apply a film, a low fluidization air temperature is often used because of the low heat of vaporization of the solvent. A problem might arise when the dew point of the fluidization air is allowed to vary as changes in the season occur.

The method to avoid the weather effect it is necesary either to control the dew point of the air or to raise the temperature of the fluidization air. If possible, it is preferable to use a much higher fluidization air temperature because this tend to minimize the weather effect. However, a very high inlet air temperature can cause spray drying of droplets. Also, if the product remains too dry and hence is subject to attrition the product yield decrease. With certain thermoplastic polymeric systems a very high inlet - air temperature can also cause agglomeration : The most desirable setting for the inlet-air temperature is one that allows for equilibrium between the application of the solvent as a liquid and its subsequent evaporation so that the film forms properly. For this reason, the heats of vaporization of any solvents that are present in the coating system must be taken into consideration when selecting the inlet-air temperature.

The optimization of temperature of the product may be based on the properties of the substrate and the coating. It is not unusual to find that the inlet-air temperature must be altered to arrive at similar product temperature in different equipment.

4. Fluidization Air Volume

An air-volume indicator should be used to monitor airflow. Although an adjustable damper typically is used to control the fluidization air volume occlusion of the outlet-air filter or of the product bowl screen can cause resistance to airflow, and this might not be noticed unless the processer is equipped with an air volume indicator. Because changes in air volume affect the fluidization pattern as well as heat exchange that is, evaporation of the solvent and drying of the product such changes might also affect the film formation process and consequently the performance of the finished product.

5. Batch Size

Batch size is a variable that infrequently requires attention or adjustment. To determine batch size, the bulk density of the substrate is multiplied by the working volume of the processer

6. Type of Equipment

Ideally, the type of fluid-bed equipment to be used should be selected during the product development phase, several factors must be considered. For example, the length of the expansion chamber is related to the type of product to be coated whether powders, granules, pellets or tablets. Because the position of the outlet temperature probe varies in different type and sizes of equipment.

7. Nozzle Height

In a conventional top-spray fluid-bed coster, it is possible to minimize the size of the coating zone-the region through which droplets must travel-by positioning the nozzle at the shortest possible distance from the static bed. This maximizes the concentration of particles in the coating zone.

8. Drying Time

The effect of drying time on the performance of the end product is more critical when latex or pseudolatex films are applied for controlled release. This is because the rate and degree of coalescense depend not only on the temperature of the drying air but also on the length of the drying phase.

While many similarities exist for equipment supplied by the various vendors, opportunities for differentiation exist with :

- Clamping system (compressed air or hydraulic)
- Explosion protection
- Filter-bag assemblies
- Heating units (conventional stream or electric)
- Specialized designs, with taller expansion chambers that facilitate appropriate deceleration when coating small particles.

Fluidized Bed Coating of Polymeric Aqueous Dispersion

In many works concerning with sustained release dosage forms which used aqueous polymeric dispersions controlled drug release rate, Surelease® and many types of Eudragit® were often used in preparation of sustained

release dosage forms. In many types of Eudragit®it, Eudragit® NE 30D was rarely used in preparation.

Many workers studied preparation of sustained release dosage forms used aqueous polymeric dispersions as film former by means of the fluidized bed coating techniques.

Schmidt and Nicmann (1993) investigated the effect of application temperature on the dissolution profile of sustained-release theophylline coated with Eudragit RS 30D in a miniature fluid-bed coater called Mini WiD-Coater. The dispersions were plasticized with varying amounts of triethyl citrate (TEC), dibutyl phthalate (DBP) , and ploye thylene glycol 6000 (PEG) and applied at different temperatures ranging from 25 to 45^{0}C. The result showed that at a coating level of 4% (0.7 mg/cm^2) sustained release profiles were obtained from dispersions plasticized with TEC or DBP. By reducing the amount of plasticizer from 20 to 10% films with higher permeabilities were obtained. This effect was compensated by temperature.

The investigation of Palmieri, Wehrle and Stamm (1995) also studied sustained release theophylline granules by means of the fluidized-bed coated technique. Spherical granules of theophylline, micro crystalline cellulose and lactose are prepared in a high speed granulator using an original method. Successively, the fraction of granules selected is coated with Eudragit® RS 30D .Finally, these granules are compressed into tablets of different hardness. Dissolution studies reveal a zero order release of theophylline from the coated granules. After compression, the kinctics is modified but the tablets remain efficient to control the theophylline release during 8 hours.

Dyer, Khan and Auton (1995) investigated the effect of processing variables on the rate and mechanism of drug release from ibuprofen pellets coated using aqueous polymeric dispersions by fluidized bed technique. Uncoated pellets containing 60,70 and 80% ibuprofen were coated with aqueous polymeric dispersions of polymethacrylates (Eudragit® RS 30D and Eudragit® RL 30D), ethylcellulose (Surelease®) and silicone elastomer films. The high drug loading of these pellets adds special interest to this study. Drug release from uncoated pellets appears to follow first-order Kinctics. The application of a polymeric membrane to uncoated cores has the effect of retarding drug release.

The air suspension technique was employed to prepare controlled release pellets of Salbutamol (as the sulphate) (Govender,Dang or and Chetty, 1995). The aim of the present study was to determine the influence of various film coating additives on the release characteristics and surface morphologh features of salbutamol sulphate pellets coated with Eudragit® RS 30D. Microgrphs of the cross-sections of pellets with higher concentrations of Eudragit® RS 30D indicated the formation of thicker polymer membranes which accounted for the slower drug release rates. Hydroxypropyl methylcellulose (HPMC) inclusion in the polymer film coating increased salbutamol release rates. A slower in vitro release of salbutamol was observed with higher concentrations of the hydrophobic antitackiness agent, magnesium stearate.

Vecchio, Fabiani and Gazzaniga (1995) investigated the using of coloidal silica as a separating agent in film forming processes performed with aqueous dispersion of acrylic resins (Eudragit® RS 30D, Eudragit® RL 30D). Talcum is normally utilized as an antiadherent and polishing agent but its problems connected with tendency to form sedimentation. On the bases of these observations, the aim of this research work is to evaluate the possibility of

substituting talcum with colloidal silica as separating agent in aqueous dispersion of film acrylic resins. Results concerning fluid bed coating processes of pellets have been reported, with particular attention to usable concentration of colloidal silica and to possible influence of these on the drug release characteristics of the systems obtained.

Eudragit® E 30D was utilized in conjuction with talcum and xantan 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.

Amighi and Moes (1995) investigated the evaluation of thermal and film forming properties of acrylic aqueous polymer dispersion blended. Aqueous acrylic polymer dispersion were blended in order to improve processing and film formation from acrylic polymers with poor film forming properties according to the physico-chemical and pharmacokinetic requirements of the active substance. Heterogeneous film structures are generally obtained from blends containing an association of hard acrylic polymer (Eudragit® RS 30D, S 100) with the soft Eudragit® NE 30D when the drying temperature is lower than the minimum film forming temperature (MFT) of the hard acrylic polymers.

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

Theophylline granules ware prepared as sustained release dosage form by aqueous dispersion of ethylcellulose (Surelease®)using fluidized bed coating technique. Several additives were evaluated and methyl cellulose was used in testing. The in-vitro theophylline release was relatively linear and pH independent, and could be varied in a predictable manner by manipulating the coat thickness. In addition, when the coated pellets were subjected to additional thermal treatment, the drug release was stable after storage for one year.

Porter (1989) investigated the characteristics of ethylcellulose (Surelease®) film coating system, and discuss those factors (including those relating to the substrate, coating formulation and coating process) that can influence the behavior of such systems. The result showed that ethylcellulose has become a polymer widely used in pharmaceutical film coating, especially when it is necessary to produce a modified-release dosage form.