CHAPTER I

INTRODUCTION

The objective of developing a modified-release dosage form for oral administration is to control the release of the therapeutic agent and thus control the release of drug absorption from the gastrointestinal tract. One way of accomplishing this is by forming release-controlling membranes around drug-containing pellets or granules (Harris and Ghebre-Sellassie , 1989).

Film coating is one of the accepted methods of prolongation of drug release from granules (Friedman, Donbrow and Samuelov , 1979). Fluidized-bed techniques have gained considerable popularity in the application of controlled-release coatings (Mehta, Valazza and Abele , 1986). Its main advantages over the pan coating method are as follows : (a) irregular particles may be coating directly, (b) loss of material is small, (c) the process may be automated and does not require learning the " art " of coating, and (d) it is very rapid (Friedman and Donbrow , 1978).

The coating material may be soluble or insoluble in the fluid or digestive system. In the case of soluble coating material, the dosage form may include a variety of granules or cores having different thickness. The release rate in such a system may be controlled by dissolution of the coat or diffusion of drug through the coat or both processes. However, with insoluble coating materials, the release process will be controlled solely by diffusion through the film coat. Some of the most common insoluble polymer candidates are methacrylate ester copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate and ethylcellulose.

Eudragit® NE 30D [Poly (ethylacrylate methylmethacrylate) aqueous dispersion] is a film coating formulation which had sustained release action characteristic. The use of water-dispersed systems instead of solvent based organic solutions leads to protection of the pollution and solvent toxicity which have resulted in strict government regulations concerning solvent emissions together with the expense and explosion hazards. The Eudragit® NE 30D films are insoluble in water and do not dissolve in gastric or intestinal fluid. However, they are swellable in water and give pH-independent permeable membranes. The release time of drug from these polymers can be adjusted by varying the thickness of the film. Eudragit® NE 30D provides coatings that are highly impermeable to drug when it is used alone. The permeability of films can be increased by mixing hydrophilic and/or higher permeable substances such as poly(ethylene glycol), methylcellulose, hydroxypropyl cellulose, poly(vinylpyrrolidone), lactose, sorbitol and glycerine (Li et al., 1989 ; Fukumori, 1994 ; Amighi and Moes, 1995).

The coating morphology and dissolution characteristics of the finished product can be affected by the variables of fluidized bed process such as : the spray mode, processing time, atomizing air pressure, fluidization air temperature, fluidization air volume (Jones , 1985).

In a fluidized bed coating, a liquid feed is sprayed onto a bed of solid particles for film deposition on each particle. The liquid feed can be applied by using one of the three spray modes : top spray, bottom spray or tangential spray. Since the spray mode determines not only the spray pattern of the coating formulation, but also how the sprayed droplets impinge and spread on the substrates, it is expected to have a significant impact on the film structure (Mehta et al., 1985). Therefore, the spray mode is an important process variable that affected the film structure and release properties of coated granules (Yang et al., 1992 and Mehta et al., 1986).

The atomizing air pressure is one of the process variables that directly affected the droplet sizes of coating dispersion before impinged on the cores or granules. It is conceivable that at a high atomizing air pressure finer droplets of the coating dispersion are produced. The resulting films on the substrates should be more continuous and less permeable. However, a previous study reported that the result was contradicted the above conclusion (Li and Peck , 1990). It was indicated that coating at high atomizing air pressure released the active ingredient at a faster rate. Hence, the atomizing air pressure should be adjusted to be an optimal value in order to achieved a satisfactory in vitro release rate.

Theophylline, a xanthine derivative, has been selected as the model drug to be investigated. It is widely used not only as an effective bronchodilator in the treatment of bronchial asthma and other respiratory diseases but also as a prophylactic drug for controlling the symptoms of chronic asthma (Winter, 1982 ; Sa, Bandyopadhyay, and Gupta, 1990 ; Hendeles, Massanari, and Weinberger, 1991). Its half-life is approximately 4-9 hr. and the therapeutic range is 10-20 μg/ml (Joknman, Schoen-maker, Grimeberg and Zeevw, 1981). Due to this short half-life of theophylline, it makes the inconvenience for patient to repeatedly take oral conventional dosage form, which may be as frequent as every six hours (Georgarakis et al., 1990). This significant problem has made theophylline an ideal candidate for administration as sustained or controlled-release preparations.

The present work is a study of the preparation of controlled-release theophylline granules by means of fluidized bed coating techniques and investigation of the effect of various coating levels of aqueous polymeric dispersion coated on granules including various ratios of the polymer blends between Eudragit® NE 30D and other hydrophilic substances on the release rate profile of the drug. Furthermore, the effects of spray mode and atomizing air pressure on the film structure and release properties of granules were also studied.

OBJECTIVES

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

1. To prepare controlled-release granules of theophylline by coating with poly (ethylacrylate methylmethacrylate) aqueous dispersion using fluidized bed technique.

2. To determine the optimal level of poly (ethylacrylate methylmethacrylate) aqueous dispersion coating which has the amount of drug release comparable to the requirement specified in the US pharmacopoeia.

3. To study the effects of spray mode and atomizing air pressure on the physical properties and release characteristics of coated granules.

4. To study the influence of various ratios of polymer blends between hydroxypropylmethylcellulose or ammonio methacrylate copolymer, type A and poly (ethylacrylate methylmethacrylate) aqueous dispersion used as the coat on the physical properties and release characteristics of coated granules.

LITERATURE REVIEWS

1. Controlled-Release Drug Delivery Systems

Sustained-release dosage forms are developed for a variety of reasons such as they may improve patient compliance, reduce unexpected toxic effect due to high peak concentration and improve efficiency in treatment because of the less fluctuations in drug level.

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 (Chien, 1983).

In the exploration of oral controlled drug administration, one encounters three areas of potential challenge :

(1) Drug delivery system : Development of a viable drug delivery system which is capable of administering a therapeutic agent at a programmed rate for a duration required for an optimal treatment.

(2) Gastrointestinal transit time : Prolongation of the gastrointestinal residence time, so the drug delivery system developed can reside at the vicinity of absorption site for sufficient long period of time to deliver all the drug loading dose.

(3) Hepatic first-pass elimination : If the drug is subjected to an extensive hepatic "first-pass" elimination, preventive measures should be developed to minimize the extent of hepatic "first-pass" metabolism.

The majority of oral controlled-release drug delivery systems being widely marketed relies on dissolution, diffusion or a combination of both mechanisms to

generate a slow release of drug to the gastrointestinal milieu (Hui, Robinson and Lee, 1987). Drug delivery systems with diffusion controlled release mechanisms and various conditions for controlled release of drug, together with the appropriate equations for data treatment have been extensively discussed (Flynn, Yolkowsky and Roseman, 1974 ; Harland and Peppas, 1989 and Ronade, 1991).

Basically, there are two approaches of diffusion controlled systems that have been developed over the past of two decades, the matrix devices and the membrane-controlled devices. In the matrix system, solid drug particles are either dispersed in an insoluble matrix (Foster and Parrott, 1990), or layered on the placebo core with water insoluble polymer (Chang and Himmelstein, 1990 and Scott and Hollenbeck, 1991), or prepared in the form of micropellets (Thoma, 1989 ; Janicki and Jedras, 1989 and Harland and Peppas, 1989), or microcapsules (Harland et al., 1988 ; Forni, 1990 and Nixon and Wong, 1990). A membrane-controlled device consists of a central reservoir of a drug enclosed by a polymeric membrane that allows the drug to diffuse from the reservoir at a predetermined rate. Since diffusion through a membrane is a simple approach to obtain a predictable release rate, membrane-controlled devices have been widely used (Phuapradit et al., 1995).

Membrane Diffusion-Controlled Drug Delivery Systems (Chien, 1983)

Membrane diffusion process has been successfully applied in the development of controlled release drug delivery systems for transdermal controlled administration of some drugs such as nitroglyserin and scopolamine through the intact skin. These membrane diffusion-controlled drug delivery systems are known to use a prefabricated microporous membrane to meter the release of therapeutic agents. Membrane diffusion process has also been utilized in the development of oral controlled-release drug delivery systems in which the microporous membranes are produced in the gastrointestinal tract directly from a non-porous polymer coating.

Several potential developments, which has been proven feasible, are outlines as follows :

1. Microporous membrane-coated tablets

It is prepared by first compressing aqueous soluble drug particles into a core tablet with appropriate pharmaceutical excipients and then coating the tablet with a layer of non-GI-eroding polymer, e.g., the copolymer of vinyl chloride and vinyl acetate. The polymer coating contains a small amount of water-soluble pore-forming inorganic substances, e.g., magnesium lauryl sulfate, to create porosity when tablet is in contact with gastrointestinal fluid. The porosity and rigidity of the polymer coating can be varied to give a slow or fast release at constant rates.

2. Solubility membrane-controlled solid dosage form

It is also prepared by first compressing aqueous soluble drug particles into a core tablet with appropriate pharmaceutical excipients and then coating the tablet with a layer of thermoplastic polymer, e.g., polyvinyl chloride. The polymer coating contains at least 80 % of plasticizer, e.g., dioctyl phthalate, to create a solubility of membrane in the gastrointestinal tract. The rate of drug release can be controlled and predetermined by regulating the concentration of plasticizer in the polymer coating.

3. Enteric controlled-release tablets

The tablet which is designed to release a drug labile to gastric fluid only in the intestinal fluid at a controlled rate is prepared by coating a core tablet with a combination of intestinal fluid-insoluble polymer, e.g., ethylcellulose and intestinal fluid-soluble polymer, e.g., hydroxymethylcellulose phthalate. In the intestinal tract, hydroxymethylcellulose phthalate component is dissolved away by the intestinal fluid,

leaving a microporous membrane of ethylcellulose, which renders a controlled release of drug in the intestine.

4. Multi-laminated sustained-release tablets

The tablet is fabricated by first dispersing a loading dose of drug in layers of water-soluble carboxymethylcellulose (CMC), sandwiching the drug-loaded CMC layers in-between layers of crosslinked carboxymethylcellulose, which is water insoluble, but water swellable, and then compressing these layers under high pressure to form a multilaminated tablet, which is then coated with a suitable polymer coating material. In the gastrointestinal tract, the crosslinked CMC layers become swollen and gelatinous and create a colloid gel barrier, which controls the release of drug from the CMC layers.

5. pH-independent controlled-release granules

The granules are designed for the oral controlled release of acidic or basic drugs at a rate which is independent of the variation in pH conditions along the gastrointestinal tract. They are prepared by blending an acidic or basic drug with one or more buffering agents, e.g., primary, secondary or tertiary salt of citric acid, granulating with appropriate pharmaceutical excipients to form small granules, and then coating the granules with gastrointestinal fluid-permeable film-forming polymer, e.g., cellulose derivatives.

The polymer coating acts as a permeation-controlling membrane, so that when the gastrointestinal fluid passes through the membrane, the buffering agents adjust the fluid to an appropriate constant pH, at which the drug dissolves and permeates through the membrane at a constant rate regardless of the location in the alimentary canal.

6. Polymer-coated drug-resin preparation

This preparation is designed to provide a controlled release of a therapeutic agent at a rate which is independent of any variation in pH conditions, enzymatic activities, and contents of the gastrointestinal tract. It is prepared by first adsorbing an ionizable drug onto the ion-exchange resin granules, such as codeine base and Amberlite (RTM) IRP-69, and then, after filtration from the alcoholic media, coating the drug resin complex granules with a water-permeable polymer, e.g., a modified copolymer of polyacrylic-methacrylic ester, and then spray-drying the coated granules to produce the polymer-coated drug-resin preparation.

7. Thixotropic bilayer tablets

Each layer of the bilayer tablet is prepared by dissolving or dispersing, if not soluble, the drug(s) in a gel made from different levels of Thixcin R (hydroxy-glycerol ester of a monobasic C_{16}-C_{18} fatty acid) in a solvent, e.g., ethanol. Solvent is then evaporated to give a drug dispersing matrix, which can be screened, granulated and compressed into a core tablet. By varying the ratio of drug to Thixcin R, the rate of drug release can be controlled.

In the gastrointestinal tract, Thixcin R absorbs water and becomes a semi-rigid mass. It behave as a hydrophobic sol in which thread-like aggregates interlock and disperse throughout the liquid medium.

Of some concern in the design of oral controlled-release products is the influence of physiological variations in the gastrointestinal (GI) tract, including the pH of GI fluids, digestive enzymes, gastric emptying time and peristaltic activity, all of which can effect the performance of the dosage form and the resulting blood drug concentration. Oral controlled-release dosage forms such as coated beads, which spread through the GI tract, offer the potential for less statistical variation in gastric

emptying rates and overall transit times. They can also maximize drug absorption and prevent dose-dumping, which may be more likely to occur when a single-unit controlled-release system is used (Ghebre-Sellassie et al., 1985).

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 and in the development of both aqueous and organic solvent-based polymeric coating systems (Friedman and Donbrow, 1978).

2. Water-base Coating System

Organic solvent-based polymeric solutions have traditionally been used for coating. By appropriate selection of organic solvents or their mixtures, a variety of compounds can be dissolved in solutions to make the products display the functions desired (Fukumori et al., 1991). However, the high cost of solvents, high price of solvent recovery systems, strict air quality controls, and potential toxicity and explosiveness of solvents have motivated pharmaceutical and food supplement processors to remove organic solvents from the coating process (Chang, Hsiao and Robinson, 1987).

As a result, water-based systems have been developed for pharmaceutical dosage forms instead of organic solvent-based polymeric solutions because of their environmental and economic advantages.

There are still many problems to be overcome for wider applications of aqueous dispersions to pharmaceutical multiparticulate dosage forms. While film formation in polymeric solution systems (either aqueous or organic) is easily achieved by drying solutions, the polymeric particles in dispersions have to be fused for the formation of continuous films. Some complicated processes are involved in

the formation of continuous films. This brings about some additional difficulties in coating using aqueous dispersion systems. For their efficient application to pharmaceutical dosage form, a clear understanding of the mechanisms of film formation may be required (Fukumori, 1994).

Film-Forming Mechanism of Aqueous Polymeric Dispersions

The formation of films from an aqueous polymeric dispersion such as latex or pseudolatex involves the deposition of droplets of the dispersion on a substrate followed by evaporation of water and the coalescence of the polymer particles into a continuous film.

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 polymer particles in a dense mass play a more importance role. It can be calculated using the Lapace equation for pressure, $P = 2y / r$, where y is the interfacial tension between water and air and r is the radius of the polymer particles or the curvature of the aqueous meniscus. Both mechanisms were assumed by Bindschaedler et al. (1983) to be valid also in film-coating processes. When the radius of the polymer 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 polymeric dispersion 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 minimum film-forming temperature (MFT).

The space between the polymer particles in the dense sphere package is only 26 % of the whole volume. So the shrinkage 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 (Lehmann, 1989).

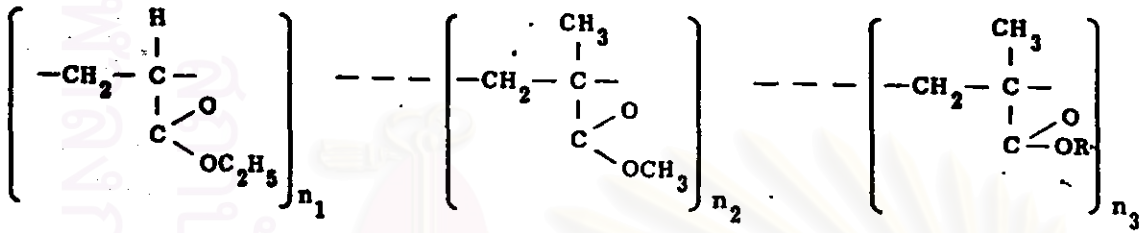
3. Film-Former Used in Coating Formulation

Eudragit®NE 30D [Poly(ethylacrylate methylmethacrylate) aqueous dispersion]

Eudragit®NE 30D is the aqueous dispersion of a neutral copolymer latex synthesized by emulsion polymerization. It consists of ethylacrylate (EA) and methylmethacrylate (MMA) in ratio 2:1. The structural formula of this polymer is presented in Figure 1. The average molecular weight is 800,000. The latex contains 30 % solids including some of polyethylene nonyl phenylether as an emulsifier. A sticky powder that tends to form lumps can be prepared by freeze-drying or other drying processes but is not commercially available. The polymer has no functional groups and is practically neutral. Therefore the films prepared from this latex are insoluble in water and in aqueous buffer solutions over the entire physiological pH range but will swell in water and give medium permeable membranes. The permeability is independent of the pH. Eudragit®NE 30D was described in the Federal Register under "Food Additives" as safe for use as a food-contact surface for articles intended for packaging and handing food including heating of prepared food (Lehmann, 1989 and Gopferich and Lee, 1992).

This polymer is used mainly for sustained-release and transdermal drug formulations. The MFT is around 5 °C, 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

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 1 Structural formula of Methacrylate ester copolymers.

protective coating. 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.

Eudragit®NE 30D possesses a very high binding capacity and can therefore be used with a relatively large quantity of auxiliaries 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 suspended 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 polyoxyethylene alkylphenyl ethers can be used. 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. Cab-O-Sil is effective as an additive to prevent sticking of small coated particles during storage, especially at elevated temperature and high humidity.

Due to its film properties, Eudragit®NE 30D can be used in the formulation of coated beads for controlled drug release. The Eudragit®NE 30D films are permeable to water and active substance release via diffusion processes. The release times of controlled-release formulations can be adjusted by varying the thickness of films. Furthermore, the permeability of Eudragit®NE 30D film can be increased by adding several water-soluble substances such as sucrose, lactose, and other saccharides, starch, micronized cellulose, poly (vinyl alcohol) and polyethylene glycol. Water-soluble cellulose ethers have limited compatibility. They stimulate slow agglomeration and coagulation within several hours or days (Lehnmann, 1989 and Fukumori, 1994)

Eudragit®NE 30D can be mixed with both aqueous dispersion of anionic methacrylic acid copolymer and cationic methacrylic ester copolymer in any

proportion (Figure 2). The main purpose of mixing these polymers is to modify the drug release profiles and to improved processing and better film properties (Lehmann and Dreher, 1988).

Amighi and Moes (1995) investigated the effect of blending, in different proportions, Eudragit®NE 30D with the anionic methacrylic acid copolymers (Eudragit®L 30D, S 100) on the theophylline release rates from coated pellets in the pH-gradient dissolution media. The result showed that the release rate was significantly accelerated and depended on the proportion of the anionic polymer (Eudragit®L 30D, S 100) presented in the blend, the higher was the polymer content, the higher was the dissolution pH-dependency of the dosage form. Furthermore, the thermal and film forming properties of polymer blends were also studied. Heterogeneous film structures were obtained from blends containing an association of hard acrylic polymers (Eudragit®RS 30D, S 100) with the soft Eudragit®NE 30D when drying temperature was lower than the MFT of the hard acrylic polymers.

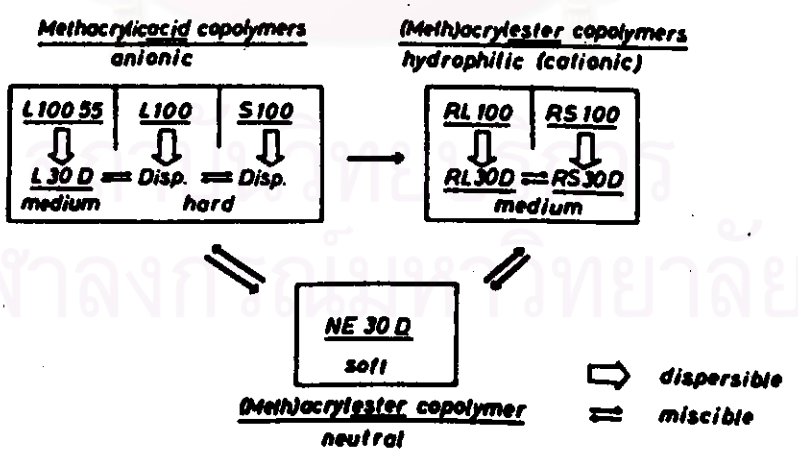


Figure 2 Combination of Eudragit aqueous dispersion (Lehmann and Dreher, 1988).

Eudragit®RL 30D [Ammonio methacrylate copolymer, type A aqueous dispersion]

Eudragit®RL 30D is an aqueous dispersion contains a copolymerizate of ethylacrylate (EA) and methylmethacrylate (MMA) with trimethylammonioethyl methacrylate chloride (TAMCl) in ratio 1:2:0.2. The structural formula of this polymer is given in Figure 1. The average molecular weight is 150,000. These copolymers are produced by bulk polymerization and are commercially available as solid granules (Eudragit®RL 100) or as milled polymer powder. The solid bulk polymer can be directly emulsified in hot water without any additive to a stable aqueous dispersion. The formulation of a latex-like aqueous dispersion is obviously caused by the hydrophilic ammonium groups. The commercial aqueous dispersions, Eudragit® RL 30D, contains 30 % polymer content with 0.25 % sorbic acid as a preservative but no emulsifier.

Eudragit®RL 30D films are water-insoluble, and their permeability, which is independent of pH, depends on the content of quaternary ammonium groups and more permeable than those of Eudragit®NE 30D. Because Eudragit®RL 30D contains MMA-rich ester components (EA/MMA 1:2), their softening temperature are higher than those of NE 30D (EA/MMA 2:1). The MFT of the pure dispersion is between 40-50 °C. The addition of 10-20 % plasticizer is necessary to reduce the MFT below 20 °C in film-forming process. Most effective plasticizers are triethyl citrate and triacetin. Also water-insoluble plasticizer could be added to the aqueous dispersions in the form of emulsions in a 1 % aqueous solution of Polysorbate 80. There is obviously some influence of added plasticizer on the permeability of the resulting films.

The compatibility of these latex-like dispersions with the widely used additives talc, titanium dioxide, pigments, and others is generally acceptable and very similar to that described above for the neutral Eudragit®NE 30D. The pH of the

dispersion, which is normally in the range of 5-6, should be kept nearly constant and additives added preferably in the form of aqueous suspensions or solutions of the same pH (Lehmann, 1989 and Fukumori, 1994).

The hydrophilic quaternary ammonium groups with their positive charge in the polymer are highly responsible for the permeability of the films. The diffusion rate of dissolved drug molecules through membranes of Eudragit®RL 30D is so high that the release from coated tablets or particles with a film thickness of 10-30 μm is very fast and normally reaches nearly 100 % within 10-30 min. Such films can be used as fast-disintegrating protective coating (Lehmann, 1989).

The mixture of Eudragit®RL 30D with RS 30D, an aqueous dispersion of copolymer of EA:MMA:TAMCl in ratio 1:2:0.1 which formed the less permeable films, are generally used in film coating controlled-release preparations. By different permeability but unlimited miscibility of both types, a wide range of permeability can be established, so that the system can be adapted to the diffusion properties of many drugs in a narrow range of film thickness (Lehmann, Petereit and Dreher, 1994).

The drug release rates from theophylline pellets coated by using the blends of Eudragit®RL 30D and RS 30D were studied. A wide range of dissolution profiles was obtained simply by changing the ratios of the two polymers. Compared to the dissolution results of uncoated pellets, the drug release was very slow and practically linear as a function of time with Eudragit®RS 30D while practically unmodified with Eudragit®RL 30D coated pellets. The use of readily permeable Eudragit®RL 30D appeared to be as effective as the use of pore forming agents or hydrosoluble polymers for controlling the membrane permeability, so that the design of film coated pellets can be easily realized by selecting the proper RS 30D/RL 30D ratio and coating thickness (Amighi and Moes, 1995).

Bianchini et al. (1993) produced the extended-release d-indobufen pellets by coating with the aqueous dispersion of ethylcellulose or copolymer mixture of acrylic esters with different permeability characteristics (Eudragit®RS 30D and RL 30D). The result indicated that coating with the mixture of Eudragit®RS 30D and RL 30D was more suitable to reduce the drug release rate than ethylcellulose coating and by increasing the amount of more permeable polymer (Eudragit®RL 30D), analogous results in terms of release rate improvement were obtained. This effect was also found by El-Mahrouk et al.,1993 , Lehmann and Petereit, 1994 and Rafiee-Tehrani and Sadegh-Shobeiri, 1995.

Potassium chloride tablets were coated with mixtures of Eudragit®RS 30D and RL 30D acrylic latexes that also contained a plasticizer (triethyl citrate or acetyl tributyl citrate) and a pore-forming agent (urea). It was found that the Eudragit® RS 30D:RL 30D ratio had the greatest effect on the release rate, and both lag time and burst strength were most affected by the urea level (Jensen et al., 1995).

Mixing of anionic dispersions from Eudragit®L 100-55, L 100 and S 100 with the hydrophilic, slight cationic methacrylate dispersions RL 30D/RS 30D are sometimes useful when the solubility of the coated drug substance decreases with increasing pH, which is observed mainly with salts of weak amines. In mixed films the enterosoluble component dissolves in neutral to weakly alkaline intestinal fluid, the permeability of the coating increases and compensates for the reduced solubility of the drug, so that a more constant release rate over the whole pH range can be obtained (Lehmann, 1989).

Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC), a cellulose derivative, is widely used as an excipient in oral and topical pharmaceutical formulations. HPMC is primarily used as tablet binder, in film-coating and as an extended release tablet

matrix. It is also used as an emulsifier, suspending agent, stabilizer, thickening agent and protective colloid.

HPMC is an odorless and tasteless, white or creamy-white colored fibrous or granular powder. Its structural formula is shown in Figure 3. It is soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol and ether, but soluble in mixtures of methanol or ethanol and dichloromethane. HPMC powder is a stable material although it is hygroscopic after drying. Solution are stable between pH 3-11. Increasing temperature reduce the viscosity of solution. It is unstable in extreme pH conditions and incompatible with oxidizing materials. HPMC is classified according to its substituent groups, composition and viscosity. It is available in several grades which may be distinguished by appending a number indicative of the apparent viscosity, in cps., of a 2 % w/w aqueous solution at 20 °C. HPMC of lower viscosity (less than 15 cps.) is commonly used in film coating and is produced by depolymerization of higher viscosity HPMC (Wade and Weller, eds., 1994).

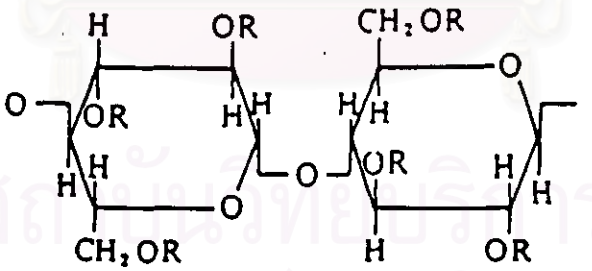


Figure 3 Chemical structure of HPMC.

An application of HPMC for film coating have become popular, taking place of the classic sugar coating of tablets, since it gives a superior appearance, acts as protective coatings for fragile tablets and can mask color and unpleasant taste. It

main reason that HPMC is preferred as a film coating in the initial stage is that it dissolves in both organic solvents and water over the entire biological pH range. This means that film coating can be done using an organic solvent system and the film formed is expected to dissolve in the digestive juices leading to a complete release of the active ingredients (Tondachi, Hoshi and Seigawa, 1997).

HPMC may be used as the basis for hydrophilic matrices for controlled release oral delivery. It altered the drug release profile by forming a gel layer, its composition being dependent on polymer to drug ratios and the molecular weight of HPMC. The polymer that formed a gel which was least susceptible to surface erosion and dissolution showed greatest retardation in drug release. In systems where the polymer gel remained intact, the drug diffused through the gel and the release pattern was linear with the square root of time. Thus, the rate of dissolution medium entering the compressed matrix, the rate of diffusion drug in gel, the thickness and the integrity of gel would influence the drug release pattern (Wan, Heng and Wong, 1990).

Dissolution studies of indomethacin controlled release tablets showed that for a poorly water soluble drug, the polymer to drug ratio, the viscosity grade of HPMC and the particle size of the drug were important in controlling the release of drug and were more critically than the water soluble drugs. Furthermore erosion of the HPMC matrix was suggested to be the only mechanism by which poorly soluble drugs were released from HPMC matrix (Ford, Rubinstein and Hogan, 1985b).

HPMC was also used to produce hydrophilic matrix of propranolol hydrochloride, aminophylline and promethazine hydrochloride. It was found that the major factor controlling drug release was the drug:HPMC ratio and a plot of percentage of drug dissolved against square root of time produced a straight line (Ford, Rubinstein and Hogan, 1985a, 1985c).

It is well known that addition of an hydrophilic additive to a polymer film will increase the permeability characteristics of that film (Shah and Sheth, 1972 ; Donbrow and Samuelov, 1980 ; Ghebre-Sellassie et al., 1984 and 1987). The addition of HPMC in the polymer films was commonly used to increased the drug release from coated particles. The release rate of drug was increased and depended on the proportion of HPMC presented in the films, the higher the HPMC content, the higher the dissolution of the dosage form. This effect has been found by several investigators (Kannikoski et al.,1984 ; Gilligan and Li, 1991).

Gilligan and Li (1991) produced the sustained-release dextromethorphan hydrobromide pellets by coating with an aqueous dispersion of ethycellulose containing HPMC. It was found that increasing the percentage of HPMC in the polymer film increased the release rate of drug from pellets. In addition, the effects of storage and conditioning of pellets system, prior to release studies, were also investigated.

Kannikoski et al. (1984) modified the properties of ethylcellulose-coated verapamil hydrochloride granules by the addition of HPMC. The result indicated that the ratio of ethylcellulose to HPMC had a major influence on drug release rate. Incorporation of 10 % HPMC in the coating led to a 10-90 % increase in the release rate of verapamil hydrochloride. The variations of the percentage of increase were attributed to the different nature of the plasticizers employed and the viscosity grade of ethylcellulose. This effect was also found by Kohri et al. (1986) who reported that the release rate of nifedipine from granules composed of nifedipine, HPMC, ethylcellulose and corn starch, increased with an increase in HPMC in the granules.

However, Zhang et al. (1990) described the influence on drug release of adding HPMC to an aqueous dispersion of ethylcellulose using chlorpheniramine maleate and acetaminophen as model drugs. Of particular interest in this case was the demonstration that the addition of a water-soluble polymer need not always

increase the rate at which a drug is release through the membrane. The addition of HPMC increased the release rate of chlorpheniramine, but decreased that of acetaminophen, through the membrane. This may be because by the addition of HPMC increased both the drug solubility within the film and the drug diffusion coefficient through the film in case of chlorpheniramine but the addition of HPMC increased the drug diffusion coefficient and decreased drug solubility in case of acetaminophen.

4. Model Drug

Theophylline anhydrous is a xanthine derivative. It has been selected as the model drug to be investigated in this study. It is still widely used as an effective bronchodilator in the management of asthmatic patients. It is used both as a prophylactic drug and to prevent acute exacerbation of asthma (Sa, Bandyopadhyay and Gupta, 1990).

The structural formula of theophylline anhydrous is given in Figure 4. Its empirical formula is $C_7H_8N_4O_2$ and a molecular weight of 180.17. Theophylline anhydrous is also described under the following chemical names :

(1) 3,7-dihydro-1,3-dimethylpurine-2,6(1H)-dione

(2) 1,3-dimethylpurine-2,6(3H,1H)-dione

(3) 1,3-dimethylxanthine

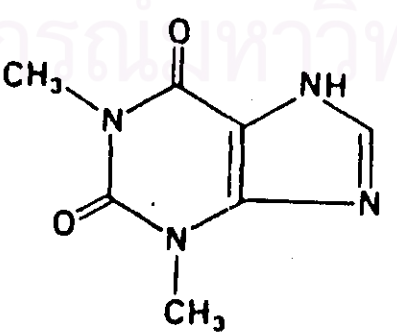


Figure 4 Chemical structure of theophylline.

Theophylline anhydrous is white, odorless, crystalline powder with a bitter taste. Its saturated aqueous solution is neutral or slightly acid to litmus. Its 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. Its melting range is 270-274 °C. It is stable in air but sensitive to light, with the appearance of a yellow discoloration following extended exposure. Solutions of theophylline are stable over a wide range of pH although they may decompose at low and high pH values.

Pharmacokinetics study reveals that theophylline has a relatively short half-life of 4-9 hr and the therapeutic range is 10-20 μg/ml (Joknman, Schoen-maker, Grimeberg and Zeevw, 1981). This short half-life makes the inconvenience for patient to repeatedly take oral conventional dosage form, which may be as frequent as every six hours (Georgarakis et al., 1990), and makes theophylline an ideal candidate for administration as sustained or controlled-release preparations.

Absorption of theophylline in the gastrointestinal tract is delayed by the presence of food. 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 reached in 1 to 2 hr (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 progressively more severe at higher serum concentrations. Tachycardia, in the absence of hypoxia, fever, of administration of sympathomimatic drugs, may be an indication of theophylline toxicity. Anorexia, nausea and occasional vomiting, diarrhea, insomnia, irritability, restlessness and headache commonly occur (Gennaro et al., 1990).

5. Film Coating Equipment

Coating equipment has derived from two basic principles such as the traditional pan coaters and the fluidized bed.

Fluidization is a process in which a bed of small solid particles is suspended and agitated by rising stream of gas which enables a thorough gas-solid contact throughout the bed (Yang et al., 1992). This technology has been used in a number of industries for diversified applications, ranging from limestone calcination, preparation of synthetic gasoline, petrochemicals, and even in the design of nuclear reactors (Zenz, 1980). During the last 30 years, fluid-bed technology has increasingly been utilized by the pharmaceutical industry in various unit operations, including drying, granulation, pelletization and coating (Mehta, 1989 and Olsen, 1989b). The rapidity of operation, the ability to control variables, the uniformity of coat produced and the fact that it can be used to coat particles varying greatly in size and shape are some of the main advantages of the process. Furthermore, the process does not restrict either the kind of coating materials used (solution , suspension, emulsion, latex and hot melt) or the solvent employed in the coating fluids (Wurster, 1982).

In a fluid-bed coating process, a liquid feed is sprayed onto a bed of solid particles for film deposition on each particle. The liquid feed can be applied by using one of the three spray modes : top spray, bottom spray or tangential spray (Jone, 1994 and Yang et al., 1992).

Top Spray Method

The conventional top spray method presented in Figure 5 has been used for more than a decade for coating. It evolved from the fludized bed dryer commercialized more than 30 years ago.

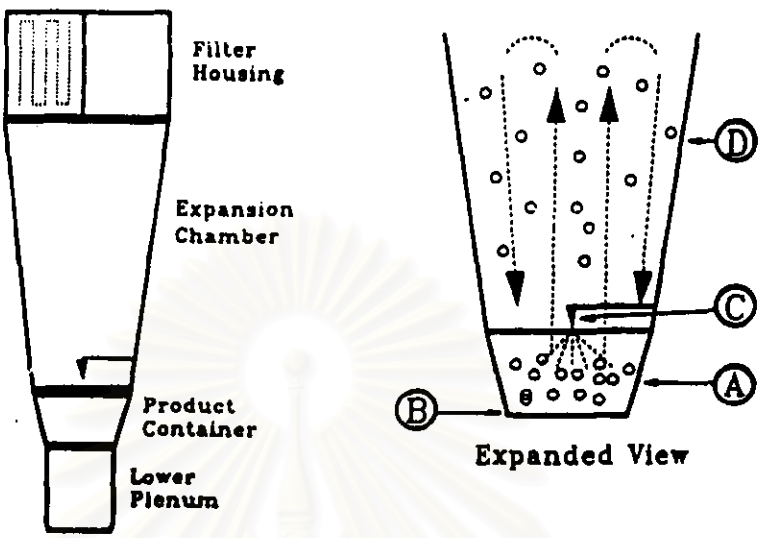


Figure 5 Top spray coater : (A) product container ; (B) air distribution phase ; (C) spray nozzle ; (D) expansion chamber (Jones, 1994).

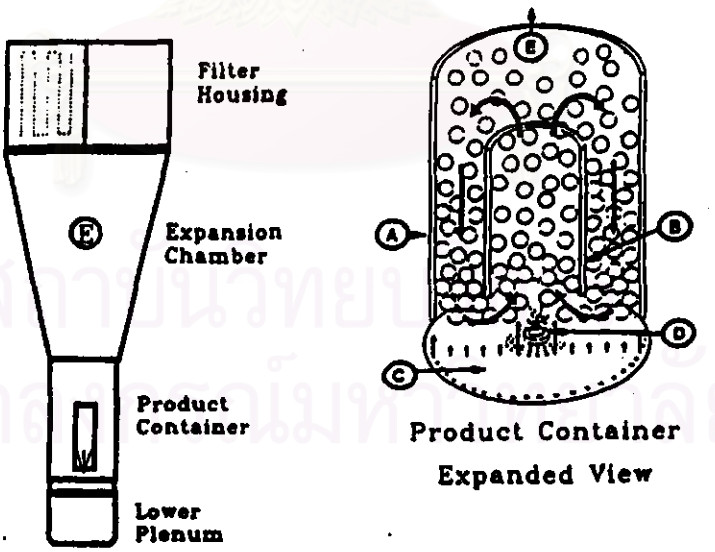


Figure 6 Wurster bottom spray coater : (A) coating chamber ; (B) partition ; (C) air distribution plate; (D) spray nozzle; (E) expansion chamber (Jones, 1994).

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 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 become 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) where drying takes place. The wider diameter in this zone permits deceleration of the particles to below entrainment velocity. The particle fall back into the product container and continue cycling throughout the duration of the process.

Bottom Spray Method (Wurster Process)

The Wurster process was invented by Dr. Dale Wurster, Professor of Pharmacy at the University of Wisconsin, in 1959. This technique is significantly different from those discussed previously.

The component of Wurster machine is illustrated in Figure 6. The coating chamber (A) may be cylindrical or slightly conical. Inside, a cylinder about half the diameter of the base of the chamber, referred to as a partition (B), is mounted in the center and slightly above the gas distribution plate (C). In the center of the plate, a nozzle (D) is positioned and sprayed the coating liquid concurrently with the fluidization air. The porosity of the plate is designed with large holes in the area beneath the partition and smaller holes in the remaining of the plate, except for one ring of large holes at the perimeter. The design of the plate is such that more air enters the partition than the surrounding area to generate a circulatory motion of particles.

The fluidized particles enter the partition, travel upward through the spray zone for receiving a layer of coating material and dry in the expansion chamber (E). Then the particles decelerate and fall into the area outside the partition, from where they are driven horizontally back into the bottom of the partition to start the next circulatory cycle. In contrast to the top spray method, the fluidization pattern is much more controlled in the Wurster system.

Tangential spray method (Rotary Fluidized Bed Process)

The tangential spray method or rotary fluidized bed process was conceived to combine high shear granulation speed and energy with fluid bed drying efficiency for producing higher density granulation than typically possible in conventional fluid bed granulators. This technique is being used to produce micropellets (100-600 μm) from very fine powders and macropellets (700-2000 μm) from layering the drug particles to some type of material. The component of this machine is illustrated in Figure 7.

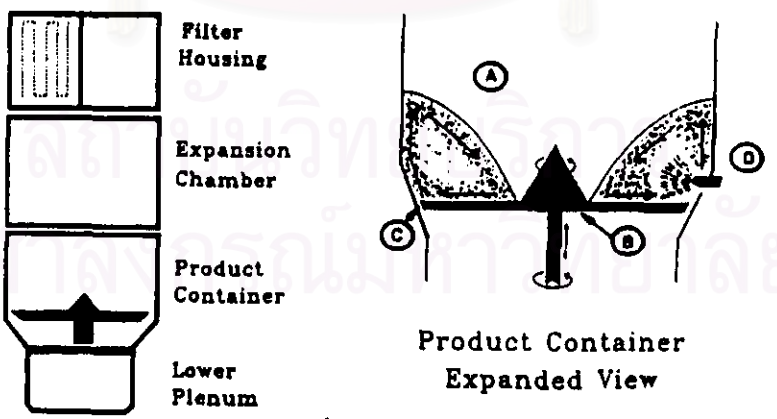


Figure 7 Rotor tangential spray coater : (A) produce chamber; (B) variable-speed disc ; (C) disc gap or slit ; (D) spray nozzle (Jone, 1994).

The product container consists of an unbaffled cylindrical chamber (A) with a nonperforated, rotating horizontal variable-speed disc (B) at its base. The disc and chamber are constructed such that a gap (C) existed at the perimeter of the disc through which process air is drawn. The velocity of air depends on the disc gap and the fluidization air volume. During fluidization, three forces combine to provide a helical pattern around the periphery of the product container. Centrifugal force created by the rotating disk causes in-process material to flow to the outside of the processing container, air velocity through the gap provides acceleration upward, and gravity cascade 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 the particles. The particle cycling time of this technique is very rapid, hence, the films are uniform in thickness.

The three fluid-bed processes offer different advantages and disadvantages, as shown in Table 1, and consequently the performance requirements of the finished product and suitable volumes of the product must be considered when selecting a coating process for a particular product (Mehta, 1988).

Fluidized bed is possible to encapsulated the small particles which could be applied not only to spherical micro-tablets and pellets with a diameter of 0.5-1 mm, but also to compact granules with finer and more irregular-shaped particle under 0.5 mm in diameter with no particle agglomeration at optimal operating conditions. (Lehmann and Dreher, 1979). Moreover, the axisymmetrical particles were also coated with this technique and gave the uniform, reproducible deposition of coating materials on the substrates (Yum and Eckenhoff, 1981).

Table 1 Characteristics of three fluid-bed coating processes

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

Each approach has it advantages and disadvantages, depending on the batch size of product being coated, functionality of the final coating, type of coating formulation being applied (e.g. solutions, polymeric dispersions, hot melts) and 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 granules, (c) homogeneity of the coat in each batch of granules and (d) identity of coating in repeated batches (Friedman and Donbrow, 1978).

In addition to the three method of spraying, almost 20 other variables are involved in the fluidized bed coating process for controlled-release products. The process variables, as well as the effects of the variables on the properties of the polymer film, are the significant parameters that affected the properties of the products. The optimization of process variables depend to a large degree on the type of fluidized bed process that is used. In general, the coating morphology and dissolution characteristic of products can be effected by the variables of the fluidized bed process such as :

1. Spray rate

The primary objective of particle coating is to envelop each particle with sufficient coating material to achieve the desired function. 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, at a given atomization air pressure and volume, affects the size of droplets and the degree of wetting. Increasing the liquid spray rate at a given atomization air pressure will result in larger droplets and a higher possibility of overwetting the coating substrates. Slowing the spray rate may cause electrostatic problems because of low humidity in the bed, especially at high temperature settings. Although accelerating the liquid spray rate increases the droplet size, this also allows for a reduction in the processing time that is necessary (Chang, Hsiao and Robinson, 1987 and Mehta, 1988).

The spray rate factor is also determined by the size of the particles of the substrate, the viscosity and the 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, it has been demonstrated in the literature that the dissolution rate of the drug can be affected by the spray rate (Russo, 1984). In addition, the atomizing air pressure that is selected might determine the spray rate in terms of the size of droplets.

2. Atomization air pressure

A method that is chosen for dispensing liquid into the bed of fluidizing particles is of fundamental importance. Several types of spray nozzle systems are available, including hydraulic, air-atomizing, and ultrasonic. The majority of the nozzle used in fluidized bed processors is the air-atomizing nozzle. In this type, the liquid is supplied at a low pressure and is atomized into droplets by air. As mentioned previously, it is necessary to minimize agglomeration and to provide uniform film characteristics by keeping the size of the droplets small relative to the size of the particles to be coated. In general, the higher the atomization air pressure, the smaller the size of the droplets at any given spray rate. However, excessively high atomization pressures may result in the loss of coating materials or the breakage or attrition of the substrates. Excessively low atomization pressures may cause overwetting of the core and bonding to the side wall. Because of these possibilities, atomization pressure is another process variable that must be monitored during the coating process (Chang, Hsiao and Robinson, 1987 ; Mehta, 1988 ; Olsen, 1989 and Turkoglu and Sakr, 1992).

The size and design of the fluidized bed equipment must also be considered when establishing the parameter of atomization air pressure. For example, pressures that do not affect the fluidization pattern of a Wurster particle coater with a long expansion chamber can blind the exhaust filters of a Wurster column that has a short expansion chamber (Mehta, 1988).

Furthermore, the dissolution rate of the drug and film formation can be affected by the atomization air pressure. This effect was investigated by varying atomization air pressure used for producing the coating spray on the release characteristics of coated potassium chloride tablets (Li and Peck, 1990). The results indicated that the tablets coated at a high atomization air pressure release the active ingredient at a faster rate. As mentioned above, at a high atomization air pressure finer droplets of the coating dispersion are produced. The resulting tablet coatings should be more continuous and less permeable. However, the result of this study contradicted the above conclusion. A cause of this result was that the unheated compressed air was delivered by the distribution tube through the periphery of the spray nozzle, atomizing the coating dispersion and flowing concurrently with the heated fluidizing air into the coating chamber. When the coating was conducted at a high atomization air pressure, the coating chamber probably was flooded with a large volume of cool compressed air which would cause a localized temperature drop and also produced a negative effect on the spreading of the coating dispersion. These might lead to the formation of a more porous and permeable film coating. Therefore, the atomization air pressure should be adjusted to be an optimal value to achieved a desired in vitro release rate of the drug.

The effect of atomization air pressure on the variation of film thickness for fixed particle size range and distribution was investigated. Beads with a size distribution in the no. 14-20 mesh range were coated with an aqueous polymeric dispersion using fluidized bed units. The results indicated that for the bottom spray mode, a reduction in the atomizing air pressure, while substantially reducing differences in fluidization patterns, had only a marginal effect in reducing the differences in film thickness (Wesdyk et al., 1993).

3. Inlet-air temperature

The fluidization air temperature is a key variable in the coating process. A low fluidization air temperature, however, might lead to a problem commonly known as the weather effect (Jone, 1985). 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 fluidization air is allowed to vary as changes in the seasons occur.

To avoid the weather effect it is necessary either to control the dew point of the air or to raise the temperature of the fluidization air. If the product is sensitive to heat, the ambient air can be preconditioned to control its dew point and, therefore , its impact on the drying rate. If possible, it is preferable to use a much higher fluidization air temperature because this tends 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 can 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 the inlet-air temperature was selected.

In many instances, it might be necessary to optimize the temperature of the product 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 temperatures in different equipment (Mehta, 1988).

For aqueous dispersion system such as latex and pseudolatex, the temperature of the inlet air serves the dual function of evaporating the water and softening and coating and coalescing the latex spheres. To generate a continuous film, the temperature in the column must be higher than the minimum temperature for film formation. If the temperature is too high; it may cause electrostatic interaction and agglomeration because of excessive drying and softening of the latex film. The minimum temperature for film formation should be used as guideline for selection the temperature of the inlet air (Chang. Hsiao and Robinson, 1987). In general, the application temperature should exceed the minimum film-forming temperature by 10 to 20 °C (Lehmann, 1989 and Schmidt and Neimann, 1993). This result was also found by Laicher et al. (1995) who investigated the influence of temperature on in vitro release of drug by coating theophylline pellets with an aqueous ethylcellulose dispersion and a latex polymer dispersion (Eudragit® L 30D and RS 30D) in a fluidized bed coater at different temperature. In addition, the slowest in vitro release was determined in this product temperature range.

The effect on film formation of bed temperatures in fluidized coating was demonstrated by Yang and Ghebre-Sellassie (1990) using an Aquacoat® formulation applied to water-soluble diphenhydramine hydrochloride pellets. This result showed that the optimum coalescence of formulation was achieved when the bed temperature was kept between 30 and 40 °C. Coating applied outside this temperature range resulted in the formation of poorly coalesced films and faster release rates. The fast release rates of pellets coated at a low temperature were attributed primarily to drug migration into the film layer during the coating process and to incomplete film formation due to hardening of the uncoalesced polymer spheres. At high temperature, the rate of evaporation of water is so fast that it does not allow the migration of drug but the fast release rates observed were to be due to the development of porous films during coating process.

4. Fluidization air volume

Because sluggish or vigorous fluidization can cause such problems as bonding to the side wall and attrition of the core substrate, the proper volume of fluidizing air should maintained through the coating process (Chang, Hsiao and Robinson, 1987). Changing in air volume affect the fluidization pattern as well as heat exchange, that is, evaporation of solvent and drying of the product. Such changes might also affect the film formation process and consequently the performance of finished product (Mehta, 1988 and Parikh, 1991).

The influence of fluidization air volume on the coating thickness and drug dissolution was evaluated by Hossain and Ayres (1990) using an Aquacoat® formulation applied to acetaminophen pellets. It was found that coating with and without a base plate to modify air volume showed significant differences mean coating thickness. Removal of the base plate resulted in increases in air volume and mean coating thickness. The explanation of this result was explained that the increased air flow may have increased the fraction of atomized coating solution applied to the target pellets and thus may have decreased the amount lost to the coating chamber walls and exit air. Therefore, in vitro release rate of acetaminophen from coated pellets was decreased when the coating was applied with the increased air flow.

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 processor (Mehta, 1988). Batch size was found to affect the release profiles of coated products, but not to the same extent in each spray mode or chamber.

Yang et al. (1992) studied the effect of batch size on the deposition of coating and release profile of drug by coating propranolol hydrochloride pellets with an aqueous dispersion of ethylcellulose. The result showed that the pellets coated using a batch size of 600 g with the top spray mode and granulation chamber released the drug at a slightly slower rate than similarly coated pellets from a batch size of 300 g. However, for the bottom spray mode using the same chamber, the batch size was found to have dramatic effects on the release profiles of the coated pellets. It appeared that batch size was a parameter that needed to be considered in the coating process.

In addition, the effect of batch size on the release rates of coated pellets in a large piece of equipment, Glatt GPCG-5 with tangential spray, was examined. Increasing the batch size from 5 to 8 kg did not appear to have any significant effect on the release profiles. However, since the fluidized bed coating equipment is usually used for development work, it would be more desirable to keep the batch size constant if batch-to-batch comparison is to be made.

6. Nozzle height

Although many products are coated using the top-spray, the bottom-spray and tangential-spray methods might be more logical approaches for coating fine particles. In a conventional top-spray fluidized bed coater, 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 (Mehta, 1988).

The influence of nozzle height setting in a top-spray fluidized bed coating unit on drug release characteristics from coated pellets was investigated. Coating with the nozzle above the product resulted in blow back of droplets, loss of coating materials, and consequently, faster release of drug than that located in the bed. It was expected

that coating efficiency and coating quality were decreased when the nozzle was positioned further away from the product bed (Yang et al., 1992 and Porter and Ghebre-Sellasie, 1994).

7. Mode of spraying

As mentioned previously, there are three modes of spraying that can be used to applied the coating formulation onto a bed of solid particles for film deposition in a fluidized bed coating. Each mode offers different advantages and disadvantages, and consequently the performance requirements of the finished product and suitable volumes of the product must be considered when selecting a coating process for a particular product. Mode of spraying determines the spray pattern of the coating formulation and how the sprayed droplets impinge and spread on the substrates. Therefore, the spray mode is an important variable that affected the film structure and release properties of coated products (Mehta et al., 1985, 1986 and 1988).

This effect was studied by several worker (Mehta et al., 1986 ; Yang et al., 1992 ; Iyer, Augsburger and Parikh, 1993 ; Wesdyk et al., 1993). For example, Mehta et al. (1986) reported that the release profiles obtained from coating caffeine pellets with aqueous enteric system (Eudragit® L 30D) using three techniques were similar. In contrast, when an organic system (Eudragit® S 100) was used, a satisfactory release profile depended on the selection of an appropriate fluidized bed technique. The bottom-spray and tangential-spray techniques appeared to perform satisfactorily when organic system was used. The top-spray technique, however, did not appear to be the optimal choice for organic system. The results were also achieved when aspirin granules were coated with both of enteric systems using all three techniques.

An aqueous-based dispersion of ethylcellulose (Aquacoat®) was used to coat propranolol hydrochloride pellets using different spray modes in fluidized bed coating

machines (Yang et al., 1992). Dissolution data and morphology studies of coated pellets showed differences in the nature of coatings. The sustained-release profiles of pellets coated under similar conditions using two spray modes (top spray and bottom spray) indicated that the bottom-spray coated pellets released the drug at a slower rate than the top-spray coated pellets. The scanning electron photomicrographs (SEM) clearly exhibited a rough and flaky appearance of top-spray coated pellets, as compared to a smooth and even surface of bottom-spray coated pellets.

8. Type of equipment

Ideally, the type of fluidized 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 (Mehta, 1988).

The dimensions and geometry of coating chamber are varied from one fluidized bed coating machine to another. Chamber geometry influences particle motion and distribution, and therefore, affects the deposition of coating materials on the substrate. As a result, the differences in the product release may be attributed to this effect. For this reason, it is essential that the coating conditions be optimized on a case by case basis (Yang et al., 1992).