4-19-2016 12:00 AM

Dry Powder Coating of Pharmaceutical Pellets with a Novel Rotary Fluidized Bed

Yunhan Zhang
The University of Western Ontario

Supervisor
Dr. Jesse Zhu
The University of Western Ontario

Graduate Program in Chemical and Biochemical Engineering
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

Abstract

The conventional coating of pharmaceutical pellets is achieved by liquid-based coating techniques using a fluidized bed or a pan coater. However, many restrictions and drawbacks such as long processing time and large energy consumption exist in the above method. Dry powder coating technique is a novel solventless coating technique that is able to mitigate the problems of liquid-based coating. In this study, a newly invented coating apparatus called rotary fluidized bed (RFB), was applied for the coating of pharmaceutical pellets by a dry powder coating process. The RFB has a unique structure where the hot fluidizing air is further aided by the rotation to ensure a uniform coating. Results of SEM micrographs indicated the piroxicam pellets formed continuous and dense coating film in the RFB. In-vitro drug release tests confirmed that the dry powder coated pellets successfully achieved immediate release, sustained release and delayed release with Eudragit® EPO, Eudragit® RS/RL and Acryl-EZE, respectively. The optimal operation conditions were as follows: curing temperature 2 h, curing temperature 50 ^{o}C, RFB rotating speed ~20 rpm, liquid plasticizer spraying rate ~0.25 g/min and fluidizing air flowrate ~35 L/min. The RFB demonstrated a comparable film formation quality and coating efficiency with the pan coater, while superior to the fluidized bed. For the more difficult-to-coat micronized pellets (0.1-0.3mm), the RFB presented better applicable potential than the other two apparatus. In conclusion, the RFB is a promising dry powder coating apparatus for pharmaceutical pellets coating.

Keywords: pellets coating, dry powder coating, rotary fluidized bed, drug release, fast release, sustained release, delayed release, Eudragit® EPO, Eudragit® RS/RL, Acryl-EZE

Acknowledgements

I would like to express my sincere appreciation to my supervisor Dr. Jesse Zhu for his encouragement, guidance, support and inspiration throughout this endeavor. He encouraged me to think independently and guided me every step of the way, professionally and personally.

I sincerely thank Ms.Yingliang Ma, the research scientist, for all her helpful guidance, constructive suggestions and kind encouragement during the progress of this work. Her inspirational knowledge of the pharmaceutical coating field was of great importance to this research.

Much appreciation is extended to Qingliang Yang for his constructive suggestions, kind encouragement and helpful guidance along the way. Many thanks go to Mr. Jianzhang Wen and Mr. Michael Zhu for their help in maintaining the experimental unit.

Finally, I would like to thank my parents for their endless support and encouragement. Special thanks to my boyfriend Jiangshan Liu for his company and support throughout my life in Canada.

Table of Contents

List of Figures

List of Tables

Chapter 1
Introduction

1.1. Pharmaceutical coating

In the pharmaceutical coating industry, the coating of solid dosage forms are applied for different purposes such as immediate release, sustained release and delayed release. Among then, immediate release is essentially aimed at taste masking, easy identification by the color of coating, protection of the active pharmaceutical ingredient (API) from damage by the environment and so on. Sustained release allows the API to release over an extended period of time that prolongs the therapeutic effect. Delayed release is to release the API at a time instead of release immediately after oral administration. All the above-mentioned purposes can be achieved with different coating materials.

Among the present coating techniques, liquid-based coating is the most common one for coating of both large dosage forms such as tablets and small dosage forms such as pellets. The liquid-based coating consists of organic solvent coating and aqueous coating. The coating materials are dissolved/dispersed in the organic solvent/water, followed by being sprayed onto the surface of the solid dosage forms, and a continuous coating film is achieved with the evaporation of the organic solvent/water. Conventional Pellets coating is usually accomplished by a fluidized bed or a pan coater.

However, the liquid-based coating of pellets has many restrictions and drawbacks. As for organic solvent coating, the usage of the organic solvent may come with toxicity and inflammability, which definitely brings potential hazards. For aqueous coating, it is not appropriate for the moisture sensitive API. Besides that, the pellets tend to agglomerate easily due to their relatively large specific area and small particle size, which leads to a non-ideal coating. Moreover, both the organic solvent coating and aqueous coating require large amounts of hot fluidizing air to maintain the constant temperature of the

coating system, and to evaporate the organic solvent and water. These not only result in energy consumption but also long processing time.

To overcome the above-mentioned problems, a lot of endeavor has been done to improve the technique of pellet coating. Many solventless coating techniques have been designed to avoid the use of organic solvent and water, which significantly overcome the major drawbacks of the liquid-based coating. Dry powder coating is one of the novel solventless coating techniques that have drawn great attention in the pharmaceutical industry. The dry powder coating of small dosage forms such as pellets and particles can be applied in a rotating pan coater and a fluidized bed coater. The coated pellets have been shown to achieve immediate release, sustained release and delayed release successfully. However, limitations still exist with these two apparatuses. For the fluidized bed, a large amount of hot fluidizing air is required to maintain stable fluidization of pellets and constant temperature in the system. The agglomeration is an inevitable problem that usually happens in a fluidized bed system. In terms of the rotating pan coater, when the solid dosage forms have a relatively small size and weight, it is difficult to handle.

A novel apparatus called rotary fluidized bed (RFB) has been designed for the pharmaceutical pellets coating using dry powder coating technique. The RFB has a unique structure that introduces a small amount of fluidizing air in the coating system. The fluidizing air can efficiently work together with a rotation action to prevent the agglomeration of the pellets during the coating process. In comparison to the organic solvent coating, it is more environmentally friendly since no toxic organic solvent is required. In addition, the processing time and the temperature can be reduced dramatically in contrast to the aqueous coating. This project is aiming to investigate pellet coating using the RFB with dry powder coating technique.

1.2. Objectives

The main objective of this project is to investigate the application of the RFB in pellets coating using dry powder coating technique, including the following parts:

Firstly, to realize immediate release, sustained release and delayed release with the dry powder coated piroxicam pellets using Eudragit® EPO, Eudragit® RS/RL and Acryl-EZE as the coating materials, respetively.

Secondly, to optimize the process conditions of pellets coating in regarding to curing time, curing temprature, RFB rotating speed, plasticizer spraying flowrate and fluidizing air flowrate.

Finally, to compare the operation conditions and the performance of the coated pellets in the RFB with the other two typical coating apparatus, the rotating pan coater and the traditional fluidized bed.

Chapter 2
Literature Review

2.1. Types of drug release

Drug release profiles can be divided into the following types: immediate release, delayed release and sustained release. Different release types have their unique release profile. Figure 2.1 shows the typical drug release profiles of the three release types. The modifications of the drug usually aim at the stability and safety improvement as well as the therapeutic profile and efficiency enhancement.

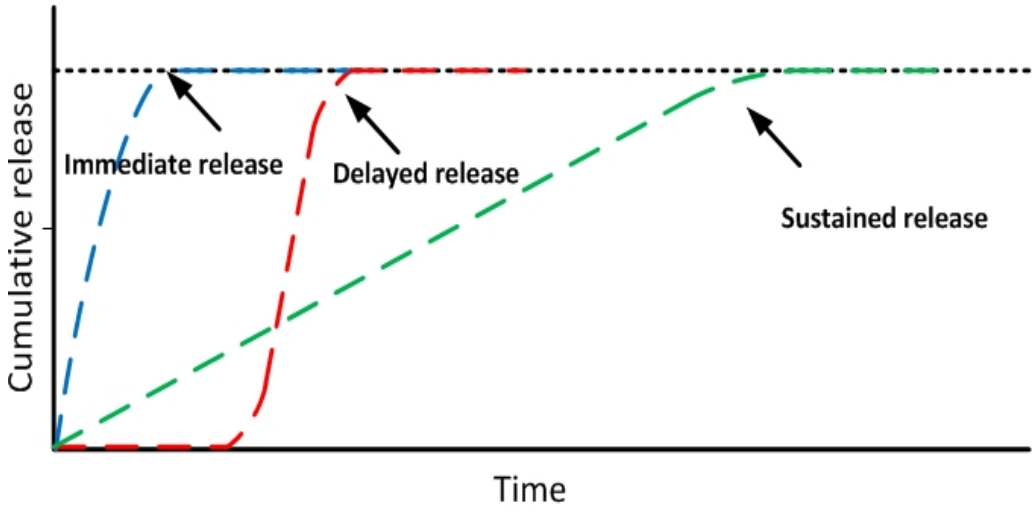

Figure 2.1 Different types of drug release profiles

2.1.1. Immediate release

This type of release is commonly applied in pharmaceutical coating industry today, and is aiming at a rapid dissolution of drug after oral administration, which means to get the active pharmaceutical ingredient (API) into the blood stream and take action to the site as quickly as possible. Usually, the fast release coated drug release to 100% within 30 min. Reasons for immediate release coating are as follows: unpleasant taste or odor masking, easy identification, drug protection, etc. Water-soluble polymers are usually served as the

coating materials in the immediate release coating.

2.1.2. Sustained release

Sustained release, which is also called extended release, refers to the system that allows drug to be released over an extended period of time to achieve prolonged therapeutic effect after oral administration[1]. Based on the different goals of drug delivery, the length of the sustained release time varies from 8-10 hours to 24 hours. Usually, this type of coating is achieved by the coating of water-insoluble polymers.

The most obvious characterizations of this type are: first of all, the plasma concentration can be maintained at a therapeutic range in the blood, which reduces the irritation in the gastrointestinal tract and avoid the side effect of the drug. Second, the dosing frequency can be decreased from dosing immediate release drug several times a day to only once a day by dosing sustained release drug.

2.1.3. Delayed release

The definition of delayed release is the system formulated to release the active pharmaceutical ingredient (API) at a time instead of release immediately after oral administration[1]. The disintegration site of delayed release coated solid dosage forms can be a specific region of the intestinal tract. The drug is considered to stay in the stomach for about 2 h and pass to intestinal tract after the first 2 h. The coating polymers that are used for reaching the above aim will dissolve as the pH changes, which means the API will begin to release when the solid dosage forms move from the low-pH environment (stomach) to the high-pH environment (intestinal tract). And once the dosage forms reach the high-pH environment, the release profile is similar to the immediate release.

The coating of delayed release is required due to the following reasons: firstly, to prevent the drug from irritating the stomach; secondly, to protect the API from degradation under

the low pH environment of the stomach; finally, to target the drug absorption to a place along the intestinal tract beyond the stomach.

2.2. Controlled Drug Release Mechanism

The controlled drug release mechanism of the previous mentioned three typical drug release types can be divided into two systems, diffusion controlled drug release system and erosion/degradation controlled drug release system. The mechanism was introduced by Wnek and Bowlin detailedly[1].

2.2.1. Diffusion-controlled drug release system

Diffusion is defined as the action of drug molecules when stimulated by the change of external environment[2]. Diffusion-controlled drug release systems can be classified into two kinds: matrix system (monolithic system) and reservoir system (core-shell system).

In matrix system that is also called monolithic system, the API composes with a polymer to form a matrix structure, and this special structure will react as a swelling phenomenon. The swelling phenomenon is a uniform expansion of the composite matrix, which leads to the appearance of opening pores that occupied the whole structure. The size of the opening pores has to be much greater than the API molecule so that the diffusion can take place. The diffusion of the drug from the polymer controls the release rate. As the release time increases, the drug release rate decreases.

In the reservoir system that is also named core-shell system, the drug core is encapsulated in a polymer membrane, and is released driven by the difference between the drug and the surrounding environment[3]. Because the reservoir is coated with a permeable polymer, when worked with water, the drug can diffuse through the membrane; meanwhile, the outside water can swell the reservoir structure. Therefore, it is obviously that the swelling phenomenon is not as uniform as the matrix structure dose. Also, the pore size of the reservoir structure has to be greater than the drug molecule for the

purpose of effective diffusion. Furthermore, the diffusion drug release is dominated by the rate of the diffusion through a water-insoluble barrier.

2.2.2.Degradation/ Erosion-controlled drug release system

In degradation/erosion controlled drug release system, basically, the drug and polymer are combined either in the physical form or chemical form. In the physical form, the drug is encapsulated in the polymer matrix, and releases in response to the erosion of the polymer mass. In the chemical form, the drug attached to the chains of polymer, which generates chemical bond between the drug and the polymer. When the chemical bond breaks, the drug release starts.

Furthermore, the drug degradation can be classified into two categories depended on the drug erosion location, which are bulk erosion and surface erosion[4]. In bulk erosion, as the solution penetrates throughout the entire polymer matrix, the polymer composite will degrade uniformly, which means the volume of the polymer composite remains constant while the density decreases. On the contrary, when it comes to surface erosion, usually, the polymer used in the matrix is hydrophobic, and thus the erosion will firstly take place on the surface when interface with solution. Obviously, for the case of surface erosion, the density of the polymer matrix remains constant while the volume decreases.

2.3. Coating materials

As mentioned above, the coating film, depending on the special aspects of use, works either for protection or functional control. Reasons for applying coating are: taste masking, light and moisture protection, appearance improvement, mechanical resistance enhancement and drug release modification. Generally, the most commonly used materials in the coating of solid dosage forms are semi-synthetic copolymers of cellulose derivatives and synthetic methacrylate polymers. By changing the functional groups or mechanical properties of the polymers, the coating film is able to modulate different types of drug release profiles[2].

2.3.1. Polymers for immediate release

The coating polymers aiming at immediate release are mostly water-soluble polymers, which are able to dissolve immediately to guarantee fast release without postponement. Today, most common employed immediate release polymers are cellulose ethers such as hydroxypropyl methylcellulose (HPMC, shown in Figure 2.2), and methacrylate-based polymer developed by Evonik (trade name: Eudragit® E).

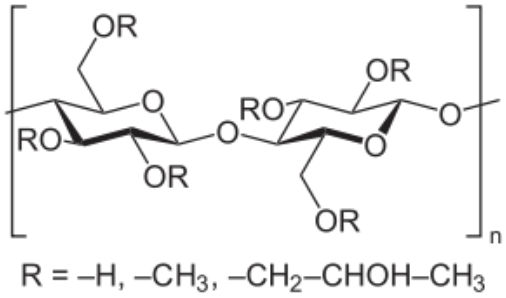

Figure 2.2 Hydroxypropyl methylcellulose molecular structure

HPMC has a very good solubility not only in water but also in organic solvent and is commonly used from the coating of early days. Furthermore, apart from of being the immediate release polymer, HPMC can also work as porogenic agent in the sustained release formulations[1].

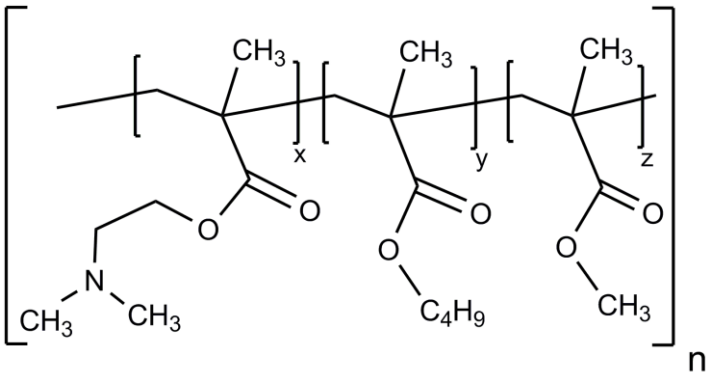

Figure 2.3 Eudragit® E monomer structure

Eudragit® E, as shown in Figure 2.3, is a cationic copolymer, which is comprised of dimethyl-laminoethyl methacrylate, butyl methacrylate and methyl methacrylate with a ratio of 2:1:1. Eudragit® E has three forms of availabilities, which are named as Eudragit® E100 (granules), Eudragit® E12, 5 (organic solution) and Eudragit® EPO (powder), respectively. This type of polymer is able to dissolve in gastric solutions up to pH5.5, which implies that it is insoluble in saliva, but will dissolve in stomach rapidly[3].

2.3.2.Polymers for sustained release

As mentioned above, polymers employed in sustained release (extended release) are usually insoluble in water and independent from pH along the gastrointestinal tract, which effectively increase the therapeutic effect and compliance of patient[4]. Commonly used polymers for such purposes are ethyl cellulose (EC, shown in Figure 2.4) and Eudragit® RL and Eudragit® RS (shown in Figure 2.5) developed by Evonik.

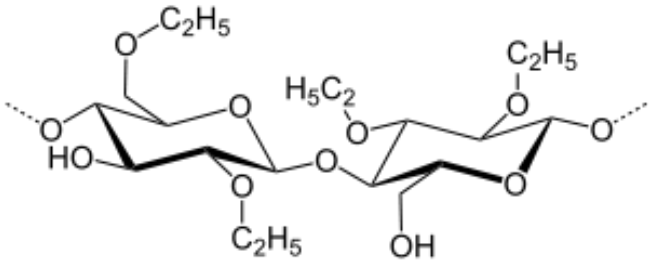

Figure 2.5 Ethyl cellulose molecular structure

EC, also named Aquacoat ECD and Ethocel in industry, is permeable in water in the environment of GI tract, which assures the control of release rate. During the coating process, liquid plasticizers are required for EC in order to form a coating film due to its high glass transition temperature (T_g=133^{o}C) [4].

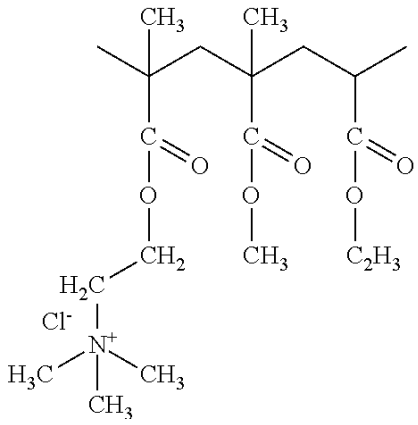

Figure 2.4 Chemical structure of Eudragit® RL and Eudragit® RS

Eudragit® RL and Eudragit® RS (shown in Figure 2.5) are comprised of ethyl acrylate, methyl methacrylate and a small amount of methacrylic acid ester with quaternary ammonium groups (trimethyl-ammonioethyl methacrylate chloride) that serves as salts to assure the permeability of the coating film. Those quaternary ammonium groups will be ionized when contact with solution. This will lead to the swelling and opening pores of the coating film. The only difference between the two polymers is the content of quaternary ammonium groups. In Eudragit® RL, the molar ratio between the quaternary

ammonium groups to neutral methacrylic acid ester groups is 1:20, while this ratio is 1:40 of Eudragit® RS. Obviously, Eudragit® RL has double content of quaternary ammonium groups compared to Eudragit® RS and thus has a higher permeability. Different drug release rates can be obtained through adjusting the thickness of the coating film and changing the ratio of the two polymers in the formulation[5].

2.3.3. Polymers for delayed release

Polymers employed in delayed (enteric) coating are equipped with the ability of protecting the API from being damaged in the acid environment of gastrointestinal (GI) tract. Meanwhile, these polymers have to dissolve easily when travelling to the small intestine that has higher pH value. Similarly to immediate release, the most common polymers served for delayed release coating are cellulose-based and methacrylate-based polymers.

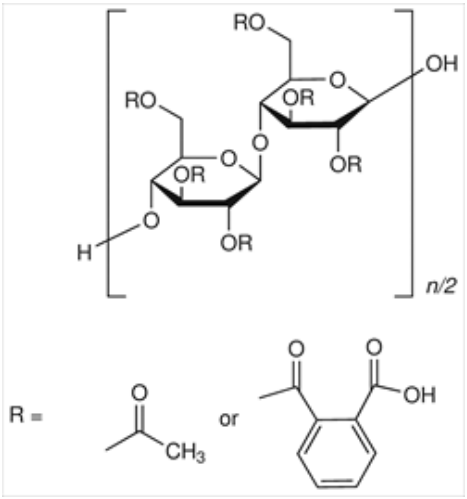

Figure 2.6 Cellulose acetate phthalate molecular structure

In the early age of delayed release coating, shellac was one of the earliest natural polymers to meet this requirement[6]. Later on, cellulose acetate phthalate (CAP, shown in Figure 2.6), a synthetic cellulose-based polymer has become a popular semi-synthetic enteric coating material since it has a good performance of acid resistance and high solubility in intestine environment of pH 6.0 to 6.4[7].

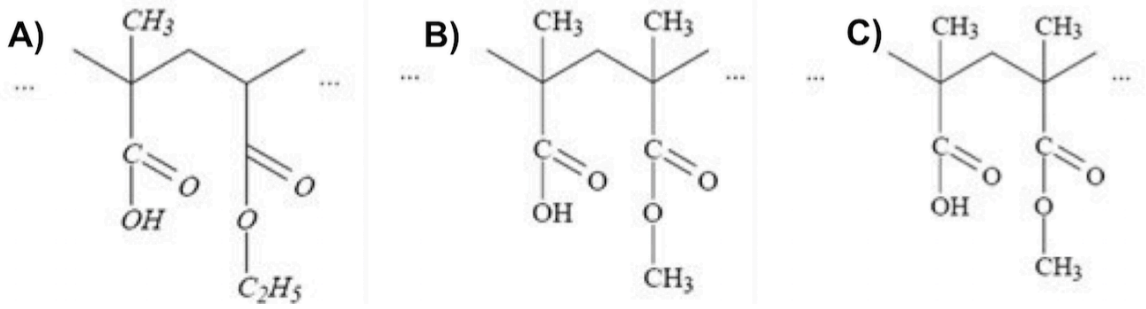

Figure 2.7 Chemical structure of A) Eudragit® L 100-55,
B) Eudragit® L 100 C) Eudragit ® S 100

At present, Evonik, a German company focused on specialty chemicals, has developed several polymers for the enteric coating. The polymers are either in the form of organic solution or powder. Among the above-mentioned products, Eudragit® L100-55, Eudragit® L100 and Eudragit ® S100 (shown in Figure 2.7) are three powder form polymers that perform differently in the dissolution property based on the pH value. Eudragit® L100-55, also known as Acryl-EZE MP, is applied for the first section of the small intestine-duodenum, and is able to dissolve in the media with pH above 5.5. Eudragit® L 100 is aiming at delivery the drug to the middle part of small intestine-jejunum, and thus is soluble in pH higher than 6.0. Eudragit® S is used for targeting the drug to the last part of the small intestine, i.e. ileum, and dissolves in pH above 7.0. Particularly, in terms of the molecular structure of the enteric polymers, most of them contain carboxylic acid groups, which assure the strong protection of the API under low pH circumstance.

2.3.4.Plasticizers

In the pharmaceutical coating industry, polymers applied for coating usually form brittle films, and thus fail to modulate the desired drug release profiles[8]. With the addition of plasticizers, the above-mentioned problem can be improved. Usually, plasticizers are water-insoluble materials with low molecular weight (200-1000) and high boiling point at

room temperature[9]. Among the polymers, triethyl citrate (TEC) and polyethylene glycol 400 (PEG400) are two typical plasticizers that are widely used in the pharmaceutical coating industry. Particularly, TEC is a suitable plasticizer for Eudragit® RL and Eudragit® RS, and PEG400 is appropriate for Eudragit® EPO and Acryl-EZE[10-12].

Plasticizers are functionalized by incorporating themselves between/in the polymer chains, increasing the free volume, so as to decrease the glass transition temperature (T_g) of the polymers, improve the film flexibility and control the drug release[12-14]. By applying a suitable amount of plasticizer, the plasticizer will first stay on the surface of the solid dosage forms before being absorbed, which actually enhance the capillary force between the coating polymers and the surface of the solid dosage forms. Therefore, the coating efficiency is enhanced[15, 16]. Moreover, in electrostatic dry coating technique, plasticizers also play an important role in increasing the electrical conductivity, improving the deposition of the coating materials on the solid dosage forms[10, 11, 17].

The selection of an appropriate plasticizer for a certain coating polymer is of great importance in the coating process. Key factors are as follows: one is the spreading behavior of the plasticizer, and the other is the application amount and the compatibility between the plasticizer and coating polymer. Specifically, the spreading behavior can be characterized by measuring the contact angle of the plasticizer on the coating film and estimating the surface energy of the coating polymer. Viscosity data can give potential information of the plasticizing activity[18]. Moreover, the solubility of the coating polymer in the plasticizer can help to meet the requirement of a good compatibility[9, 19]. The applied amount of the plasticizers is another key factor in order to form a continuous coating film[20]. Excessive amount of plasticizer may cause sticking problems while not enough amount may lead to brittle coating film. As a result of this, looking for the suitable amount of plasticizer becomes a critical condition for a coating process[8, 21].

2.4. Solvent-based coating processes

In modern pharmaceutical coating processes, the solvent-based coating methods are widely used, which includes sugar coating, organic solvent coating and aqueous coating. The sugar coating was first invented in the 19th century[1]. After several decades, the organic solvent coating technique appeared in 1930s and began to take place of the sugar coating in 1950s. Aqueous film coating then replaced part of organic solvent coating owing to its more environmental-friendly properties[22].

2.4.1. Sugar coating

The main principle of sugar coating is masking the bitter flavor of the drug, and sacharose is one of the commonly used sugars in this coating method. The process consists of four basic steps: sealing, subcoating, syruping and polishing.

Sugar coating has many restrictions and drawbacks. One major disadvantage is its long processing time. Under some conditions, it can take up to 5 days to finish the sugar coating process. What's more, difficulties in the standardization of coating procedures and the strict demand of high-level operators also indicate the complexity of the operating conditions. Another disadvantage is the possibility of the breedly bacteria and mold. This happens not only during the storage period, but also in each coating procedure[1].

2.4.2. Organic solvent coating

The appearance of organic solvent coating decreases the long processing time dramatically and overcomes the difficulty in complex operations compared to sugar coating. Actually, this technique came out in 1930 but not commercialized until 1954 by Abbott Laboratories. Figure 2.8 shows the schematic of organic solvent film coating process, wherein the coating materials are dissolved in the organic solvent to form a solution. The solution is sprayed through a nozzle onto the solid dosage forms. Heat is

required in the following curing procedure to evaporate the organic solvent and the coating materials will form a continuous coating film.

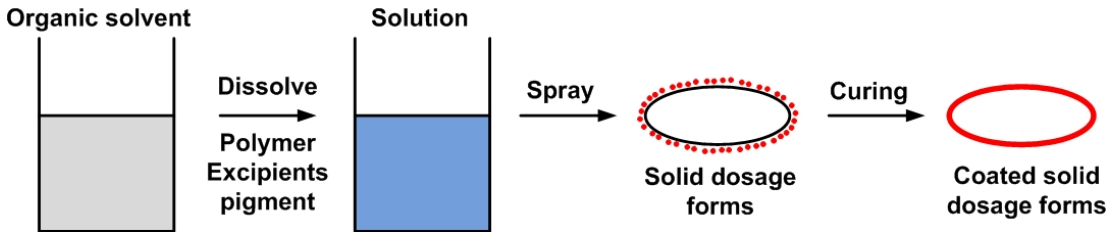

Figure 2.8 schematic of organic solvent coating

The organic solvent film coating provides a better and more precise control of the coating process thanks to the development of the coating apparatus. As a result of this, the reproducibility of the process and the uniformity of the product from different batch are efficiently increased. In addition, not only large solid dosage forms such as tablets but also small solid dosage forms such as pellets can be coated by this technique (Details of pellets coating with organic solvent coating technique will be introduced in Chapter 2.3.4).

However, several restrictions and drawbacks still exist in this method. Firstly, the concentration of the coating polymers in the organic solvent is usually dilute, thus it takes really long processing times to reach an ideal coating thickness and coating level. Also, it is not available for coating materials with high viscosity as the nozzle is easily blocked. In addition, the organic solvents may be toxic and inflammable, which brings potential hazards during the evaporation step. The cost of after-treatment and recovery of the organic solvent are both very expensive. Moreover, because the organic solvent is removed through evaporation, the solvent residual may have a chance to remain in the coating, which indicates a potential safety danger. [1, 22]. Therefore, for some water-soluble polymers, aqueous film coating begins to take the place of organic solvent film coating[23].

2.4.3.Aqueous coating

The aqueous coating method successfully eliminates the usage of organic solvent, which is a great improvement of this method. The aqueous coating method has a similar coating procedure as the organic solvent coating method. The aqueous dispersion that contains the coating materials is sprayed onto the solid dosage forms and curing for a certain period of time to form a coating film, heat is provided continuously during the curing step[23]. The film formation mechanism of aqueous coating is different from the organic solvent coating. The coating materials, instead of dissolving in the aqueous phase, disperse in water to form a suspension or solution. As shown in Figure 2.9, the film formation essentially can be divided into three stages. Firstly, the aqueous dispersion deposits on the surface of the solid dosage forms after being sprayed. Then, as the water evaporates during the curing step, the polymer particles begin to compact together and followed by the particle deformation in the second stage. Finally, as the water evaporates continuously, the particles diffuse and coalesce with each other and form a continuous coating film.

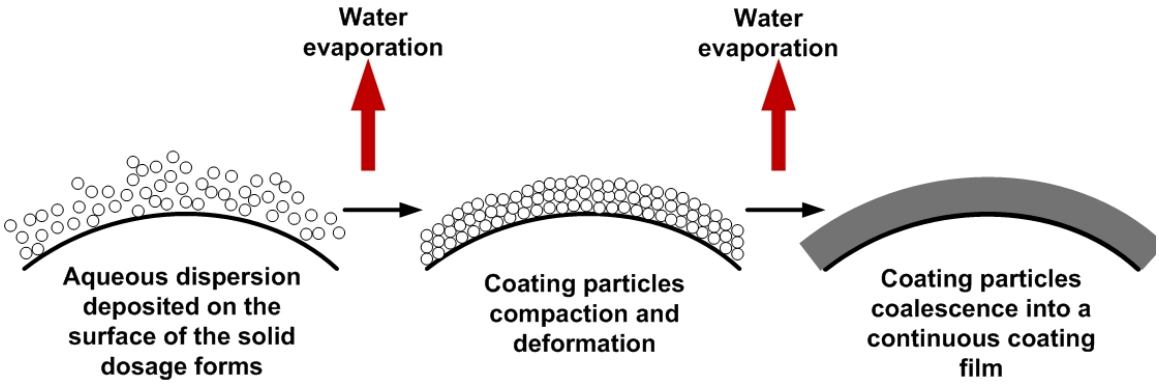

Figure 2.9 Film formation mechanism of aqueous coating

Whereas, some restrictions still exist in the aqueous film coating method. One of the major limitations is the huge energy required to evaporate the water during the process

since water has a higher boiling point than the organic solvent. Another disadvantage is that the processing time is much longer than the organic solvent coating method due to the relatively high vaporization latent heat of water. Both of the above-mentioned drawbacks increase the coating cost and the energy consumption of the process. Furthermore, some coating polymers may not well-dispersed in water and can cause nozzle blockage, and thus only organic solvent film coating can be applied to these materials. Moisture is another key factor that plays an important role in the coating process. If the API is moisture sensitive, the remaining moisture in the coating film can cause stability and storage problems[24]. In summary, not only for aqueous coating, but also organic solvent coating, the balance between the applying solvent (either water or organic solvent) and its evaporation is the main restriction of these two kinds of coating methods[25].

2.4.4. Pellet coating with organic solvent/aqueous coating techniques

Coating of small dosage forms such as pellets with the organic solvent coating method or aqueous coating method is most commonly achieved by the fluidized bed, which basically includes three types of solution spraying locations, top-spray, side-spray and bottom spray[26]. The bottom-spray is reached by the Wurster apparatus invented by Wurster in 1966[27]. Today, it is one of the most common units of coating equipment for pellet coating in the pharmaceutical coating industry. The schematic of Wurster fluidized bed is shown in Figure 2.10[28]. The Wurster fluidized bed consists of a solution-spraying nozzle located at the bottom, a distributor plate and a Wurster tube that is placed in the center of the column. During processing, the pellets are fluidized and coated with the coating material sprayed from the bottom spray nozzle. Furthermore, the unique structure leads the fluidized pellets to circulated between the Wurster tube and the outside column, which ensures a uniform and continuous coating film. Moreover, Hampel has came up with a continuous pellets coating by the addition of a separation tube with the Wurster fluidized bed with organic solvent coating technique[29].

Drawbacks of this technique are obvious. Large amount of hot fluidizing air is required in this apparatus not only to maintain the fluidization of the pellets, but also necessary to keep a constant temperature of the system for moisture evaporation. This increases the energy consumption as well as the operation cost dramatically. Furthermore, long processing time is required to achieve an ideal coating level due to the restriction of the solvent coating method.

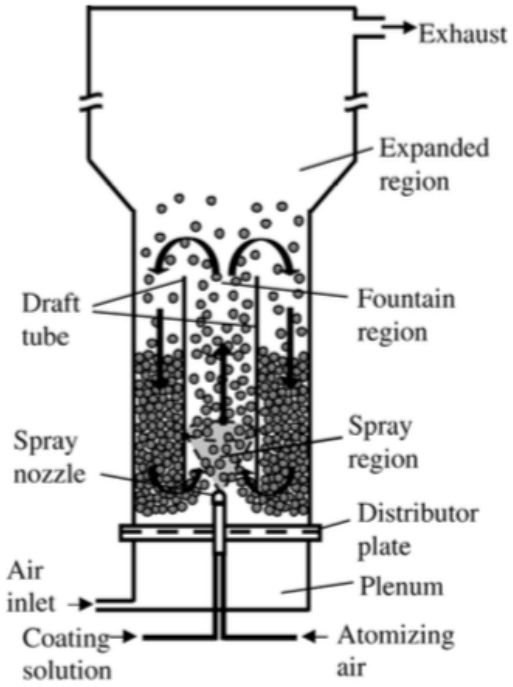

Figure 2.10 Schematic of Wurster fluidized bed coating equipment

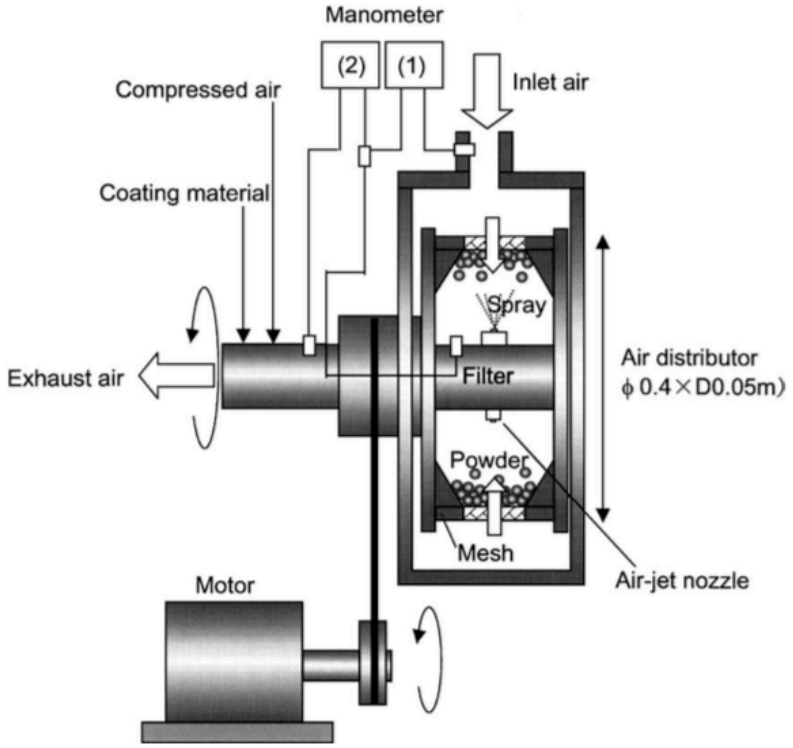

Figure 2.11 Schematic of the rotating fluidized bed coater

Apart from the Wurster fluidized bed, another apparatus for coating of small dosage forms using aqueous coating method is a rotating fluidized bed coater generated by Satoru Watano[30]. In Satoru's study, the rotating fluidized bed was aimed at coating fine particles (Geldart Group C powder) with the HPLC aqueous solution. The schematic of the rotating fluidized bed is shown in Figure 2.11. The rotating fluidized bed mainly contains a rotatable cylinder covered with meshes, a plenum chamber and a filter placed in the center part of the cylinder. During the coating process, the aqueous solution was sprayed through the nozzle located on the central filter, and the particles were fluidized with the help of the strong centrifugal force. However, a large amount of hot fluidizing air is still required in this apparatus in order to maintain the fluidization of the particles and evaporate the moisture, which dramatically increases the energy consumption. Long processing time was required due to the nature drawbacks of aqueous coating.

2.5. Solventless coating processes

As solvent-based coating has some inevitable drawbacks, today, pharmaceutical coating processes tend to come up with some solvent-free coating techniques, which completely avoid the use of organic solvent and water. Solventless coating reduces the processing time and cost of solvent evaporation significantly. Also, the expense of the solvent follow-up disposal can be decreased dramatically.[25, 31] Typical solventless coating techniques basically include compression coating, holt-melt coating, supercritical fluid coating, photocurable coating and dry powder coating. Particularly, dry powder coating is a novel solventless coating technique that has drawn great attention in the pharmaceutical coating industry. Dry powder coating includes several coating techniques such as electrostatic-infrared powder coating, infrared-heat powder coating, plasticizer powder coating, etc. Detailed introduction of dry powder coating will be introduced in Chapter 2.5.

2.5.1. Compression coating

Compression coating, also named press coating, is mainly applied for the coating of tablets. It is comprised of a drug core and an outer shell. The drug core is enclosed in the outer shell and thus different drug release patterns can be modulated by the selection of inner drug cores and outer layer materials. Also, the outer shell has great influence on the mechanical strength and stability of the coated tablets[32].

Conventionally, the compression coating process is accomplished by firstly compressing the drug core, and followed by compressing the outer layer materials around the drug core. A major problem related with the technique is the location of the inner drug core. The drug delivery performance of the coated tablet is not desirable assuming that the location of the drug core is not in the center[33]. This problem was solved by Ozeki et al. who designed a one-step-dry-coated tablet manufacturing method (OSDRC system). This method has been successfully applied to modify delayed release, and the API release time

and release profile can be controlled by adjusting the thickness of the outer layer [32, 34, 35]. Hariharan and Gupta reported a similar process, in which a modified three-layer tablet press was used and the drug core and coated tablets are made simultaneously[36]. Tahra et al. found that HPMC was suitable for sustained release using compression coating method[37]. Cellulose derivatives, for example, hydroxypropylmethylcellulose (HPMC), hydroxyethlcellulose (HEC) and hydroxypropylcellulose (HPC) are appropriate polymers for the outer layer materials to modify controlled release and sustained release in compression coating[32].

Compression coating has some unique features. Firstly, it is able to modulate controlled release and sustained release, and particularly, it allows the drug core to be coated with some incompatible coating polymers. Moreover, it also available for the coating of those tablets that contain two kinds of APIs with different target area[25]. However, the compression coating has some drawbacks as well. One of the major limitations is the large coating thickness. The drug loading is limited due to the thick outer layer. It also restricted by the compressibility of the coating materials. Moreover, for the small dosage forms, such as pellets, that have quite small drug loading and volume, the compression coating technique is not suitable and efficient when applying to this kind of substrates.

2.5.2.Hot-melt coating

In hot-melt coating process, as its name indicates, the coating material is applied in the molten state on the substrate and followed by a cooling solidification step, in which no solvent is required. This technique has been researched for stability improvement, taste masking and sustained release[31]. The release performance of the coated drug is determined by the coating material and is influenced by several factors such as pH, heat contact with digestive enzymes during diffusion, penetration behaviors, etc.[38].

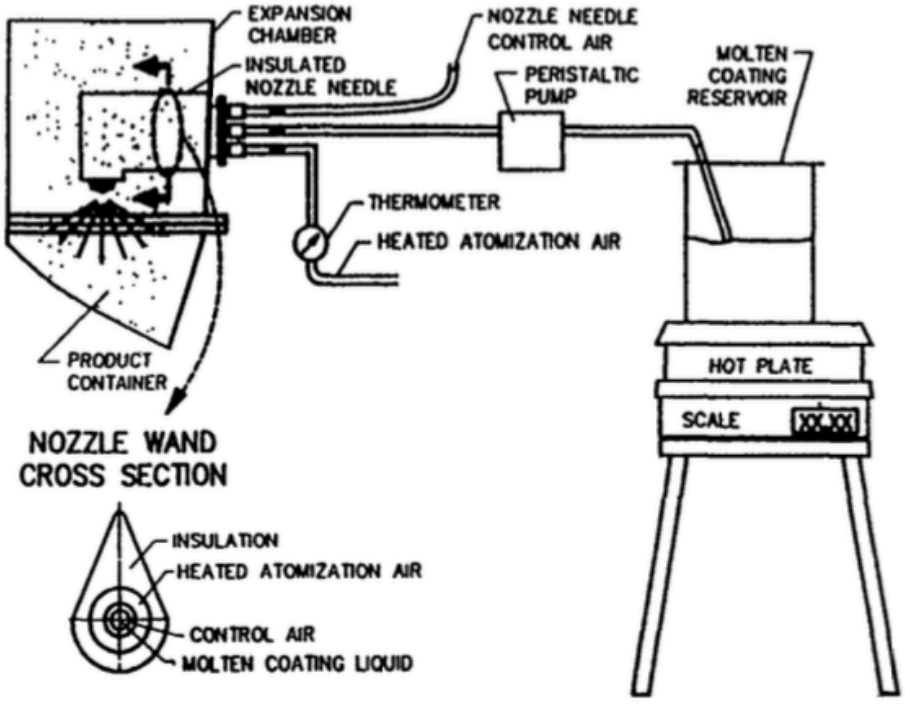

Figure 2.12 Schematic of the hot-melt coating process[40]

In general, the process of hot-melt coating can be divided into four stages: warming up of equipment, preheating of substrate, melting and spreading of the coating material and finally cooling and congealing of the coating[39]. A schematic of the hot-melt coating process is shown in Figure 2.12. The equipment is a modification of conventional fluidized bed coater, and consists of a coating material molten system, an insulated nozzle for the spraying of coating agent and a modified fluidized bed[40]. When

processing, the coating agent is introduced at a high temperature (around 150 ^{o}C) constantly. As a result, the hot-melt coating materials must be equipped with low melting points, stable physical and chemical properties, good flowability and sprayability[38]. Commonly used coating materials in hot-melt coating technique are usually derived from natural animal and plant sources, such as partially hydrogenated soybean oil, partially hydrogenated palm oil, partially hydrogenated cottonseed oil and partially hydrogenated castor oil, paraffin wax, to name a few[31, 38-40].

In summary, hot melt coating is useful for coating of small dosage forms such as small granules, pellets and particles. Moreover, coating polymers with low melting point is suitable to be applied in this method and the process can be accomplished within a short time. However, many APIs of the drug cores cannot sustain under high temperatures because they are very easy to decompose or damage. In addition, the selection of coating materials is very limited. Many commonly used pharmaceutical coating materials usually have high melting point, and dilution is required if applying with the hot-melt coating technique. Therefore, the hot melt coating still has some restrictions to achieve high quality coatings.

2.5.3.Photocurable coating

The photocurable coating method is mainly based on a free-radical polymerization reaction. Wherein, the functional groups in the photocurable materials react due to the illumination of an UV/visible light source and achieve a crosslinking reaction. The process can be finished within a short time[41]. The photocurable coating system contains three key components: an UV/visible light source, functionalized liquid monomers/prepolymers as the photocurable materials and photoinitiator or/and photo sensitizer[42]. Depending on the monomers/prepolymer and the photoinitiator applied, the polymerization reaction generated by the light could be free radical, cationic or anionic mechanisms[43]. During the polymerization reaction, the functionalized liquid

monomers/prepolymers transform from the liquid state to the coating film. The most widely applied photocurable coating materials is acrylate-functional pre-polymers[44].

Wang and Bogner were the first who applied the solventless photocurable coating technique to pharmaceutical area. They coated nonpareil beads with silicone polymer derivatives[45]. Later on, Bose and Bogner extended the technique to modifying immediate and sustained drug release profiles[46]. The release profiles are modulated by the adjustment of the coating materials, the layer numbers and the coating thickness. The film formation of the coating relies on the concentration of the photo-initiator/photosensitizer, the intensity of the light source and the illumination time of the light[47].

In summary, the photocruable coating method is a chemical reaction-based technique and is suitable for APIs that are sensitive to high temperature. Both tablet coating and pellet coating can be achieved with this technique. Moreover, the processing time is quite short compared to liquid-based coating techniques. On the contrary, for light sensitive drugs, this coating method is not a good choice. The UV photocurable polymers are still not generally recognized as safe (GRAS listed)[25]. Therefore, the application of this technique to the pharmaceutical field still needs further exploration.

2.5.4. Supercritical fluid coating

Supercritical fluid coating is another novel solventless coating technique. The definition of supercritical state is a state that the temperature and pressure of a substance are above its critical temperature and critical pressure. Under this state, the phase state between liquid and gas is not obvious, which indicates that it can act like gas or behave like liquid. In addition, at the point close to critical state, a small change in pressure or temperature may result in great variation in physical and chemical properties[48].

The process can be accomplished by the following steps: firstly, to dissolve the coating agent in the supercritical fluid (supercritical carbon dioxide), then to disperse the coating materials in the medium, finally to achieve the coating by a rapid expansion of the supercritical solutions[49]. One of the common processes of supercritical fluid coating in pharmaceutical field is rapid expansion of supercritical solutions (RESS), as shown in Figure 2.13[49-51]. The most commonly used supercritical solution is supercritical carbon dioxide. Since it has relatively low critical temperature (31.1 ^{o}C) and critical pressure (72bar), its supercritical state is able to be achieved near room temperature. In supercritical state, carbon dioxide has liquid-like density and dissolubility, and gas-like diffusivity. Therefore, carbon dioxide is a suitable choice for supercritical state[52].

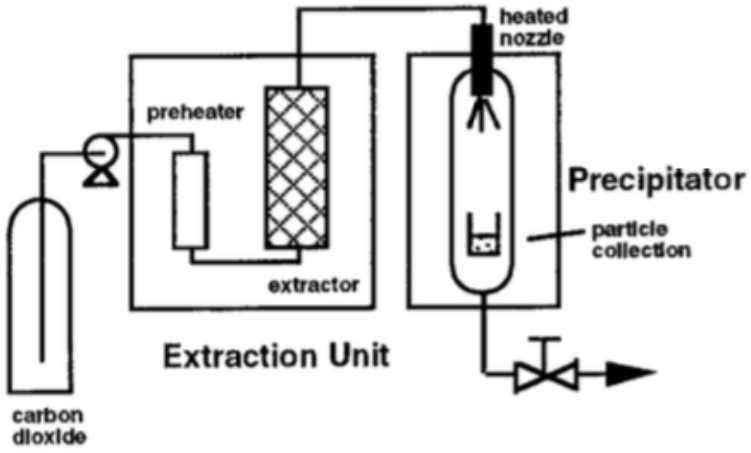

Figure 2.13 Schematic of rapid expansion of supercritical solutions (RESS) process

All in all, the supercritical fluid coating is beneficial to small dosage forms coating, such as pellets and glass beads[50, 51, 53, 54]. In addition, the coating process can be completed within a short time owing to the quickl elimination of the supercritical fluid. Whereas, this technique still has some restrictions. Firstly, most coating materials have a relatively low solubility in the supercritical fluid, which limit the properties of the coating materials. Secondly, the drug core should remain insoluble during the whole coating

process. Finally, the cost of the equipment is relatively high. Since the supercritical fluid in this process is in a high-pressure state, some special equipment that meets this demand needs to be investigated when applied in pharmaceutical industry[25].

2.6. Dry powder coating

Dry powder coating belongs to solventless coating, and can be divided into several coating techniques, including electrostatic-infrared powder coating, infrared-heat powder coating, plasticizer powder coating and electrostatic-heat-plasticizer (PEH) powder coating. This novel coating technique has began to draw great attention from the pharmaceutical industry owing to its unique characteristics such as short processing time, high coating efficiency, and low energy consumption, to name a few.

2.6.1. Electrostatic-Infrared powder coating

Electrostatic-Infrared powder coating was first applied in automobile and paint coating industries and then 'transplanted' to pharmaceutical coating industry in the last several decades. In this technique, the coating materials, carried by air, are charged by a high voltage (up to 100kV/200μA) electrostatic spray gun, and disperse to the surface of the grounded substrates. After the electrostatic adhesion, the powders are melted to form a strong coating film under the exposure of IR radiation that serves as a heat source[55]. The efficiency of the powder adhesion on the grounded solid dosage forms is relatively high. This is because the electrons of the charged coating particles will release to the ground when in contact with the grounded solid dosage forms immediately, which won't have any resistance on the deposition of the next feed coating particles.

The coating materials and the solid dosage forms are required to be conductive. Particularly, the drug core must have a resistivity under $10^9\Omega$m for the purpose of grounding while in contact with those charged coating powders. Various methods have been applied to increase the conductivity of the drug core. One efficient way is to spray

some water on the drug core to bring moisture onto the surface, which can help to decrease the resistivity. Another method is modifying the substrate with the help of excipients such as quaternary ammonium compounds and ionic salts. These excipients increase the conductivity through the absorption of the moisture in the air, and can generate a gel layer that is electrically conductive[55].

The coating materials usually have a size that ranges from 30 to 100μm, and sometimes contains more than one component. This can avoid agglomeration so that the particles act the same. A similar particle size of the coating materials means a better deposition on the surface of the solid dosage forms and the distribution behaves more uniformly[56]. Compared to solvent-based coating, the film thickness of electrostatic powder coating is thicker, sometimes maybe twice that over solvent-based coating. Moreover, the resistivity of the coating materials has a great influence on the control of the film thickness. Usually, low resistivity ($10^8\Omega$m) indicates a poor deposition due to the loss of charge. In contrast, high resistivity ($10^{12}\Omega$m) may lead to back ionization, which also limits the powder deposition and coating thickness[57]. After the spraying process, the coating powder forms a uniform film through exposure under IR radiation. The temperature of the drug core is around 80 ^{o}C, and 120^{o}C of the coating materials[56].

Phoqus, an oral drug delivery and development pharmaceutical company, has commercialized electrostatic-infrared powder coating technique[58-61]. In their process, the deposition of the coating powder is under accurate control and the two sides of the solid dosage forms can be coated with different formulations.

In conclusion, the electrostatic-infrared powder coating is a novel technique in the pharmaceutical industry. A uniform coating film can be achieved through this method within a short processing time. Furthermore, for water-sensitive drugs, this technique is a suitable choice. Moreover, this method has been applied to both the coating of large dosage forms and small dosage forms such as fine particles (details will be given in

Chapter 2.5.5)[62]. However, some limitations still exist in this technique. Infrared heat is necessary during the film formation process, which means this is not applicable for heat-sensitive drugs. In addition, despite the processing time being short, the time required for cleaning of the apparatus is relative long, which makes the process more complicated.

2.6.2.Plasticizer powder coating

Plasticizer powder coating was first reported by Obara et al[16]. The basic principle of this technique is to feed coating materials and liquid plasticizers simultaneously from two different feeders, and followed by a curing step to achieve a continuous coating film (shown in Figure 2.14[54]). Particularly, the curing temperature must be greater than the glass transition temperature (T_g) of the coating materials.

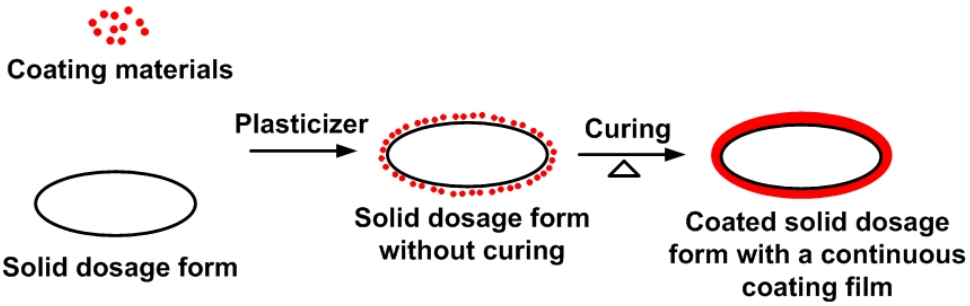

Figure 2.14 Schematic of plasticizer powder coating

During the coating process, the plasticizers increase the free volume by incorporating themselves between the polymers chains and thus result in the decrease of T_g, sometimes dramatically[12-14]. As the coating temperature can be decreased with the help of the plasticizer, the API is protected efficiently from being damaged[54, 63, 64]. Plasticizers, after being sprayed onto the surface of the solid dosage forms, can contribute to the adhesion between the coating particles and the solid dosage forms. It is beneficial for the film formation due to the improvement of viscous flow and particle deformation[65]. Furthermore, capillary forces will generate before the plasticizer immerse into the solid dosage forms, therefore, the deformation in the interstitial capillary system and the film

formation can be improved as well[16, 65].

Common used liquid plasticizers are triethyl citrate (TEC), polyethylene glycol 400 (PEG400), acetylated monoglyceride (AMG), etc. Particularly, for a certain coating polymer, a limited choice of the plasticizers can decrease its T_g efficiently.

So far, many research groups have applied the plasticizer powder coating technique to modulate fast release, sustained release and controlled release[16, 63-67]. The coating substrates can be either large solid dosage forms like tablets or small ones like pellets and particles. Usually, coating of tablets is processed in a rotating pan coater, and coating of pellets and particles are in a Wurster fluidized bed because small solid dosage forms tend to agglomerate easily due to the strong interactions and large specific surface areas. (Details of small dosage forms coating with the plasticizer powder coating technique will be introduced in Chapter 2.5.5.)

The major advantage of the plasticizer powder coating technique is the short processing time compared with solvent-based coating methods. In contrast, this technique still face challenges in some aspects. One is that the amount of plasticizers applied in the process is difficult to control. Surplus plasticizers may cause sticky effect and agglomeration of the solid dosage forms, whereas, not enough amount may result in a thin coating film and un uniform coating material deposition[54]. Thus, balance between the amount of plasticizer and prevention from agglomeration plays a critical role in the plasticizer powder coating technique.

2.6.3. Infrared-Heat powder coating

Infrared-Heat powder coating was first studied by Cerea et al. and was designed for the coating of tablets. In this technique, heat is the binding force that helps the formation of the coating film and is provided by an infrared (IR) light source[68]. Plasticizers are not required in this method. For polymers with low T_g such as Eudragit® EPO (T_g=53 ^oC), the

coating process is simple: spreading the coating material on to the tablets and curing under the illumination of the IR light source. When referred to high T_g polymers like Eudragit® RL (T_g=62 °C), Eudragit® RS (T_g=59 °C) and Eudragit® L 100-55 (T_g=127 °C), a pre-plasticization step is required, in which the coating polymer is combined with plasticizers through a hot melt extrusion process[17].

Advantages of the infrared-heat powder coating method included the elimination of plasticizers for those low T_g polymers, and the reduction of the plasticizer amount of high T_g polymers thanks to the pre-plasticization. However, the coating film accomplished by this technique is not smooth and uniform, and the thickness is large although the functional drug delivery is reached successfully. Furthermore, since the application of heat powder coating on tablets was successful, the coating of small solid dosage forms such as pellets with this method still requires further study.

2.6.4. Plasticizer-electrostatic-heat powder coating

Plasticizer-electrostatic-heat powder coating technique (PEH-Coating) is a novel pharmaceutical coating technique developed by Zhu et al[69]. As the name referred, this technique combines the application of plasticizer, electrostatic deposition and the heat together in one coating system. The liquid plasticizers help to decrease the glass transition temperature (T_g) of the coating materials, generate a capillary force and increase the electrical conductivity of the solid dosage forms. Moreover, the electrostatic spraying gun charges the coating particles with negative electrons and work together with the grounded rotating coating pan, which improves the powder adhesion on the solid dosage forms effectively. After the charged particles attach on the solid dosage forms, the electrons will release to ground due to the electrical conductivity of the solid dosage forms and the grounded pan coater, thus the next layer of the charged coating particles can easily deposit on the surface of the solid dosage forms again.

The PEH-Coating technique is achieved in a rotating pan coater. As shown in Figure 2.15, four major parts are included in this coating apparatus, a liquid plasticizer spraying system, a coating material feeder, an electrostatic spraying gun that can generate electrons together with coating materials and a grounded rotating coating pan that is temperature controllable. The overall coating process includes the following steps: firstly, the solid dosage forms are preheated in the rotating pan coater at a pre-determined temperature; secondly, a given amount of plasticizer is sprayed onto the solid dosage forms and immediately followed by the electrostatic spraying of the coating materials at a given amount; finally, the pellets are cured at a pre-determined temperature and time to form a continuous, smooth and strong coating film.

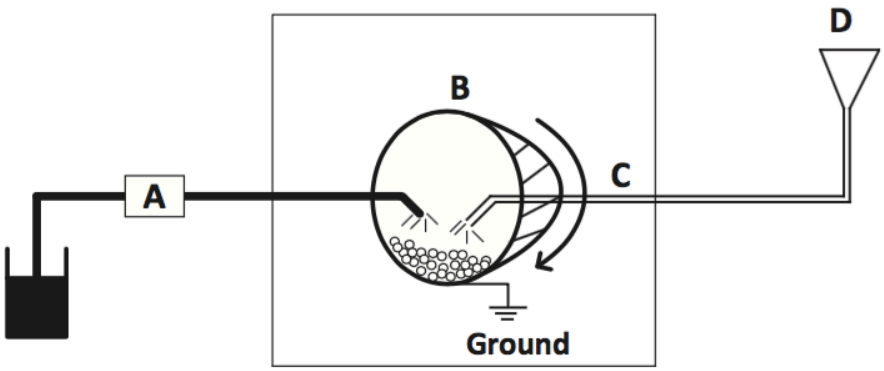

Figure 2.15 Schematic of PEH-Coating system. (A) Liquid plasticizer spraying system, (B) Rotatable coating pan, (C) Electrostatic spraying gun, (D) Coating material feeder

This technique has been applied to the coating of both large solid dosage forms such as tablets and small solid dosage forms such as pellets and successfully modified immediate release, sustained release and delayed release with relevant coating materials[10-12, 70]. Advantages of the PEH-Coating technique are clearly illustrated. It avoids the usage of the organic solvent and the water, which avoids the potential hazards of the organic solvent and shortens the processing time effectively. The coating process can be shortened to 2-3 hours. Also, since no fluidizing air is required in this technique, the energy consumption is reduced dramatically compared to the conventional

pharmaceutical coating fluidized bed coater that need large amount of hot fluidizing air to evaporate the liquid. In contrast, the restrictions of this technique still exist. The coating of those solid dosage forms with less electrical conductivity is not appropriate in this coating system. Moreover, the rotating pan coater in this technique is an 'open system', as a result, this is not a good selection for the coating of solid dosage forms with a really small size and weight. This is because during the coating process, the rotating pan coater may lead to the drop of tiny pellets, and the air from the spraying gun will blow the small pellets away.

2.6.5.Pellets coating with dry powder coating techniques

As described above, many of the dry powder coating techniques are able to achieve the coating of small solid dosage forms such as pellets and fine particles. The commonly used apparatus in dry powder coating techniques are spout-fluidized bed (Figure 2.16, applied in electrostatic-infrared powder coating), Wurster fluidized bed (Figure 2.10, applied in plasticizer powder coating) and rotating pan coater (Figure 2.15, applied in PEH powder coating).

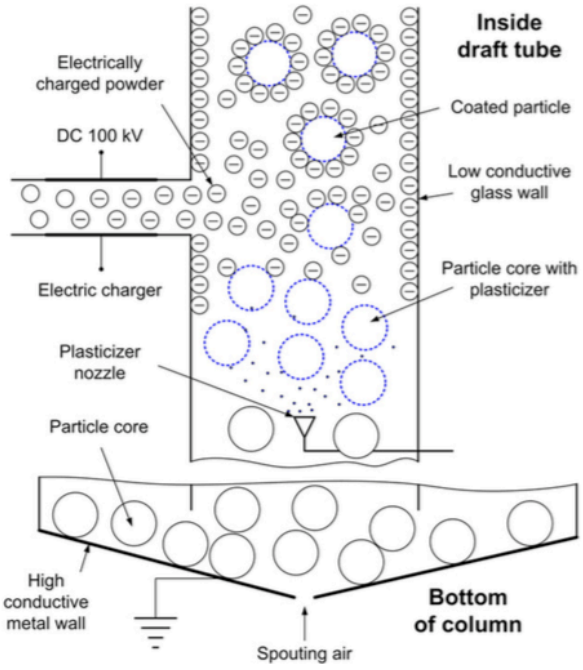

Figure 2.16 Schematic of the electrostatic spout-fluidized bed system[62]

The electrostatic-infrared coating technique has also been applied to the coating of small dosage forms such as fine particles with a spout-fluidized bed apparatus[62]. The schematic of the electrostatic spout-fluidized bed system is shown in Figure 2.16. The process was operated under a diluted and fast circulating condition in the spout-fluidized bed. Specifically, the particles were fluidized by the warm fluidizing air and were plasticized by the plasticizer nozzle located at the bottom of the column, meanwhile, the coating powders were charged with electrons by a corona gun and attached to the plasticized particles. Then the coated particles were transported from the spout-fluidized bed to a stationary system and followed with a curing step under the IR lamp at a predetermined temperature. Delayed release was successfully modified by the hydroxypropyl methylcellulose acetate succinate (HPMCAS) in this system. The advantages of this system with electrostatic-infrared dry powder coating technique are: firstly, it can avoid the agglomeration of the fine particles in the coating process effectively; secondly, it is suitable for the coating of fine particles even with a particle size less than 1mm. However, drawbacks of this technique still exist. Due to the characteristic of the fluidized bed, large amount of hot fluidizing air is required in this system, which increases the energy consumption as well as the operation cost. In addition, although the coating step in the spout-fluidized bed can be operated quickly, the curing step takes up to12 hours to achieve an ideal coating film.

Coating of small dosage forms using the plasticizer powder coating technique was available in a Wurster fluidized bed (Figure 2.10), which was investigated by Bodmeier research group[63, 64, 71]. In their study, the nonpareil pellets with a size of 0.71-0.85 mm were employed and coated with different coating materials to modify immediate release, sustained release and delayed release. During the coating process, the spraying of plasticizer and the feeding of coating materials were induced separately in a Wurster fluidized bed, and after the adhesion of the coating materials, the pellets were unloaded and transported to a curing step for another 2 h to 24 h under the predetermined

temperature. Obviously, pellet coating in a Wurster fluidized bed with the plasticizer powder coating technique decreases the adhesion between the coated pellets efficiently. The processing time can be shorten within several hours depended on the required curing time of the coating materials. A large amount of hot fluidizing air is required in this system due to the limitation of a Wurster fluidized bed, which increases the energy consumption and operating cost.

The coating of small pellets with the PEH powder coating technique was achieved in a rotating coating pan (Figure 2.15). The coated pellets were able to modulate immediate release, sustained release and delayed release with relevant coating materials successfully[12]. Details of this coating system can be found in Chapter 2.5.4.

Chapter 3
Materials and Methods

3.1. Materials

3.1.1. Powders

Eudragit® EPO, Eudragit® RS, Eudragit® RL, Eudragit® L100-55 and Colloidal silicon dioxide (AEROSIL® 200 Pharma) were provided by Evonik Degussa Corporation (Germany). Eudragit® EPO was used as the fast release coating polymer, and Eudragit® RS, Eudragit® RL were used as the sustained release coating polymers. Acryl-EZE was donated by Colorcon, Inc. (US). Acryl-EZE was used as the delayed release coating polymer and contains Eudragit® L100-55 developed by Colorcon, Inc. Talc powder was purchased from Mallinckrodt Baker Inc. (Canada). Colloidal silicon dioxide and talc powders were served as the anti-adherent agent to facilitate the coating process.

3.1.2. Plasticizers

Polyethylene glycol 400 (PEG 400) was purchased from EMD Chemicals Inc. (Ontario Canada). Triethyl citrate (TEC) was purchased from Caledon Laboratories Ltd. (Ontario Canada). The selections of liquid plasticizers were based on their performance of reducing the glass transition temperature (T_g) of the coating polymers. PEG 400 was selected as the liquid plasticizer for both Eudragit® EPO and Acryl-EZE. TEC was chosen as the liquid plasticizer for Eudragit® RS and Eudragit® RL[12].

3.1.3. Piroxicam pellets

Piroxicam pellets and microcrystalline cellulose (MCC) pellets were provided by Gaocheng Biotech Health CO., Ltd. (China). The particle size of the piroxicam pellets and MCC pellets are 0.9 -1.10 mm and 0.1-0.3 mm, respectively.

3.2. Particle size reduction and analysis

Particle size reduction is necessary for the coating powders (Eudragit® RS and Eudragit® RL) in order to achieve uniform film coating before preparing the coating formulations. A blade grind mill was employed as the particle size reduction apparatus, and an ultrasonic sieving (HK Technologies Ultrasonics Rugby, United Kingdom) was applied to select the powders with ideal particle size.

The particle size of powders was validated by a particle size analyzer (TSI Corporation, Model 3603, Shoreview, MN, USA) after the particle size reduction. The volume mean diameter D[4,3] was used as the average particle size. The calculation equation is as follows:

$$D[4,3] = \frac{\sum_{1}^{n} D_i^4 V_i}{\sum_{1}^{n} D_i^3 V_i}$$

The particle size tests were replicated three times. The average particle size of coating powders was shown in Table 3.1.

Table 3.1 Particle size of coating powders and additives

Coating powder	Average particle size, D[4,3] (μm)
Eudragit® EPO	13.3
Eudragit® RS	47.7
Eudragit® RL	40.8
Acryl-EZE	20.5
Talc	28.9

3.3. Glass transition temperature

Differential scanning calorimetry (DSC) analysis (Mettler Toledo, DSC822, Mississauga, Canada) was employed to study the glass transition temperature of both raw coating materials and coating materials with liquid plasticizers. The tests were investigated under different weight ratios between the plasticizers and coating materials. The samples (10 mg) were heated at the rate of 2 ^{o}C /min under a nitrogen atmosphere with the range from 20 ^{o}C to 200 ^{o}C. For each sample, the test was replicated twice[11]. The DSC results are shown in Table 3.2, Table 3.3 and Table 3.4.

Table 3.2 Glass transition temperature of Eudragit® EPO

Plasticizer (PEG 400) ratio (%w/w, based on polymer)	T_g (^{o}C) of Eudragit® EPO
0	53.1
10	38.8
25	31.1

Table 3.3 Glass transition temperature of Eudragit® RS and Eudragit® RL

Plasticizer (TEC) ratio (%w/w, based on polymer)	T_g (^{o}C) of Eudragit® RS	T_g (^{o}C) of Eudragit® RL
0	62	59
15	45	46.5
30	36	38
45	25	26

Table 3.4 Glass transition temperature of Acryl-EZE

Plasticizer (PEG 400) ratio (%w/w, based on polymer)	T_g (^oC) of Acryl-EZE
0	127
10	102
25	87
50	75
100	55

3.4. Characterization using scanning electron micrographs (SEM)

The surface morphology of the coated pellets was investigated by the scanning electron microscopy (SEM). An EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK) was employed to sputter coat the pellets samples. After sputter coated, the pellets samples were observed under a scanning electron microscope at 5.0 kV (SEM, Hitachi S-2600N, Ontario, Canada).

3.5. In-vitro drug release testing

In-vitro drug release profiles of the coated pellets were tested by the United States Pharmacopeia (USP) apparatus (Apparatus 2, paddle; Huanghai Rcz-6c2, Shanghai, China). Six samples with 100mg coated pellets were conducted for the three different polymers coated pellets. For Eudragit® EPO coated pellets, the drug release media was 900 mL of 0.1 N HCl solution under the temperature of 37 ^oC and the rotation speed of the paddle was 100 rpm. For Eudragit® RS and Eudragit® RL coated pellets, the drug release media was also 900 mL of pH 7.2 phosphate buffer solution under the temperature of 37 ^oC and the rotation speed of the paddle was 50 rpm. For Acryl-EZE

coated pellets, the release media was 750 mL of 0.1 N HCl solution during the first 2h and 1000 mL of pH 6.8 phosphate buffer solution (by the addition of 250 mL of 0.2 M tribasic sodium phosphate solution into the above 750 mL 0.1 N HCl solution) for another 2h, and the rotation speed of the paddle was 100 rpm. Samples were collected by a 10 mL syringe at predetermined intervals and followed by the replacement of same amount (10 mL) of fresh release media. The samples, after being filtered, were assayed using an 8453 UV-Visible Spectrophotometer (Agilent Technologies, Mississauga, Canada) at a wavelength of 334 nm for pH 1.2 HCl solution (0.1 N), 354 nm for pH 7.2 phosphate buffer solution and 353 nm for pH 6.8 phosphate buffer solution.

3.5.1.Standard curve

The drug release standard curves of piroxicam at the wavelength of 334 nm, 354 nm and 353 nm are shown in Figure 3.1, Figure 3.2 and Figure 3.3, respectively. The curves are served for the calculation of unknown concentrations of piroxicam samples collected from the in-vitro drug release testing.

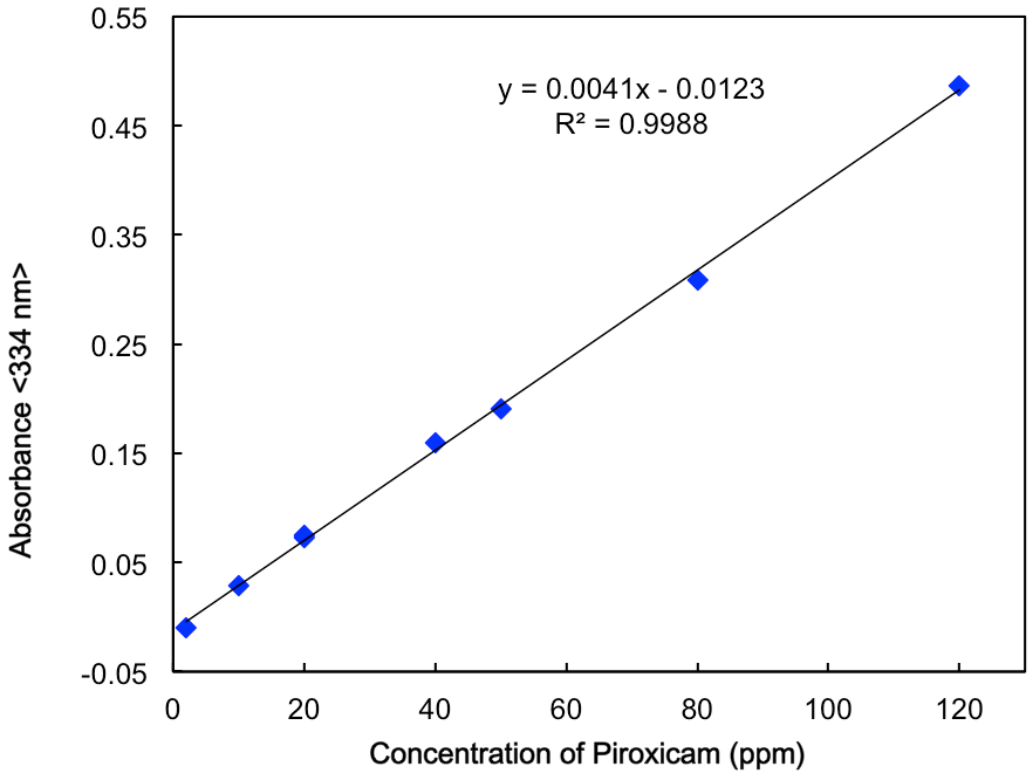

Figure 3.1 Standard curve of piroxicam (wavelength=334 nm)

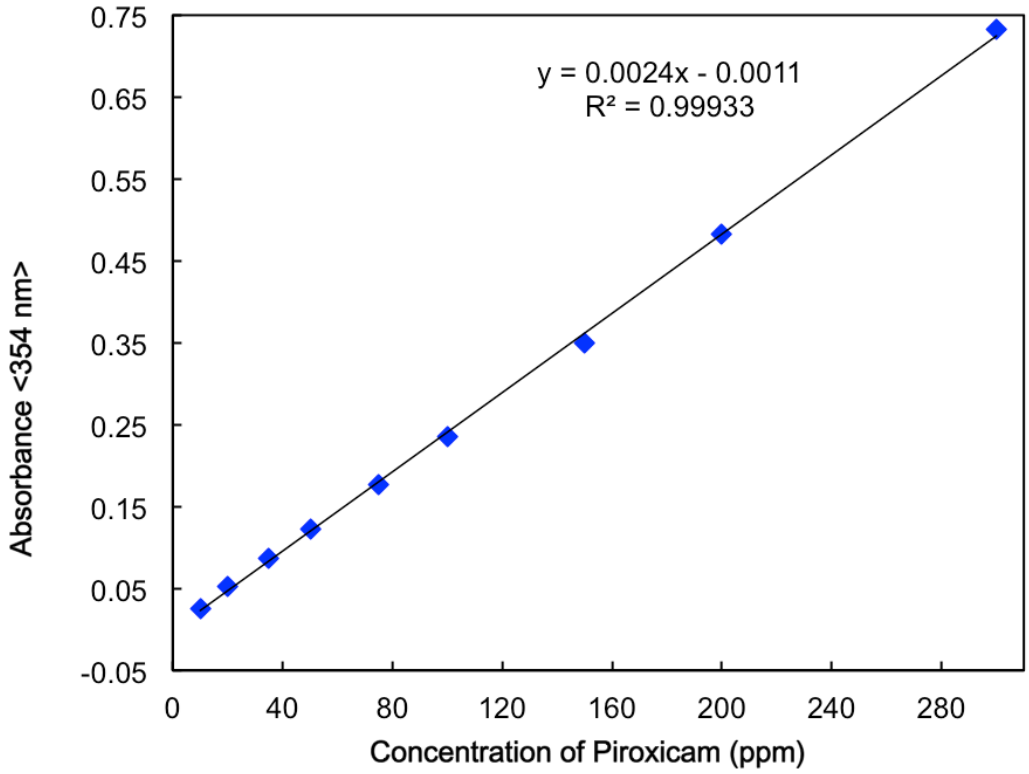

Figure 3.2 Standard curve of piroxicam (wavelength=354 nm)

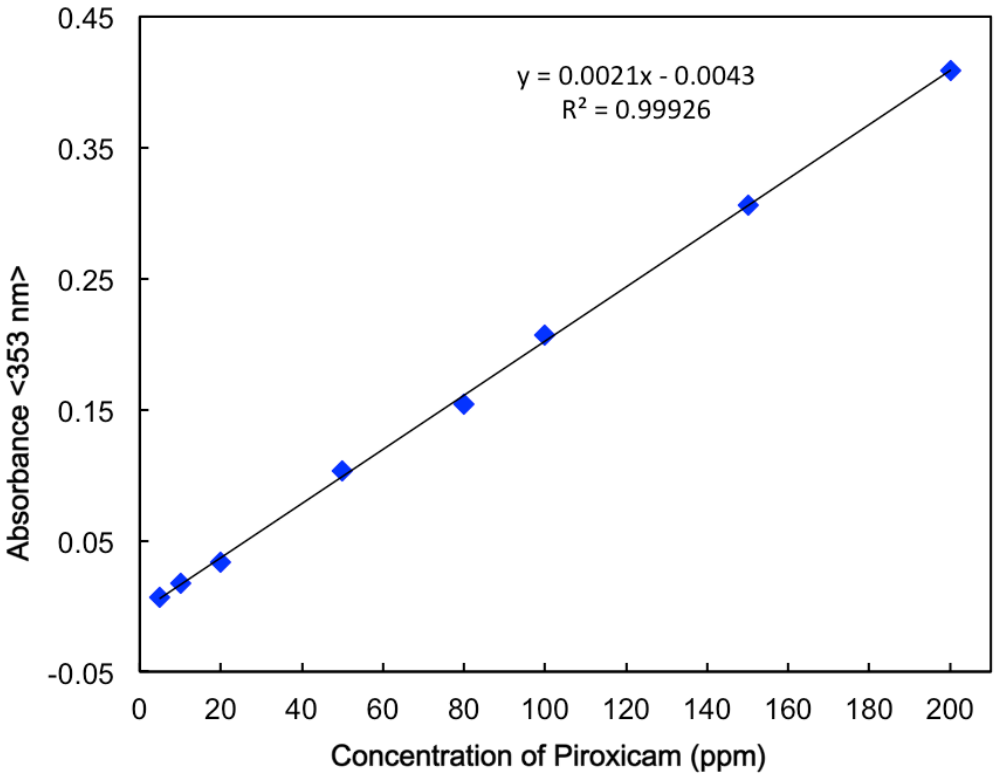

Figure 3.3 Standard curve of piroxicam (wavelength=353 nm)

3.5.2. UV-Vis spectrophotometer validation

After the creation of the standard curve of piroxicam, precision test, accuracy (recovery) test and stability test are required for the acceptability validation of the application of UV-vis spectrophotometer that is used for the measurement and analysis of the drug release from piroxicam pellets. For the release media of pH 1.2 HCl solution (0.1 N), a buffer solution containing piroxicam was scanned by the UV-vis spectrophotometer to ensure a maximum absorbency wavelength at 334 nm. For the release media of pH 7.2 phosphate buffer solution, the wavelength is at 354 nm. And for the release media of pH 6.8 phosphate buffer solution, the wavelength is at 353 nm. After the confirmation of the maximum absorbency wavelength of different release media with known concentration, the three-mentioned test (precision test, accuracy (recovery) test, stability test) were required for each of the release medium.

Precision tests

Three solution samples with a known concentration of piroxicam (not to exceed the maximum absorbency concentration of the standard curve) were prepared, and then scanned a defined amount of each sample. The standard of the precision test depends on the standard error between the three samples that are collected from the UV-vis spectrophotometer output. If the standard error is smaller than 1%, the precision test is successful. The equation for the calculation of standard error is:

$$\text{Standard Error} = \frac{\text{Standard deviation of sample}}{\text{Mean drug release concentration}} < 1\%$$

Accuracy (recovery) tests

Three solution samples of different known piroxicam concentration were prepared. The concentrations of three samples are low, medium and high. Then scanned a defined amount of each sample was scanned. The definition of the accuracy test is the difference between the true value and the mean experimental value of the release data within a confidence interval. The accuracy test is required for each of the three concentration samples. The three tests will give an overall accuracy of the UV-vis spectrophotometer. The calculation equation of percentage difference is:

$$\text{Percentage Difference} = \frac{\left|(\text{True value-Mean experimental value})\right|}{\text{True value}} * 100\%$$

Stability tests

For stability test, a solution sample of known piroxicam concentration (not exceed the maximum absorbency concentration of the standard curve) was prepared. Then the solution sample was put into one chamber of the dissolution test apparatus and the temperature of the system was 37 ^{o}C. Samples were collected with a 10 mL syringe at predetermined intervals (0 hr, 1 hr, 2 hrs, 6 hrs, 12 hrs) and scanned. Sample of 0 hr was regarded as the basis. If the experimental value of the samples through 12 hours, compared to the 0 hr basis, remained constant within a very tiny error, the accuracy test can be regarded as a success.

Chapter 4
Apparatus and Experimental Procedure

4.1. An innovative rotary fluidized bed equipment for pellets dry powder coating

Rotary fluidized bed (RFB) coating system

A new apparatus called Rotary Fluidized Bed (RFB) was designed by our research group for the coating of small dosage forms with dry powder coating technique. The apparatus structure originated from the fluidized bed that facilitated fine powder fluidizing[72] Figure 4.1 shows the schematic of this rotary fluidized bed that is seen horizontally along with the rotating axis. Wherein, the rotating part of the RFB is a cylindrical tank (diameter =12 cm, depth= 10 cm) lying horizontally. The cover of the cylindrical tank can be removed for the loading of the solid dosage forms. There is an open hole (2 cm) located in the center of the cover that serves as the inlets of the coating materials and plasticizers. Particularly, the cylindrical tank consists of two layers. The outside layer is made of acrylic and the inner side is covered with porous material (mesh). There are six chambers located between the two layers. During processing, a fluidizing air is blown in through three of the six chambers and the other three chambers serves as outlets. When rotating, the six chambers serve as inlets and outlets alternately. The rotation speed of the tank can be controlled. In addition, fluidizing air is introduced in to the rotating tank during the coating process. The air enters through the backside of the rotating tank, then circulates in the tank and flows out again from its backside. The temperature of the coating system is controlled by the fluidizing air. Figure 4.2 shows the schematic of the RFB coating system that is comprised of four major parts, the coating materials feeder, the liquid plasticizer spraying system, the RFB and the fluidizing air heating and introducing system.

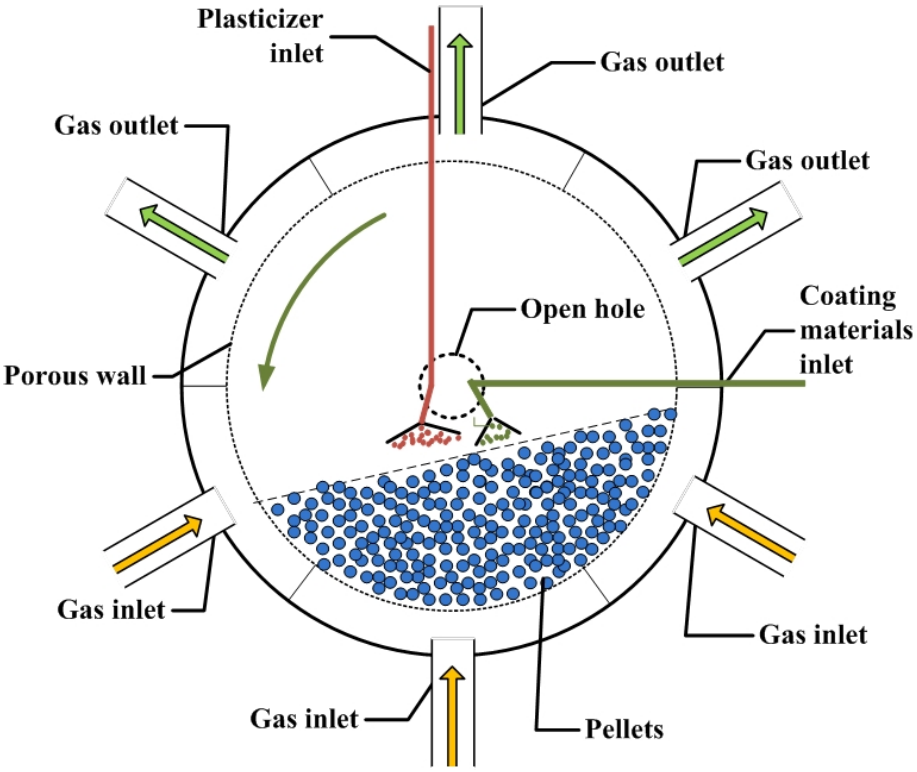

Figure 4.1 Schematic of rotary fluidized bed

The rotary fluidized bed (RFB) is an innovative apparatus for dry powder coating of small solid dosage forms such as pellets and particles. Advantages of the RFB are as follows. Firstly, compared to conventional solvent-based coating methods, the processing temperature is greatly decreased. Taking the Acryl-EZE coated pellets as an example, the processing temperature (curing temperature) using dry powder coating with RFB is 50 ^{o}C while it is always higher than 50 ^{o}C of conventional solvent-based coating. Secondly, processing time can be decreased to only 2-3 hours. For conventional solvent-based coating it usually takes up to 10-20 hours to reach the same coating level. The flow rate of fluidizing air in the RFB is less than that of liquid-based coating in fluidized bed coater. In addition, the inner side of the rotating tank is covered with porous material (mesh), which can release the moisture efficiently. Furthermore, the combination of rotation and fluidizing air successfully avoids agglomerations of pellets. Also, the fluidizing air is able

to blow the unattached coating powder away from the surface of the pellets, which can improve the smoothness of the pellet coated surface.

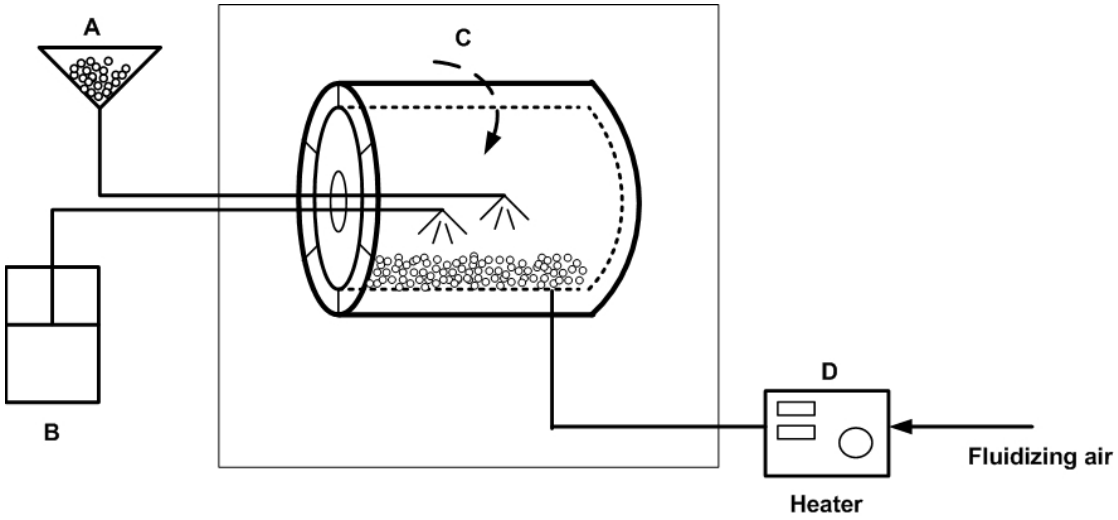

Figure 4.2 Schematic of the RFB system:(A) Coating materials feeder, (B) Liquid plasticizer spraying system, (C) Rotary fluidized bed, (D) Fluidizing air heating and introducing system

Experimental procedure and operating conditions

The experimental procedure of coating pellets using dry powder coating technique with RFB comprises five main steps: coating material formulation preparation, pellets and equipment preheating, liquid plasticizer spray, coating materials feeding and finally curing step.

The first step, preparation of coating material formulation, was to combine the coating polymers (Eudragit® EPO, Eudragit® RS, Eudragit® RL and Acryl-EZE) with additives (talc, colloidal silicon dioxide and pigment) into a homogeneous formulation. The ratio between the coating polymers and additives depended on the weight.

The second step was preheating of the equipment and pellets. In this step, 40g piroxicam

pellets were loaded into the rotating cylindrical tank and fluidizing air was introduced with a given temperature to warm up the equipment and pellets. The rotating speed of the RFB was based on the given process conditions.

Once the temperature of the pellets achieved the given temperature, the liquid plasticizer was sprayed and immediately followed by the feeding of coating materials. Before spraying liquid plasticizers, the rotation of the RFB was set to a relatively high speed that was about 70 rpm. This is because when spraying liquid plasticizers, pellets tend to agglomerate and become sticky, thus an increase in the rotating speed can avoid the agglomeration effectively. The fluidizing air was stopped before the spraying step in order to avoid the blow-away of coating materials. Liquid plasticizer was sprayed onto the pellets at a given flowrate from an atomizing nozzle. The spraying time was about 30 to 40 seconds based on the different coating polymers. It was followed immediately by a coating material feeding step. Whereby, a given amount of coating materials (usually 1-1.5 g) was delivered into the cylindrical tank. Usually, the plasticizer spray step and coating materials feed step was repeated several times until enough coating materials were deposited on the pellets and an ideal coating level was achieved. A waiting period (usually 10-20 mins) was required before the next amount of plasticizer and coating materials were feed. During the wait time, the fluidized air was re-introduced at the same processing temperature.

The final step of the coating process is the curing of coating materials that helps to form a uniform and stable coating film. The curing step began after the final spraying of liquid plasticizers and feeding of coating materials. In this step, the rotating speed and the curing time depended on the process parameters.

The coating level (%) of the coated pellets was defined as the weight gain of coated pellets over the weight of uncoated pellets, as shown in the following equation:

$$\text{Coating level (\%)} = \frac{\text{weight of coated pellets - weight of uncoated pellets}}{\text{weight of uncoated pellets}} * 100\%$$

4.2. Rotating pan coater

Rotating pan coater system

A rotating pan coater system, which was designed by our research group, was introduced for the coating of pellets with dry powder coating method. A schematic of the rotating pan coater system was shown in Figure 4.3. It consists of four main parts, a liquid plasticizer spraying system that includes an atomizing nozzle and a metering pump, a coating materials feeder, a rotating coating pan (with a diameter of 12.8 cm and a depth of 12.8 cm) and a coating materials spraying gun. The rotating speed of the coating pan and its processing temperature is controllable.

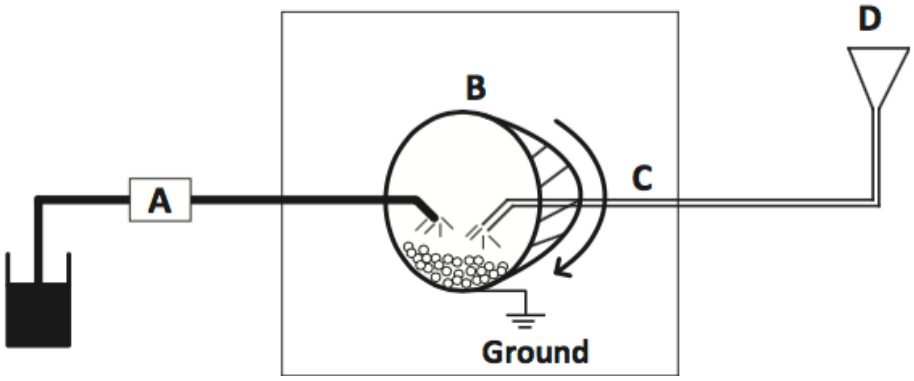

Figure 4.3 Schematic of the rotating pan coater system:
(A) Liquid plasticizer spraying system, (B) Coating pan,
(C) Coating material spraying gun, (D) Coating materials feeder

Experimental procedure

The experimental procedure using the rotating pan coater is similar to the RFB, which also contains five main steps, including coating material formulation preparation, pellets and equipment preheating, liquid plasticizer spray, coating materials feeding and finally curing step.

The first step, preparation of coating material formulation, was the same as it was in the RFB procedure. Then, the piroxicam pellets (70g) was placed in the rotating pan coater and preheated to a predetermined temperature that depended on the coating polymers. When preheating, the rotating speed was relatively slow.

Next was to spray the liquid plasticizer and feed the coating materials. Prior to the above two steps, the rotating speed was adjusted to a relatively high rate for the purpose of avoiding the pellets from agglomeration when applying the liquid plasticizer. Then, a given amount of liquid plasticizer was sprayed onto the pellets from an atomizing nozzle, followed by feeding of a given amount of coating materials right away. This step was usually repeated several times until enough coating materials were deposited on the pellets and an ideal coating level was achieved. Particularly, a waiting period (usually 10-20 mins) was required before the next amount of plasticizer and coating materials were feed.

When enough coating materials were attached onto the pellets, the curing step started. The rotating speed was readjusted to a slow rate (10-20 rpm) in order to reach a stable and uniform coating film. This step usually took about 2 hours and the processing temperature was maintained constantly at a given value.

4.3. Traditional fluidized bed

Top-spray fluidized bed system

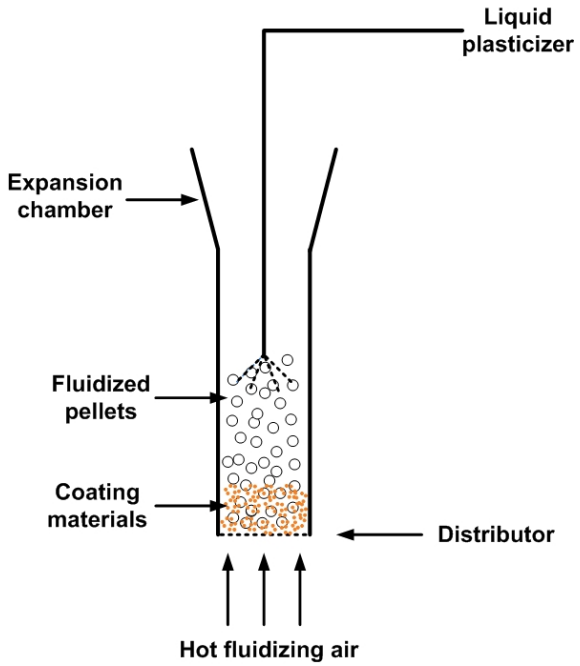

Figure 4.4 Schematic of top-spray fluidized bed

A traditional fluidized bed (column diameter=5 cm, expansion chamber diameter= 7.8cm, column height=20 cm, overall height=36 cm,) was used for dry powder coating small solid dosage forms. Schematic of the top-spray fluidized bed was shown in Figure 4.4. The pellets and coating materials were loaded in the fluidized bed above the distributor prior to a fluidization introduce. There was an atomizing nozzle placed in the middle of the fluidized bed that served for liquid plasticizer spraying. Fluidized air was induced from the bottom of the bed and the temperature of the system was also controlled by the introduced fluidizing air.

Experimental procedure

The experimental procedure of using top-spray fluidized bed was comprised of preparation of coating material formulation, pellets and equipment preheating, loading of coating materials, liquid plasticizer spray and curing step.

The preparation of the coating material formulation step followed the same procedure as the above two. Then the pellets with a weight of 70 g were loaded in the fluidized bed, and fluidizing air was introduced with a given flowrate and temperature to fluidize and preheat the pellets. When reaching the predetermined temperature, the fluidizing air was shut down and a given amount of coating materials was placed onto the distributor (The pellets were reloaded after the coating materials were settled). The next step was the liquid plasticizer spray, wherein the fluidizing air was introduced at a given flowrate, meanwhile a given amount of liquid plasticizer was sprayed from the atomizing nozzle located in the middle height of the column. At this moment, the liquid plasticizer, coating materials and the pellets contacted with each other together and the pellets were attached with coating materials immediately. The final step was the curing of the pellets, in which the fluidizing air was maintained at a constant flowrate and temperature until a uniform coating film was achieved.

Chapter 5
Dry Powder Coating of Pharmaceutical Pellets with the Rotary Fluidized Bed

5.1. Immediate release coating with Eudragit® EPO

5.1.1. Introduction

Immediate release is aiming at a rapid dissolution of drug after oral administration, which can quickly get the drug into the blood stream and take action to the site immediately. Among the commonly used immediate release coating materials, Eudragit® EPO has a good performance on taste masking which is one of the reasons of immediate release coating. Furthermore, it has already been mentioned that Eudragit® EPO is able to dissolve in gastric solutions up to pH5.5. This implies it is insoluble in the saliva but will dissolve in stomach rapidly[3].

Previous work done by our research group has shown that the pellets coating with Eudragit® EPO by dry powder coating technique was successfully achieved by a rotating pan coater[12]. In this section, the RFB was employed to dry powder coating piroxicam pellets to modulate immediate release with Eudragit® EPO. PEG400 was selected as a liquid plasticizer. The effect of coating level was also investigated. The performance and the appearance of the Eudragit® EPO coated piroxicam pellets was checked both qualitatively and quantitatively based on scanning electron microscope (SEM) and in-vitro release testing, respectively.

5.1.2. Effect of coating level

The immediate release coating formulations in this chapter followed the composition showed in Table 5.1. The mass proportion of Eudragit® EPO was 10%, which was based on the previous work done by our research group. A high mass proportion of Eudragit®

EPO can increase the film softness and achieve a dense coating film. However, this may also lead to the sticky coating film and agglomeration of pellets. In addition, talc and colloidal silicon dioxide were served as anti-adherent agents in case of sticky film that may cause agglomeration during coating process. An orange dye was added to help to observe the film formation in an easier and clearer way.

Table 5.1 Coating fomulation composition of Eudragit® EPO polymers

Formulation	Composition (wt%)
Eudragit® EPO	10.0
Talc	89.0
Colloidal silicon dioxide	0.5
Orange dye	0.5

The coating level (%) of the coated pellets was defined as the weight gain of coated pellets over the weight of uncoated pellets, as shown in the following equation:

$$\text{Coating level (\%)} = \frac{\text{weight of coated pellets - weight of uncoated pellets}}{\text{weight of uncoated pellets}} * 100\%$$

In order to study the effect of coating level, the piroxicam pellets were coated at two coating levels, the lower coating level is 8.82% and the relatively higher coating level is 19.9%. The scanning electron microcopy (SEM) was employed to observe the surface and cross section of the Eudragit® EPO coated piroxicam pellets. The SEM monographs of the high coating level pellets (19.9%) is shown in Figure 5.1. It can be seen that after curing for 120 min under a temperature of 50 ^{o}C, the coating materials has formed a uniform and smooth film (Figure 5.1A), wherein the boundaries between the coating

particles no longer exist. Figure 5.1B indicates the cross section of the coated pellets. It can be clearly observed that the uncoated piroxicam pellets were covered by a dense coating film. This proves that the Eudragit® EPO coating film performs a continuous and dense structure. Furthermore, from the SEM monographs, it suggests that this coating material is able to achieve a relatively strong and smooth coating film with the RFB.

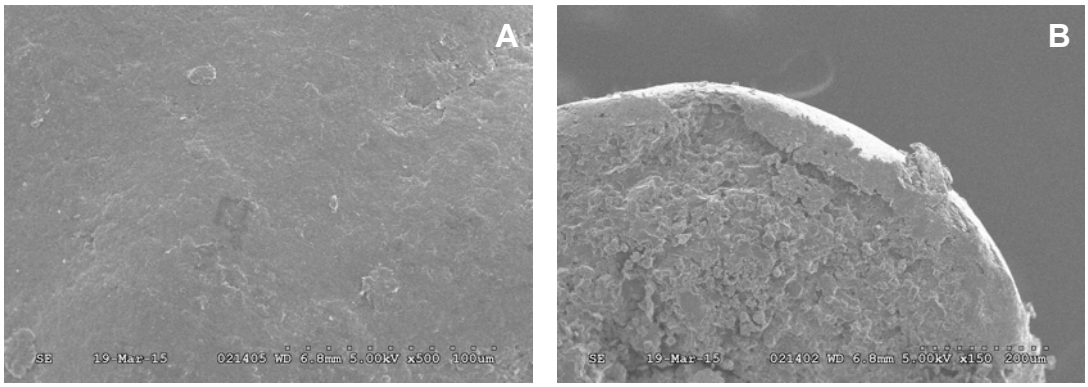

Figure 5.1 SEM micrographs of Eudragit® EPO coated piroxicam pellets curing at 50 °C, 120 min, RFB rotating speed: 20 rpm, coating level of 19.9%:(A) surface, (B) Cross section

The effect of Eudragit® EPO coating level on the drug release profiles is shown in Figure 5.2. The Eudragit® EPO coated piroxicam pellets were processed under a temperature of 50 °C and cured for 120 min. As can be seen from the release profiles (Figure 5.2), both the coated pellets were released up to 90% within 20 min and achieved 100% within 60 min. This indicated that no significant effect was influenced by these two coating levels. The reason for this is that Eudragit® EPO is a water soluble polymer and is able to dissolve in solutions with a pH below 5.5, so the higher coating level may only extend the dissolution of the coating film that is relatively short compared to the release of the drug core[3]. The drug release of the Eudragit® EPO coated pellets is erosion controlled.

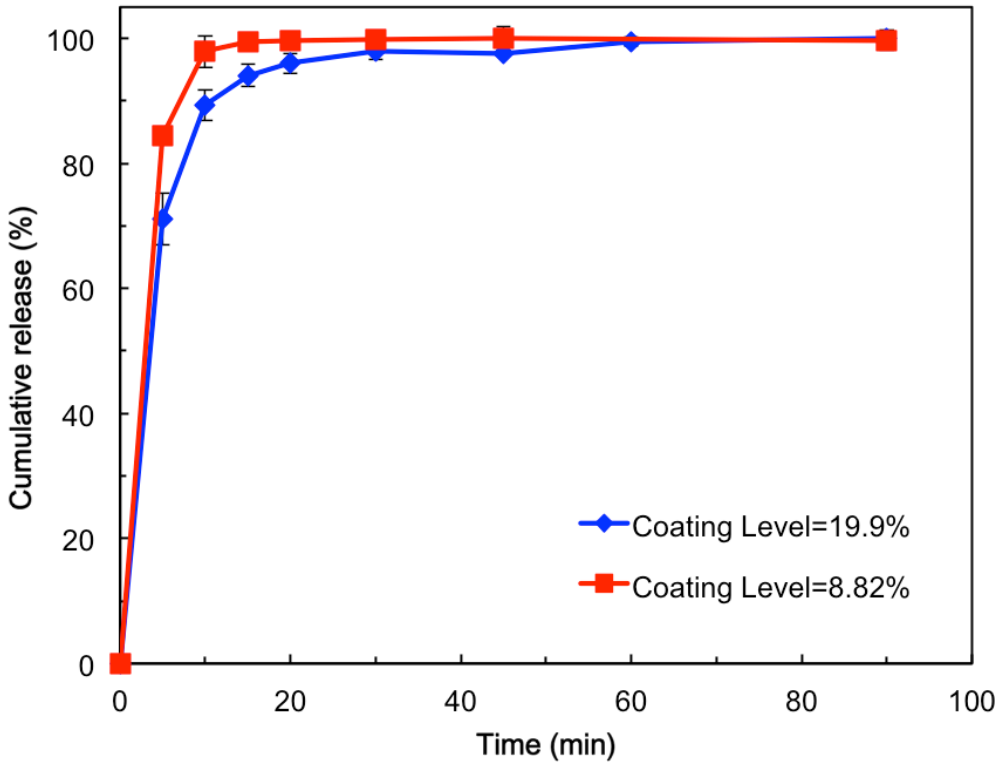

Figure 5.2 The effect of Eudragit® E PO coating level on drug release profiles. (Curing temperature: 50 °C, curing time: 120 min, RFB rotating speed: 20 rpm)

In solvent-based coating methods, the coating level of Eudragit® EPO coated pellets is generally around 20%. Herein, the pellets using RFB with dry powder coating technique can modulate immediate release with the same coating material at a relatively low coating level (8.82%). This improvement not only reduces the usage of coating materials but also reduces the processing time significantly. Also, the coating film achieved by the RFB was smooth, uniform and dense according to the SEM monographs.

5.2. Sustained release coating with Eudragit® RS/RL

5.2.1. Introduction

Sustained release is defined as a system that allows the drug to be released over an extended period of time to achieve prolonged therapeutic effect after oral administration. Eudragit® RL and Eudragit® RS are two commonly used coating materials for sustained release coating. Both two coating materials comprise of ethyl acrylate, methyl methacrylate and a small amount of methacrylic acid ester with quaternary ammonium groups (trimethyl-ammonioethyl methacrylate chloride) that function as salts to assure the permeability of the film.

Previous study done by our research group has proved that dry powder coated piroxicam pellets were able to modify sustained release with the same coating materials by the rotating pan coater[10]. In this section, the RFB was investigated to coat piroxicam pellets with Eudragit® RL and Eudragit® RS to modulate sustained release, and TEC was a suitable liquid plasticizer for these polymers. Two main factors influencing the sustained release profile were studied, the effect of coating level and the ratio of Eudragit® RS to Eudragit® RL. The performance and the appearance of the Eudragit® RS/RL coated piroxicam pellets was studied both qualitatively and quantitatively based on scanning electron microscope (SEM) and in-vitro release testing, respectively.

5.2.2. Effect of coating level

In this section, Eudragit® RS/RL (1:1) was selected to investigate the effect of coating level. The overall composition of the sustained release coating formulations is shown in Table 5.2 wherein the sum of Eudragit® RS and Eudragit® RL was 80.0%. The remaining 20% was additives including talc and colloidal silicon dioxide and a blue dye. The talc and colloidal silicon dioxide served as the anti-adherent agent. The blue dye is an insoluble dye aiming at a better observation of film formation. The section of the mass

proportion of Eudragit® RS and Eudragit® RL (80%) was in accordance with previous study done by our research group, wherein this percentage would not cause agglomeration of the pellets and was high enough to form a strong coating film as well.

Table 5.2 Overall coating fomulation composition of Eudragit® RS and Eudragit® RL polymers

Formulation	Composition (wt%)
Eudragit® RS and Eudragit® RL	80.0
Talc	19.0
Colloidal silicon dioxide	0.5
Blue dye	0.5

In the plasticizer powder coating technique, the plasticizers are functionalized by incorporating themselves between the polymers chains, which increases the free volume and thus the T_g can be decreased dramatically[12-14]. The film formation is achieved by the deformation and viscous flow of the plasticized-coating materials. The scanning electron microscope (SEM) was employed to observe the film formation of the coating materials and the effect of the coating level. Three coating levels were investigated. As shown in Figure 5.3, the surface and cross section of the Eudragit® RS/RL (1:1) coated pellets under different coating levels were observed. Obviously, as the coating level increased, the smoothness of the Eudragit® RS/RL coating film became more even (Figure 5.3A B and C). Specifically, the surface of the lowest coating level (9.23%) coated pellets still exhibited some ‘scaly structure’, which indicated the non-uniformity of the coating film. This was because the amount of coating materials was not enough to form a thick and dense coating film. This phenomenon was improved simply by increasing the coating level, which was illustrated through the coated pellets with coating

levels of 13.13% and 17.88%. The surface of the pellets with the highest coating level (Figure 5.3C) showed the smoothest and most uniform coating film, where the 'scaly structure' no longer appeared and the coating materials were well cured continuously. The cross section SEM micrograph of pellets with the highest coating level (Figure 5.3D) can proved the uniform and dense coating as well. The piroxicam pellet was evenly covered with a constant thickness (50 μm) of coating film. As a result, it can be concluded that using the RFB dry powder coated piroxicam pellets with Eudragit® RS/RL were able to achieve a continuous and uniform coating film. With better film formation was obtained at a higher coating level.

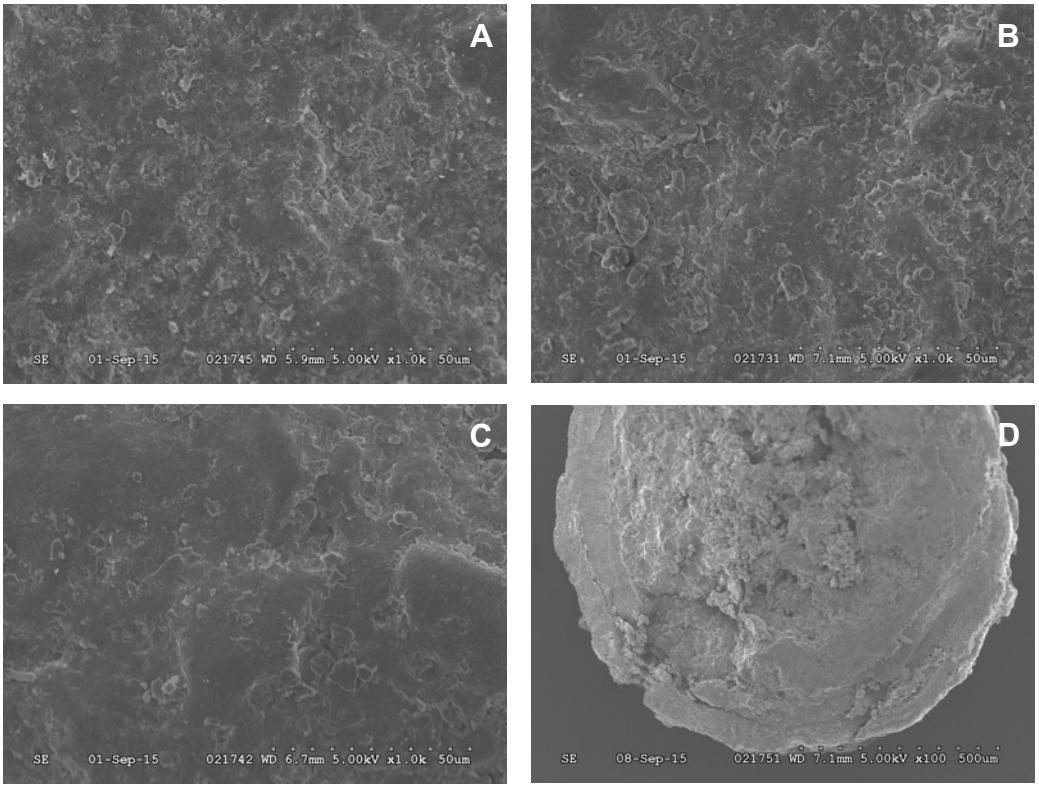

Figure 5.3 SEM micrographs of Eudragit® RS/RL(1:1) coated piroxicam pellets curing at 50 °C, 120 min, RFB rotating speed 20 rpm: (A) Coating level of 9.23%, (B) Coating level of 13.13%, (C) Coating level of 17.88%, (D) Cross section of coating level 17.88% pellets

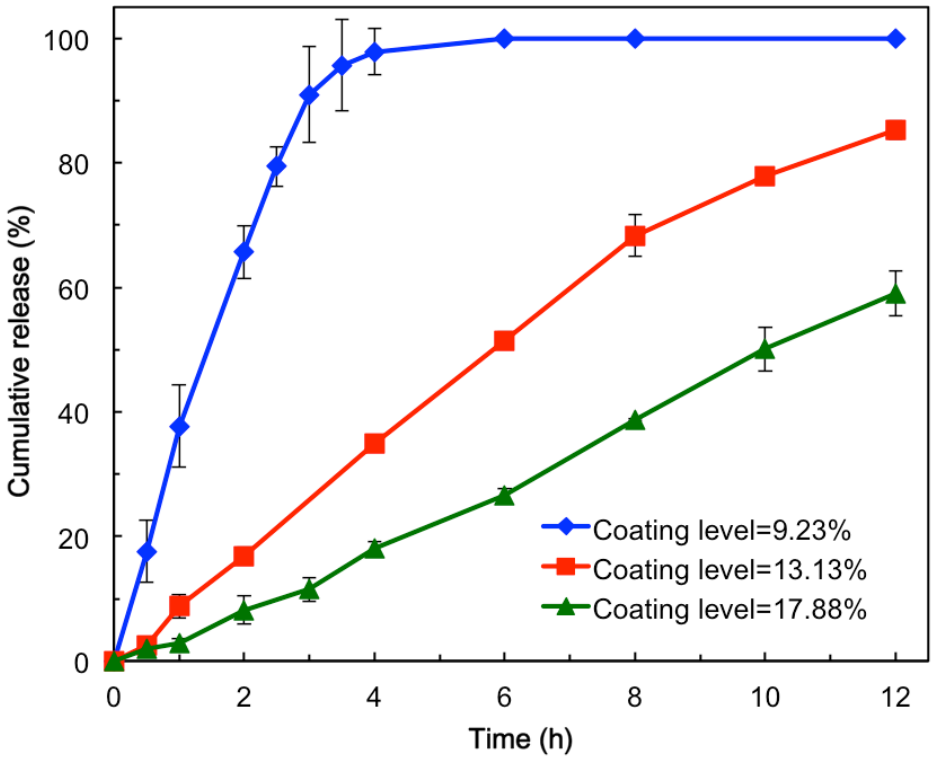

Figure 5.4 The effect of Eudragit® RS/RL coating level on drug release profiles. (Eudragit® RS/RL (1:1), Curing temperature: 50 °C, curing time: 120 min,RFB rotary speed: 20 rpm)

The effect of coating level on drug release profiles is illustrated in Figure 5.4, where in the pellets were coated with Eudragit® RS/RL (1:1) in the RFB at three different coating levels. It is clearly shown from the release profile that the cumulative release of drug decreased as the coating level increased, which corresponded to the performances of the SEM monographs above as well. The coated pellets with the lowest coating level (9.23%) showed the fastest release rate compared to the other two coating levels. It can be seen that 90% of drug released before 3 h and the rest drug continually released to 100% from 3 h to 6 h. In addition, the coated pellets with coating level of 13.13% and 17.88% released to 85% and 59% drug after 12 h, respectively. The release profiles of these two coating levels behaved lineraly, which indicated the constant release rates. Theoretically, in terms of sustained release, the appearance of the cracking films relates to the

mechanical stability of coating films and the hydrostatic pressure[73]. When the pellets contact with the release medium, a hydrostatic pressure will generate in the coated pellets. At the point that the hydrostatic pressure is over the mechanical stability of the coating film, the cracking happens. As a result of this, it is shown that the release profile of the lowest coating level (9.23%) performed a film cracking behavior, where the coating film cannot withstand the hydrostatic pressure generated inside the pellets. After the film cracking, the drug release was no longer controlled by the Eudragit® RS/RL coating film; instead, it was dominated by the diffusion through water. Thus, the release rate was much faster compared to those Eudragit® RS/RL coating film controlled release profiles (coating level of 13.13% and 17.88%). This indicates that for sustained release, pellets with low coating level has a different release mechanism from the higher coating level ones, wherein the former one is erosion control and the latter one is diffusion control.

5.2.3. Effect of ratio between Eudragit® RS and Eudragit® RL

As has been introduced in Chapter 2.3.3, Eudragit® RS and Eudragit® RL have different permeability due to the amount of their quaternary ammonium groups. Since Eudragit® RL has double content of the function groups, it is more permeable. As a result of this, it can be imagined that Eudragit® RL coated pellets perform a relatively high drug release rate compared to Eudragit® RS. Therefore, the adjustment of the ratio between the two polymers would influence the control of release rate to some extent. Three formulations of the Eudragit® RS/RL (1:2, 1:1, 2:1, mass ratio) under two different coating levels were investigated by the RFB with dry powder coating technique to study the effect on sustained release.

Scanning electron microscope (SEM) was employed to observe the surface of the different Eudragit® RS/RL ratio coated pellets with a coating level of 18%. The surface and cross section condition were shown in Figure 5.5. It can be seen that from Figure 5.5A,B and C, after curing for 2 h, both the three coating formulations (Eudragit® RS/RL

1:2, 1:1, 2:1) formed continuous and dense coating films, where the boundaries between particles disappeared and the thickness of the coating film was uniform (around 50 μm). Moreover, it was shown in Figure 5.5D that the boundary between the uncoated piroxicam pellet and the Eudragit® RS/RL coating film was clearly illustrated. It also

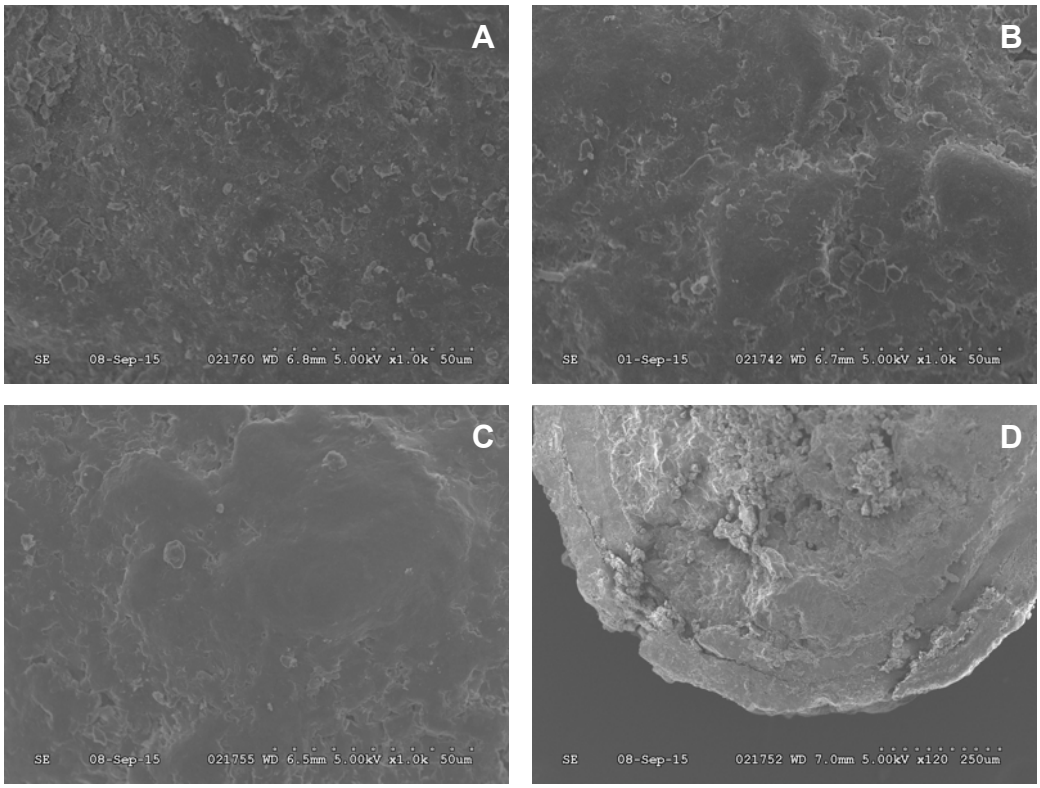

Figure 5.5 SEM micrographs of Eudragit® RS/RL coated piroxicam pellets curing at 50 °C, 120 min, RFB rotary speed: 20 rpm, coating level of 18%: (A) Eudragit® RS/RL(1:2), B) Eudragit® RS/RL(1:1), (C) Eudragit® RS/RL(2:1), (D) Cross section of Eudragit® RS/RL(2:1)

indicated the formation of a strong and dense Eudragit® RS/RL coating film.

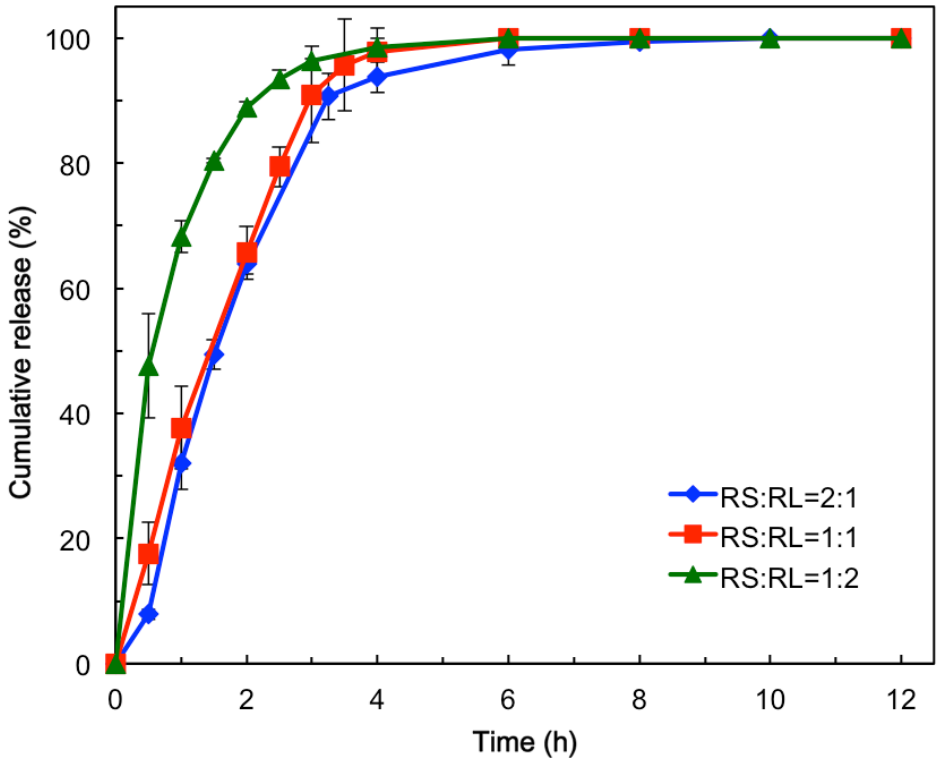

Figure 5.6 The effect of Eudragit® RS and Eudragit® RL ratio on drug release profiles. (Curing temperature: 50 °C, curing time: 120 min, RFB rotary speed: 20 rpm, coating level: 9.0%)

The effect of the polymer ratio (Eudragit® RS/RL) on drug release profiles is shown in Figure 5.6 and Figure 5.7. In Figure 5.6, the dry powder coated piroxicam pellets in RFB with a low coating level (9.0%) demonstrated no obvious effect due to adjusting the polymer ratio. All of the three formulations coated pellets released to 90% within the first 4 h and gradually reached 100% at 10 h. There was a slight tendency between the three release profiles. Pellets coated with Eudragit® RS/RL (1:2) had a faster release rate than the other two formulations, where it only took 2 h to release 90% of drug. Pellets coated with Eudragit® RS/RL (1:1, 2:1) released relatively slower, in which the 1:1 coated pellets released to 90% of the API at 3 h and the 2:1 ones took 3.25 h. Reason for this is that since the pellets coated with Eudragit® RS/RL (1:2) has a higher ratio of Eudragit® RL, the release rate, from previous work that Eudragit® RL has a high permeability and

limited swellability, and was thus faster than the other two formulations with lower Eudragit® RL content. Moreover, the reason of the fast release within a short time (4 h) is the film cracking behavior. As mentioned in the above section, the coating film cannot withstand the hydrostatic pressure generated inside the pellets since the coating level is relatively low. After film cracking, the drug release was no longer controlled by the Eudragit® RS/RL coating film; instead, it was dominated by the diffusion through water. Moreover, the release rates were quite fast at the first 3 h but suddenly reduced to slow rates after 3 h. This was mainly attributed to the relatively low coating level (9.0%). At a low coating level, coating materials attached to the surface of the pellets were not enough to form a strong and dense coating film, which results in weak coalescence between polymer molecules and cracking behavior within a short time.

The effect on drug release profiles of the polymer ratio at a higher coating level was shown in Figure 5.7. It was observed that for the pellets with a coating level of 18.0%, the drug release rate decreased dramatically as the weight ratio of Eudragit® RS increased. This denotes that by adjusting the ratios between the two polymers, the release profiles can be controlled at a wide range. Specifially, the Eudragit® RS/RL (1:2) coated pellets had a cumulative release of 72% after 12h, and the Eudragit® RS/RL (1:1) coated pellets released to 59% of drug after 12h, whereas the Eudragit® RS/RL (2:1) coated pellets only reached 38% of the cumulative release in the same time interval. As mentioned before, this was attributed to the permeability difference of Eudragit® RS and Eudragit® RL, where a higher content of Eudragit® RL performed the fastest release rate and a lower Eudragit® RL content behaved a slowest release rate. Besides, all of the three release profiles of the coated pellets at high coating level (18%) demonstrated proportional lines, which suggested the release of the drug remained at a constant rate and was controlled by the Eudragit® RS/RL coating film. Reason of this was that a higher coating level provided a thicker and more uniform coating film, which had a better control of the release profile. Theoretically, since the coating film was denser compared to the low

coating level one, the mechanical stability was strong enough to sustain the hydrostatic pressure generated in the coated pellets when immersed in the release media, thus the drug release was controlled by the coating film.

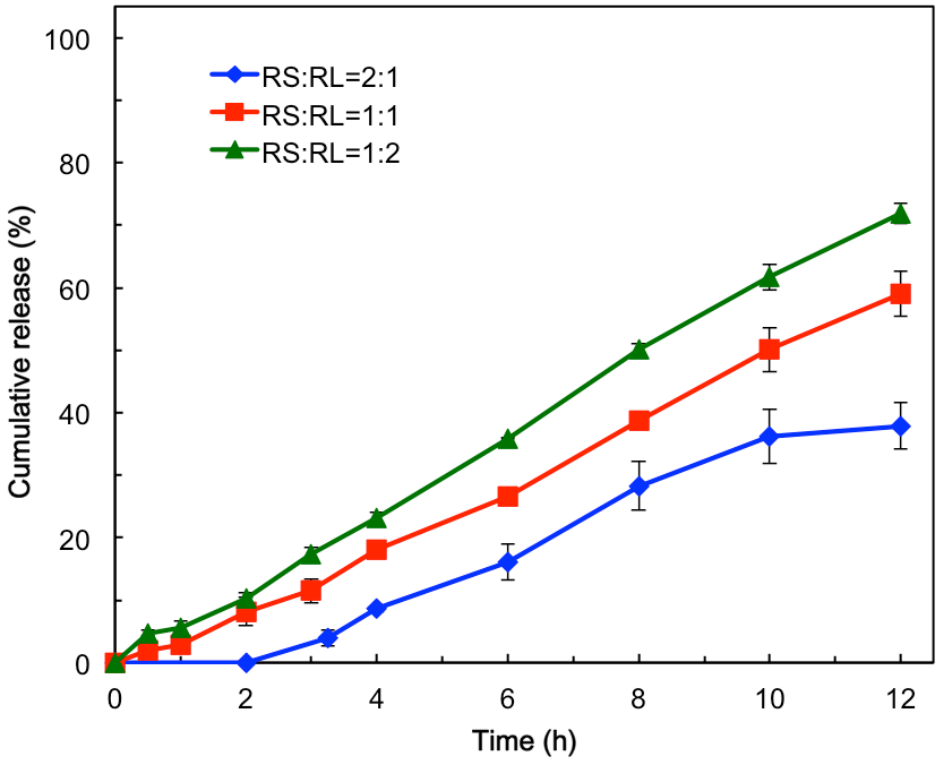

Figure 5.7 The effect of Eudragit® RS and Eudragit® RL ratio on drug release profiles. (Curing temperature: 50 ^{o}C, curing time: 120 min, RFB rotating speed: 20 rpm, coating level: 18.0%)

5.3. Delayed release coating with Acryl-EZE

5.3.1. Introduction

Delayed release refers to the system formulated to release the API at a delayed interval rather than release immediately after oral administration. The coating materials used for delayed release are pH dependent, which means they are acid resistant but, will decompose in solutions with high pH value. Also, delayed release is aimed at preventing the API from irritating the stomach, protecting the degradation of the solid dosage forms under the low pH environment of stomach and targeting the API absorption to a portion of the intestinal tract beyond the stomach. One of common used coating materials to modulate delayed release is Acryl-EZE. It is a full formulation coating material with the effective component Eudragit® L 100-55. Acryl-EZE is degradable when the pH value of the media is above 5.5, and thus it is applied to release the API at the first section of small intestine.

Previous work done by our research group reported that the dry powder coated Acryl-EZE pellets achieved by rotating pan coater were able to modulate delayed release successfully[12]. Therefore, in this section, the RFB was employed for the coating of Acryl-EZE with dry powder coating technique to modulate delayed release, and PEG 400 served as a suitable liquid plasticizer. The effect of coating level was investigated. Notice that the effects of curing time and curing temperature were also studied and will be discussed in Chapter 6.2 and 6.3 (since the curing time and curing temperature also related to the process conditions of the RFB and thus will be reported in Chapter 6). In-vitro release testing and scanning electron microscope (SEM) were employed to study the release profile and appearance of the Acryl-EZE coated pellets.

5.3.2. Effect of coating level

As Acryl-EZE is a full-formulation coating material, blue dye was added into the

formulation for better observation of the film formation (shown in Table 5.3).

Table 5.3 Coating fomulation composition of Acryl-EZE polymers

Formulation	Composition (wt%)
Acryl-EZE	99.5
Blue dye	0.5

The scanning electron microscope (SEM) micrographs were employed to observe the film formation of the Acryl-EZE coated pellets, as shown in Figure 5.8. Compared with the surface of uncoated piroxicam pellets (Figure 5.8A), the Acryl-EZE coated ones (Figure 5.8B) performed a uniform and smooth coating film. The uneven surface of the uncoated pellets no longer existed, which indicated that the piroxicam pellets were fully covered with a dense and continuous Acryl-EZE coating film. Also, the surface uniform smoothness of the high coating level (21.93%) coated pellets denoted the well curing of the Acryl-EZE coating materials. As a result, from the SEM micrographs, the Acryl-EZE dry powder coated pellets were able to achieve a smooth and dense coating film in the RFB.

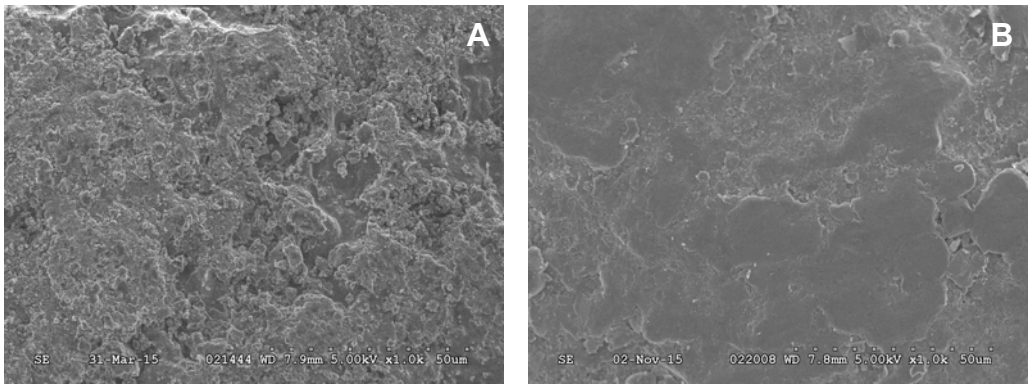

Figure 5.8 SEM micrographs of Acryl-EZE coated piroxicam pellets curing at 50 °C, 120 min, RFB rotating speed 20 rpm: (A) Uncoated piroxicam pellet, (B) Surface of coated pellets with coating level of 21.93%

In terms of enteric coating, the most important standard to balance whether the coating is qualified is the acid resistance test. It is characterized by the cumulative drug release percentage in 0.1N HCl media after the first 2 h. According to the United States Pharmacopoeia (USP) <711>, the standard of delayed release coating is obliged to be less than 10% of the cumulative drug release in the acid media after the first 2 h.

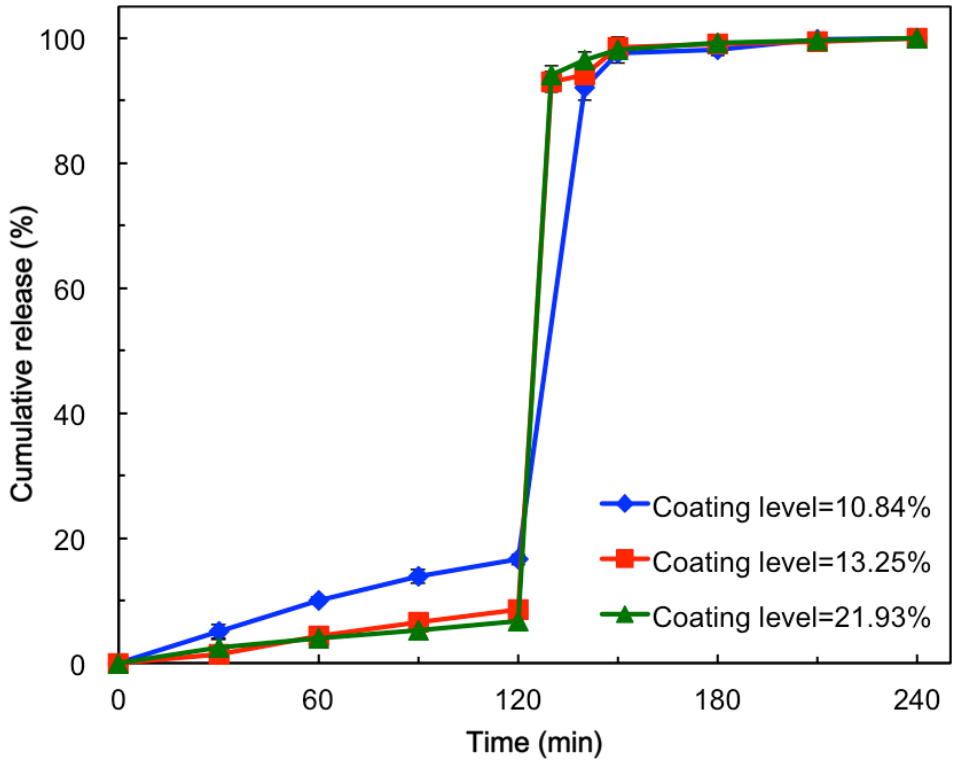

Figure 5.9 The effect of Acryl-EZE coating level on drug release profiles.
(Curing temperature: 50 ^{o}C, curing time: 120 min, RFB rotating speed: 20 rpm)

The effect of Acryl-EZE coating level on drug release profiles was performed in Figure 5.9, where three selected coating levels, from low to high, were investigated. As shown in Figure 5.9, all of the release profiles of the coated pellets showed a 'delayed release', in which little API released within the first 2 h. The lowest coating level (10.84%) performed an acid resistance of 16.6% cumulative release after the first 2 h, and the

pellets with higher coating levels of 13.25% and 21.93% showed 8.5% and 6.6% cumulative release, respectively. Both the coated pellets of three coating levels released immediately after adjusting the release media from pH 1.2 to pH 6.8 through the addition of 0.2 M tribasic sodium phosphate solution. Therefore, the pellets with the coating level of 10.84% was unqualified based on the standard of USP <711>, which released more than 10% after 2 h in pH 1.2 acid media. It showed that the pellets with higher coating levels (13.25% and 21.93%) could meet the pharmaceutical standard. It was obvious that increasing the coating level showed better acid resistance of the coated pellets and gave better release profiles. This is because the amount of the coating materials attached onto the low coating level pellets surface, compared to pellets with higher coating levels, were not enough to form a uniform and continuous coating film. This may lead to weakness of coalescence between polymer molecules during curing procedure and reduction of the coating film intensity, and finally result in the cracking effect of the coating film in the drug release test. Similarly, for high coating level coated pellets, a strong and uniform coating film was obtained, which performed a good control of the delayed release profiles.

Chapter 6
Optimization of Process Conditions

6.1. Introduction

As described in the previous chapter, RFB was successfully applied to the dry powder coating of small pellets with different coating materials (Eudragit® EPO, Eudragit® RS/RL and Acryl-EZE) for immediate release, sustained release and delayed release, respectively. This chapter reported the optimization of processing conditions in RFB. Several operating factors were studied regarding curing time, curing temperature, RFB rotating speed, liquid plasticizer spraying flowrate as well as fluidizing air flowrate. Acryl-EZE was selected as the example coating material to optimize the coating conditions.

According to the United States Pharmacopoeia (USP) <711> standard, the delayed release coated pellets have to be less than 10% of the cumulative drug release in the acid media after the first 2 h in the in-vitro drug release tests. For the Acryl-EZE coated piroxicam pellets, the process conditions can be optimized based on this standard. This indicates that the coated pellets with a cumulative release less than 10% after the first 2 h can be regarded as qualified, while those with a cumulative release more than 10% after the first 2 h did not achieve standard request. Both in-vitro drug release testing and the scanning electron microscope (SEM) were employed to study the effects of the process conditions.

6.2. Effect of curing time

In dry powder coating process where most of the coating polymers belong to thermoplastic polymers, film formation occurs once the deformation and viscous flow of the coating polymer particles happen when the curing temperature is above the glass transition temperature (T_g) of the coating polymers[65]. The viscosity of the coating

materials decreases as the temperature increases, resulting in the deformation of particles. The coalescence of the coating particles requires enough time to form a coating film. Therefore, both the curing time as well as the curing temperature results in significant influences on the film formation of the coating materials.

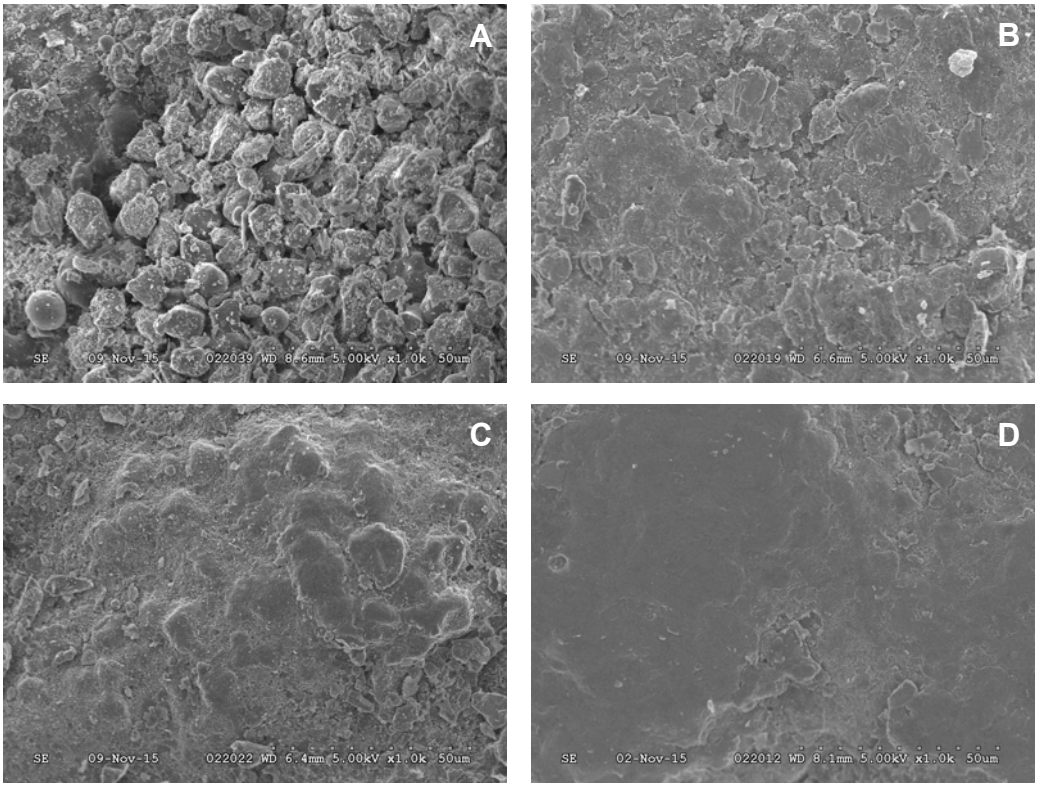

Figure 6.1 SEM micrographs of Acryl-EZE coated piroxicam pellets curing at 50 ^{o}C, RFB rotating speed 20 rpm: (A) 0 h, (B) 1 h, (C) 1.5 h, (D) 2 h

First, the effect of curing time was shown with the three intervals **(1 h, 1.5 h, 2 h)** at three temperatures, 30 ^{o}C, 40 ^{o}C and 50 ^{o}C**.** SEM was employed to investigate the effect of curing time on film formation. As shown in Figure 6.1, the Acryl-EZE coated pellets curing under 50 ^{o}C illustrated that before the curing started, the individual coating particles were clearly seen and the boundaries between the particles were distinctly observed, indicating that the coating particles were non-fused and the curing did not start immediately after the powder deposition (Figure 6.1A). After 1 h of curing, the particles began to coalesce with each other and form a smooth film, while the surface of the coated

pellets were still characterized by some voids and non-fused coating particles, and the boundaries between the particles were still visible (Figure 6.1B). As the curing time increased to 1.5 h (Figure 6.1C), most of the coating particles coalesced with no visible particle boundaries observed, denoting that a dense coating film was formed. After another half hour of curing (total curing for 2 h) (Figure 6.1D), the entire pellet was covered with a smooth and continuous coating film and the particles were no longer observed.

As mentioned above, the addition of the liquid plasticizer can decrease the T_g significantly, and when the processing temperature is above the T_g, the film formation can be achieved based on the deformation and viscous flow of the coating materials. The film formation requires a period of time to accomplish; as a consequence, increasing the curing time can help to strengthen the acid resistance of the coated pellets effectively when the curing temperature is closed to/above the T_g of the coating polymers.

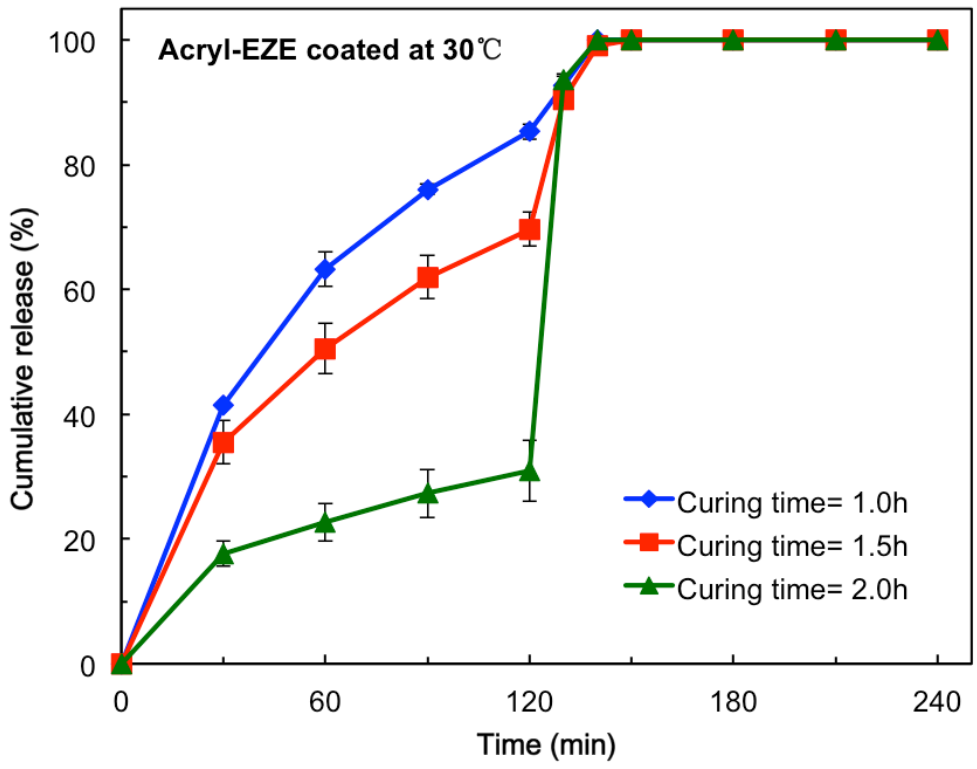

Figure 6.2 The effect of curing time on drug release profiles. (Coating material: Acryl-EZE, Curing temperature: 30 °C, RFB rotating speed: 20 rpm)

The effect of curing time on drug release profiles were studied under three temperatures. From the pellets coated under 30 ^{o}C (Figure 6.2), it is shown that the drug release profiles of the pellets with 1 h, 1.5 h and 2 h curing time performed 85 %, 70 % and 31 % cumulative release after the first 2 h in 0.1 N HCl pH 1.2 acid media. Obviously, this indicates the acid resistance of the coated pellets increased dramatically when the curing time was extended from 1 h to 2 h. The reason for this is that the film formation of the longer curing time pellets allowed better coalescence compared to the short time cured pellets, and thus the longer curing time coated pellets exhibited a lower cumulative drug release after the first 2 h. However, under the temperature of 30 ^{o}C, all coated pellets with three curing times were unqualified due to the high cumulative release that were above 10%, based on the USP <711> standard. This is because the curing temperature of this condition was 30 ^{o}C, which didn't reach the T_g of the coating material. Under this condition, the coating films of the pellets were weak and the molecules of the coating material were not fully coalesced with each other, and thus happened to crack when contacted with the release media and result in the unqualified drug release profiles.

Figure 6.3 shows the effect of curing time on drug release profiles at the temperature of 40 ^{o}C**.** Similarly, the acid resistance of the coated pellets increased as the curing time adjusting from 1 h to 2 h. The cumulative release of the coated pellets after the first 2 h with the curing time of 1 h, 1.5 h and 2 h were 28 %, 24 % and 19%, respectively. However, both the pellets under this condition were not qualified according to the USP <711> standard.

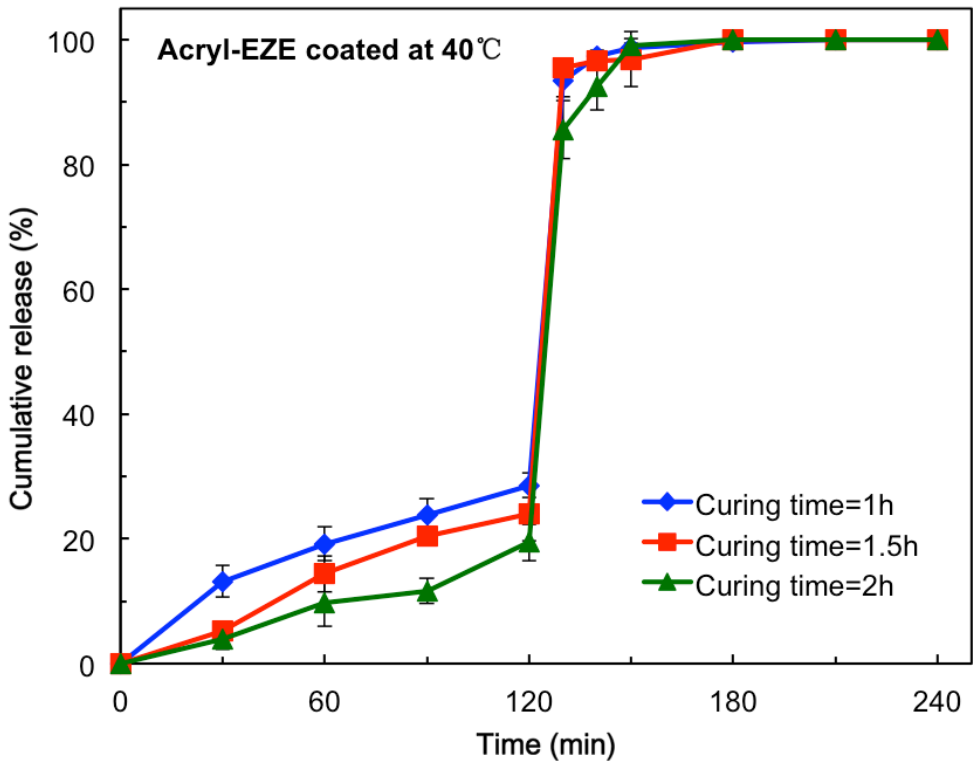

Figure 6.3 The effect of curing time on drug release profiles. (Coating material: Acryl-EZE, Curing temperature: 40 °C, RFB rotating speed: 20 rpm)

The effect of the curing time on drug release profiles of the Acryl-EZE coated pellets under 50 °C were shown in Figure 6.4. As can be seen, all of the pellets coated with the three curing time performed a cumulative release less than 20%. The cumulative release of the coated pellets after the first 2 h with the curing times of 1 h, 1.5 h and 2 h were 15 %, 9 % and 8%, respectively. According to the USP <711> standard, the pellets with curing time of 1.5 h and 2 h were qualified. Clearly, increasing the curing temperature can give a better performance of the acid resistance under this condition. As explained above, this is because the curing temperature of 50 °C was very close to the T_g of the plasticized coating polymer, which helped the better film formation. Furthermore, the pellets coated under these conditions performed very ideal delayed release profiles. The Acryl-EZE coating film can control the release of the API accurately and further proved the complete film formation of the coating materials in the RFB.

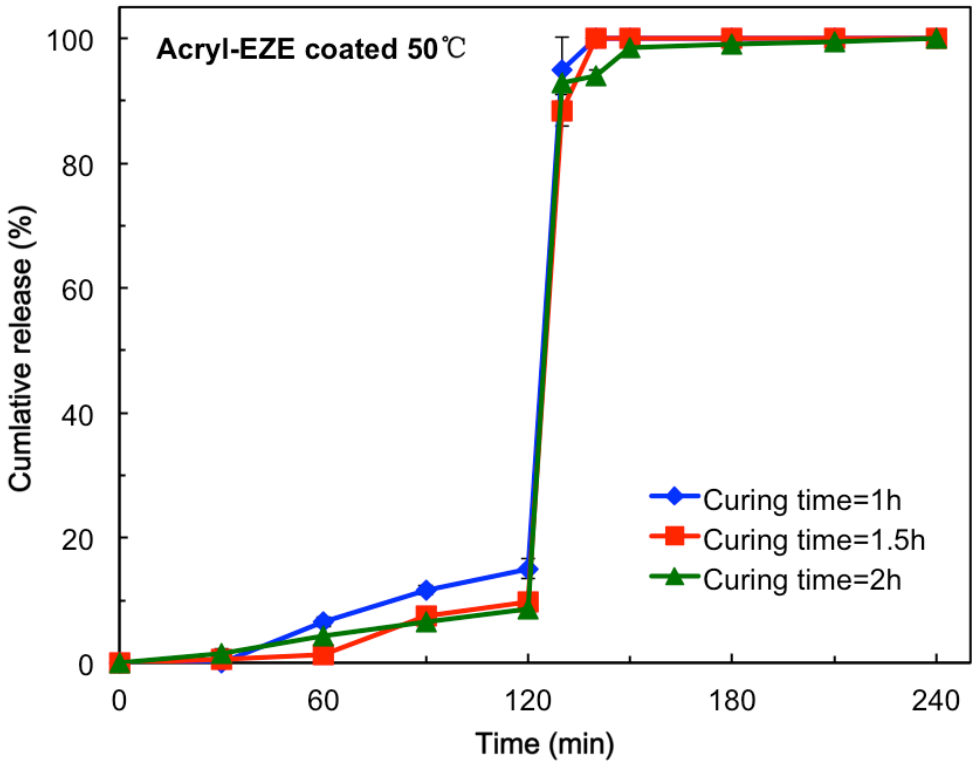

Figure 6.4 The effect of curing time on drug release profiles. (Coating material: Acryl-EZE, Curing temperature: 50 °C, RFB rotating speed: 20 rpm)

6.3. Effect of curing temperature

As mentioned above, in the coating process using the RFB with the plasticizer powder coating technique, the deformation and viscous flow of the coating polymer particles generates the film formation process when the curing temperature is close to/above the glass transition temperature (T_g) of the coating polymer[65]. Therefore, apart from the curing time, the curing temperature is another key factor that has significant influence on the film formation of the coating materials. The effect of the curing temperature was investigated for pellets coated at the temperature of 30 °C, 40 °C, and 50 °C curing for 2 h.

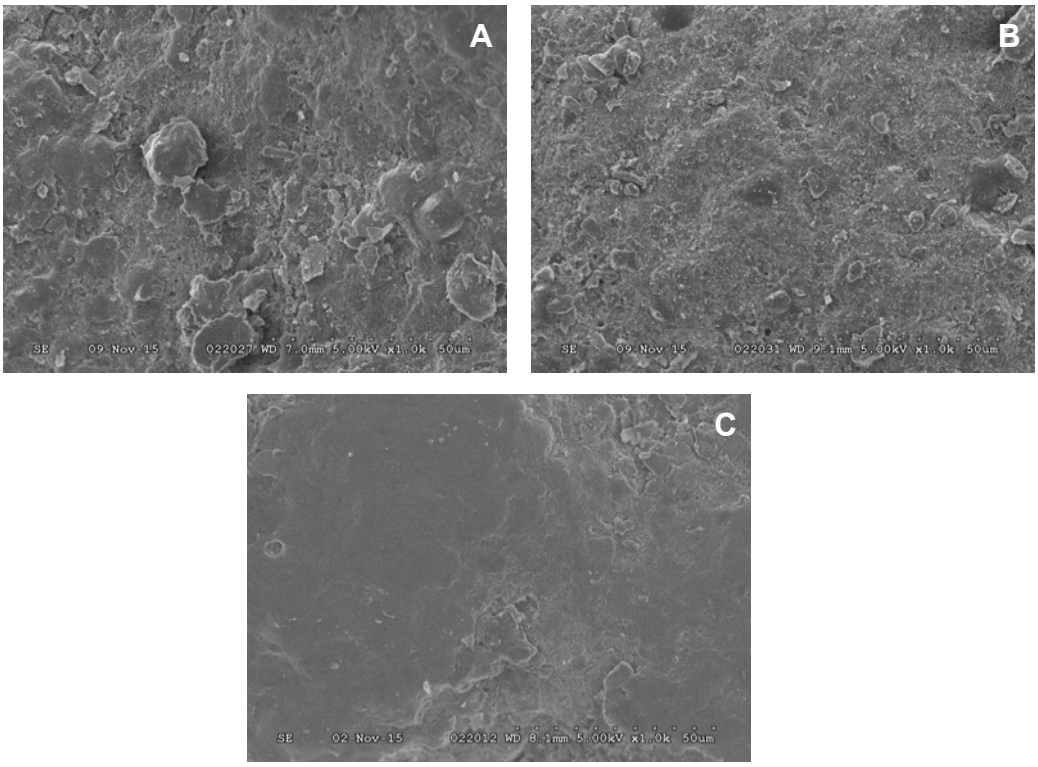

Figure 6.5 SEM micrographs of Acryl-EZE coated piroxicam pellets curing for 2 h, RFB rotating speed 20 rpm: (A) 30 ^{o}C, (B) 40 ^{o}C, (C) 50 ^{o}C

The effect of curing temperature on film formation was investigated using SEM, as shown in Figure 6.5. Obviously, both the SEM micrographs of the coated pellets curing at 30 ^{o}C and 40 ^{o}C exhibited an incomplete coating film, where the coating particles were still visible and a small portion of the particles were non-fused (Figure 6.5A and Figure 6.5B). When the curing temperature was increased to 50 ^{o}C that is closer to the T_g of the coating polymer, a uniform and continuous coating film was obtained (Figure 6.5C). Under the temperature of 50 ^{o}C, the coating particles were fused completely and coalesced with each other. There were no individual particles observed at this temperature. Compared to the coated pellets cured under 30 ^{o}C and 40 ^{o}C, the 50 ^{o}C one showed the best film formation. As mentioned above, the viscous flow and deformation starts when the temperature is close to/above the T_g of the coating materials, as a consequence, the best film formation can only be achieved when the curing temperature reaches the T_g of the coating materials.

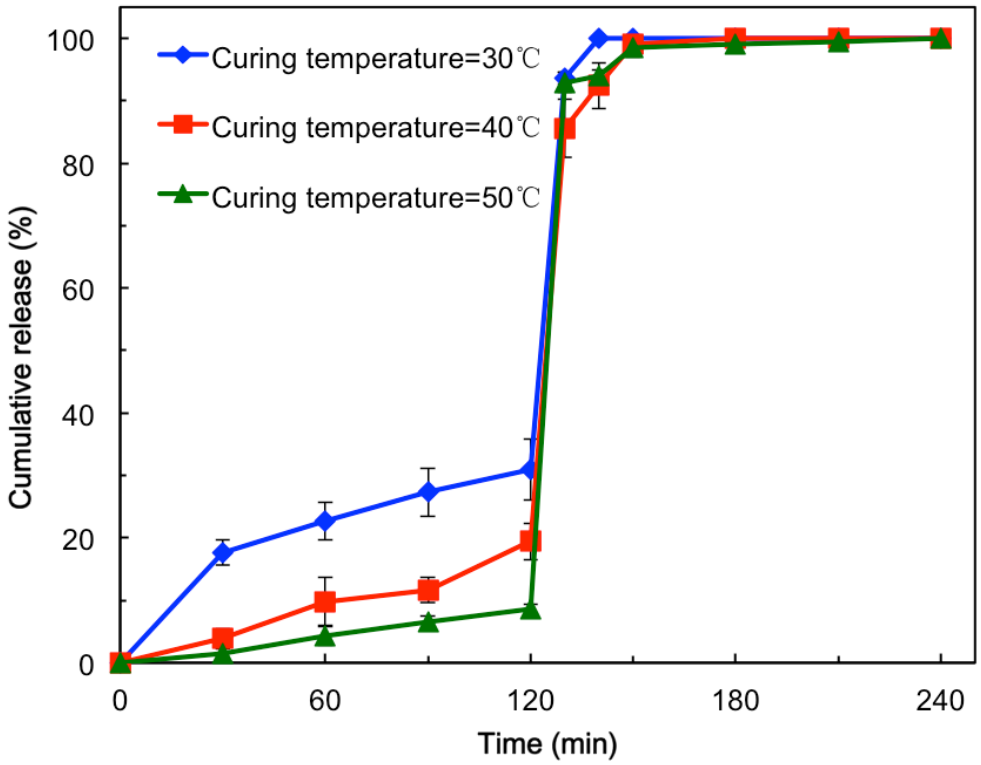

Figure 6.6 The effect of curing temperature on drug release profiles.
(Coating material: Acryl-EZE, Curing time: 2 h, RFB rotating speed: 20 rpm)

The effect of the curing temperature on drug release of the coated pellets is shown in Figure 6.6. Similar to the above results shown by the SEM micrographs, the acid resistance of the coated pellets was improved as the curing temperatures increased from 30 ^{o}C to 50 ^{o}C. Specifically, the cumulative release of the coated pellets after the first 2 h was 30 %, 19 % and 8 %, which correspond to the curing temperature of 30 ^{o}C, 40 ^{o}C and 50 ^{o}C, respectively. According to the USP <711> standard, only the pellets with the curing temperature of 50 ^{o}C were qualified because its cumulative release were under 10% during the first 2 h in 0.1N HCl solution. The reason for this is that only when the curing temperature is closed to or above the T_g of the coating polymer, the deformation and viscous flow of the coating particles could happen. And for the pellets cured at 30 ^{o}C and 40 ^{o}C, the curing temperatures were far away from the T_g, which resulted in the uncompleted film formation and unqualified acid resistance performance.

6.4. Effect of the RFB rotating speed

As described in Chapter 4, the RFB is equipped with a unique structure. It contains a rotatable cylindrical tank that consists of the inner layer and the outside layer, wherein the inner layer is covered with porous material (mesh) and the outer layer is made of acrylic. There are six chambers located between these two layers, and three of them serve as the inlets and outlets of the fluidizing air alternately when the cylindrical tank is rotating during the process. Adjusting the rotating speed of the RFB during the coating process may affect the inlet of the fluidizing air, the centrifugal force of the loaded pellets and the adhesion force between the coating materials and the pellets. All of these may affect the film formation of the coating process. Therefore, the control of the rotating speed has become one of the major factors that may have influence on the coating process.

In this section, three rotating speed of the RFB were selected, including a relatively low speed 6 rpm, a medium speed 20 rpm and a relatively high speed 70 rpm. In fact, the RFB had a limitation of the rotating speed, which ranged from 6 rpm to 75 rpm. Moreover, when the rotating speed was above 70 rpm, a short circuit would happen. This means that the pellets would attach to the wall of the cylindrical tank due to the large centrifugal force generated from the fast rotating speed. The in-vitro drug release test was employed to study the effect of the RFB rotating speed.

The effect of the RFB rotating speed was illustrated by the drug release profiles of the Acryl-EZE coated pellets, as shown in Figure 6.7. It is obviously that the drug release profile of the coated pellets with a rotating speed of 20 rpm exhibited the lowest cumulative release (8%) after the first 2 h in the 0.1 N HCl media. The pellets with a high rotating speed (70 rpm) showed a slightly higher cumulative release (13%) after the first 2 h. Compared to the two higher rotating speeds, the pellets with a rotating speed of 6 rpm had the highest cumulative release value (29%). According to the USP <711> drug

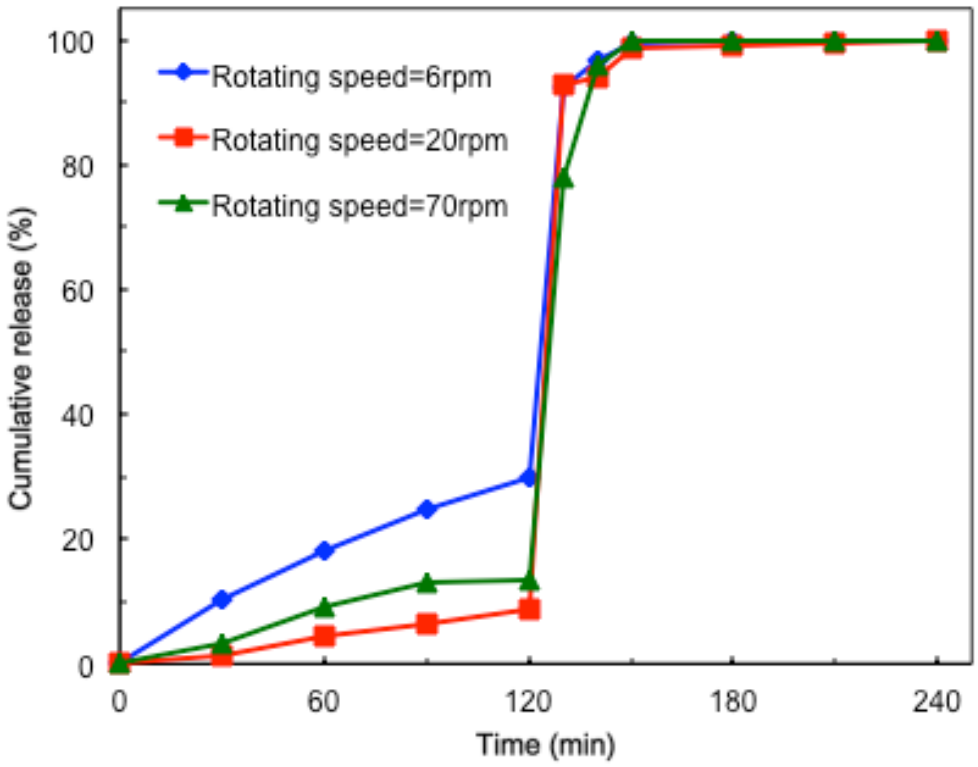

Figure 6.7 The effect of RFB rotating speed on drug release profiles.
(Coating material: Acryl-EZE, Curing temperature: 50 °C,Curing time: 2 h,)

release standard of delayed release, only the 20 rpm one was qualified, and the pellets with 70 rpm rotating speed was slightly higher than the standard. This is because under the low rotating speed (6 rpm), the relatively slow movement of the pellets was not beneficial to the formation of a uniform and smooth coating film. The coating materials may attach to each other before deposit on the surface of the pellets and the coating efficiency decreased. A relatively high rotating speed may generate strong centrifugal force of the pellets and the coating particles, and also lead to the strong tumbling of the pellets. This will result in the attachment of both the pellets and the coating particles on the wall. Moreover, as the adhesion of the coating particles may block the pores of the porous mesh, it could be difficult for the moisture to exit which may lead to the sticky coating film and bad performance on the drug release profiles.

As a consequence, the rotating speed of the RFB should be maintained at an appropriate range (around 20 rpm) where the pellets in the RFB are coated under moderate conditions.

6.5. Plasticizer spraying flowrate

As mentioned in Chapter 2.3.5, in plasticizer powder coating technique, the plasticizers addition can help to solve the problem of the brittle coating film generated from pure coating polymers. In the coating process in the RFB, plasticizers are functionalized by incorporating themselves between the polymers chains and increase the free volume, thus the T_g of the coating materials can be decreased dramatically[12-14]. Moreover, plasticizers also function as increasing the capillary force between the coating polymers and the surface of the pellets, which enhance the powder adhesion on the pellet surface and eventually increase the efficiency of coating process[12-14]. A suitable selection of a plasticizer and a accurate addition amount thus become two critical points. Since the suitable plasticizer (PEG 400) for Acryl-EZE has already been investigated by our research group, the appropriate amount of the liquid plasticizer in the RFB coating process requires further investigation.

The plasticizer addition amount is based on the spray time and flowrate. The spray time has to be matched with the coating material feed amount and plasticizer flowrate, and thus the latter factor is a key point that decides the success of the coating process in the RFB. This is because firstly, small spraying flowrate leads to a poor powder adhesion effect and further film formation is uncompleted. It will produce a brittle, discontinuous coating film and fails in the in-vitro drug release test. In contrast, large flowrate means excessive amount of liquid plasticizers addition immediately and may lead to a sticky problem. As a result, it is of great importance to find an appropriate spraying flowrate that can generate a uniform and strong coating film as well as avoid the sticking problem.

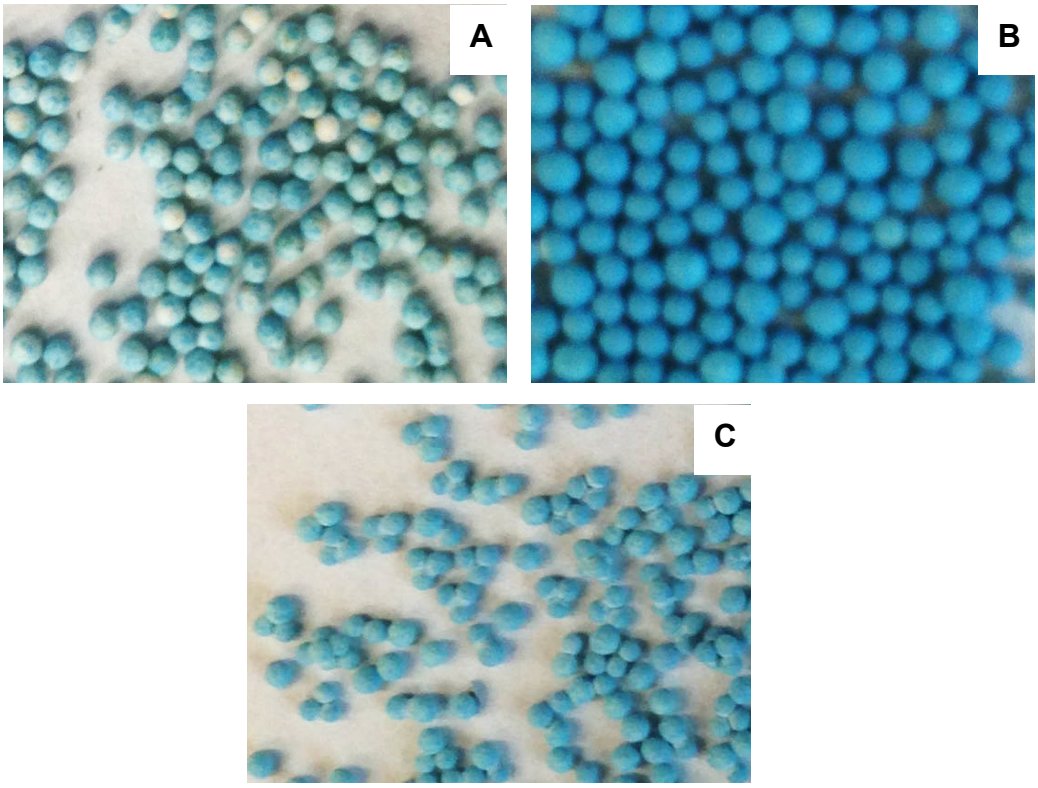

Figure 6.8 Photos of Acryl-EZE coated piroxicam pellets curing for 2 h, 50 ^{o}C, RFB rotating speed 20 rpm: (A) 0.15 g/min, (B) 0.25 g/min, (C) 1.0 g/min

Acryl-EZE was selected as the coating material and PEG 400 was a suitable liquid plasticizer of this polymer as mentioned before. The loading of the piroxicam pellets was 40 g/batch. As shown in Figure 6.8, three spraying flowrates of the liquid plasticizer were selected, including a relatively low one 0.15 g/min, a medium one 0.25 g/min and a relatively high one 1 g/min (spraying time was 30-40 s every time before the coating material feeding each time). Obviously, the pellets coated with a spraying flowrate of 0.15 g/min showed a non-uniform coating film, where the color of the coated pellets was not uniform, some were almost white while others were blue (Figure 6.8A). The coated pellets with a medium spraying flowrates (0.25 g/min) exhibited a relatively uniform appearance of the coating film (Figure 6.8,B). The coated pellets with the relatively high plasticizer spraying flowrate (1 g/min) had the deepest blue color compared to the previous two (Figure 6.8,C). Also, it can be clearly seen that some pellets were attached

to each other and generated ‘twins’, which indicated the sticky problem of the coating film due to the excessive amount of the liquid plasticizer.

Moreover, the in-vitro drug release test of the Acryl-EZE coated pellets at the plasticizer spraying rates of 0.15 g/min and 1 g/min were failed. This is because the low spraying flowrate leads to a small amount of plasticizer on the pellets surface thus further decrease poor powder deposition effect, and thus the coating film was brittle and thin. And the high spraying flowrate leads to the ‘twins’ effect, which may result in the break that appears at the edge between the ‘twins’ when immersed into the drug release media.

From the above results, the most suitable spraying rate of the liquid plasticizer in the RFB dry powder coating process is around 0.25 g/min. At this spraying flowrate, the coating film performed continuous, smooth and dense appearance and the drug release test in Chapter 5.3 were qualified. Moreover for the other two kinds of coating materials (Eudragit® EPO, Eudragit® RS/RL), this was also the appropriate plasticizer spraying rate and the drug release profiles showed good performance to modulate immediate release, and sustained release as well.

6.6. Fluidizing air flowrate

As described in Chapter 4.1.1, the fluidizing air is introduced into the RFB during processing. It not only helps the mixing of the coated pellets and the coating materials, but also works as the temperature controller in the RFB coating system. Thus, the fluidizing air is an essential part of the RFB coating system. Specifically, the flowrate of the fluidizing air introduced in the cylindrical tank is important during the whole process, which means that it has to be controlled at an appropriate flowrate, neither too small nor too large.

During the experiment, it has been found that a small flowrate may lead to long preheating time as well as poor control of the temperature in the RFB, and the pellets tended to be sticky since the small fluidizing air was not sufficient to 'separate' the 'twins'. In contrast, a large flowrate may blow away the coating materials before they deposited on the surface of the pellets and failed to form a strong coating film. It also resulted in a thin coating film and a low coating efficiency of the coating process. The following equation can be employed to calculate the actual flowrate of the inlet fluidizing air of the RFB, where the subscript 'actual' refers to the actual operating conditions, and the subscript 'reading' refers to the value read from the flowmeter and pressure gage.

$$Q_{actual} = Q_{reading} \sqrt{\frac{P_{reading} T_{actual}}{P_{actual} T_{reading}}}$$

From the experiment, the actual flowrate (Q_{actual} L/min) of the inlet fluidizing air was around 35 L/min, which was the most appropriate flowrate employed during the coating process.

Chapter 7
Comparison of Rotary Fluidized Bed, Rotating Pan Coater and Traditional Fluidized Bed

7.1. Introduction

In this chapter, the performance of RFB is compared with two typical pharmaceutical coating apparatus, a rotating pan coater and a traditional fluidized bed (top-spray. The dry powder coating technique was employed to investigate the comparison among the three. The comparison was examined in the following two aspects, process conditions and coating results.

7.2. Process conditions

Acryl-EZE and PEG 400 were selected as the coating material and liquid plasticizer to investigate the comparison of process conditions between the RFB, a rotating pan coater and a traditional fluidized bed. The process conditions include pellets loading amount, coating materials feeding amount, plasticizer flowrate, curing temperature, curing time, fluidizing air flowrate, ideal coating level, coating level and coating efficiency, as shown in Table 7.1. The equations to calculate the target coating level, coating level and coating efficiency are as follows:

$$\text{Ideal coating level (\%)} = \frac{\text{coating materials feeding amount}}{\text{weight of uncoated pellets}} * 100\%$$

$$\text{Coating level (\%)} = \frac{\text{weight of coated pellets-weight of uncoated pellets}}{\text{weight of uncoated pellets}} * 100\%$$

$$\text{Coating efficiency (\%)} = \frac{\text{coating level}}{\text{ideal coating level}} * 100\%$$

Table 7.1 Comparison of process condition

	Rotary fluidized bed	Rotating pan coater	Traditional fluidized bed
Pellets loading amount (g)	40	70	70
Coating materials feeding amount (g)	6.5	12	12
Plasticizer flowrate (g/min)	0.25	0.88	1
Curing time (h)	2	2	2
Curing temperature (^{o}C)	50	50	40
Fluidizing air flowrate (L/min)	35	-	155
Ideal coating level (%)	16.3	16.7	16.7
Coating level (%)	9	11	6
Coating efficiency (%)	55	66	36

It was shown that the RFB has the smallest pellets loading amount (40g). In the rotating pan coater and traditional fluidized bed, the loading amount is 70g. Coating material feeding amount and plasticizer flowrate depended on the powder deposition condition during the coating process and the pellets loading amount. In addition, the curing temperature of traditional fluidized bed (40 ^{o}C) was lower than the other two (50 ^{o}C), and this is because the large fluidizing air (155 L/min) introduced in the tradition fluidized bed limits its heating ability and accurate control of the temperature. Moreover, the coating efficiency of the pellets coated in the three coating systems indicates the deposition amount of coating materials on the pellets surface, which further influenced the film formation. Specifically, when the ideal coating levels were the same and the

pellets were coated under similar conditions among the three apparatus, the rotating pan coater had the largest coating efficiency (66%), the RFB ranked in the middle (55%) and the traditional fluidized bed had the smallest coating efficiency (36%). This was mainly related to the flowrate of the fluidizing air in the systems. Since there was no fluidizing air in the rotating pan coater system, the coating materials stayed in the rotating pan coater and continuously attached to the pellets, therefore it had the highest coating efficiency. While for the RFB and traditional fluidized bed, the introduced fluidizing air may have a chance to blow away the coating materials that already attached or not deposited on the pellets surface, which may result in a less amount of powder deposition on the pellets and thus lead to a lower coating efficiency. Since the traditional fluidized bed had a larger flowrate of fluidizing air, the relating pellets exhibited the lowest coating efficiency. This also indicates the worst usage of the feeding coating materials.

The energy consumption can be analyzed in a macroscopic view. During the coating process in the three systems, the usage of the fluidizing air and the heating system consumed the most energy compared to the rotation power. Since the RFB and the traditional fluidized bed both required fluidizing air to fluidize the pellets and maintain the temperature of the system while the rotating pan coater had no fluidizing air, it can be concluded that the rotating pan coater had the least energy consumption, and the RFB ranks the second, and finally the traditional fluidized bed since it required the largest amount of fluidizing air during the process.

As a result, in terms of the process conditions, the RFB and rotating pan coater are more suitable for the coating of pellets with dry powder coating technique in contrast to the traditional fluidized bed. The RFB has a smaller loading amount compared to the other two systems; however, enlarging the scale of the RFB can improve the handling ability. And the coating efficiency of RFB is not very high, but this can be improved by the addition of a recycling part that can collect the coating materials blown away by the

fluidizing air. The addition of recycling part can also improve the powder deposition on the pellets surface and thus increases the coating efficiency. In addition, the rotating pan coater performs a relatively large loading amount and a high coating efficiency, which indicates that it is suitable for coating of small pellets. However, the traditional fluidized bed showed a non-ideal temperature control of the curing temperature and a really low coating efficiency compared to the other two. Therefore, it does not have accurate temperature control ability and may require longer time to achieve the same coating level coated pellets than the RFB and the rotating pan coater.

7.3. Results of coating

In this section, the coating performance of RFB is compared with the rotating pan coater and the traditional fluidized bed regarding the coating of 0.9-1.1mm piroxicam pellets and 0.1-0.3 mm micronized microcrystalline cellulose (MCC) pellets. Scanning electron microscope (SEM) was employed to observe the surface of the coated MCC pellets.

7.3.1. Coating of piroxicam pellets

The piroxicam pellets were coated in the RFB, the rotating pan coater and the traditional fluidized bed followed with the process conditions shown in Table 7.1. The coating material was Acryl-EZE and PEG 400 was the plasticizer.

The SEM micrographs of the coated pellets were exhibited in Figure 7.1, which indicated the film formation in the three systems. It can be seen that the pellets coated in the RFB and the rotating pan coater (Figure 7.1A and Figure 7.1B) showed a quite smooth and uniform coating film. The coating particles were fused to form a complete and continuous film with no boundaries of the particles observed. Compared to the above two coating systems, the pellets coated in the traditional fluidized bed (Figure 7.1C) did not show a smooth coating film after curing for 2 h. The surface of the coated pellets was still characterized by some voids and the individual particles existed with their boundaries

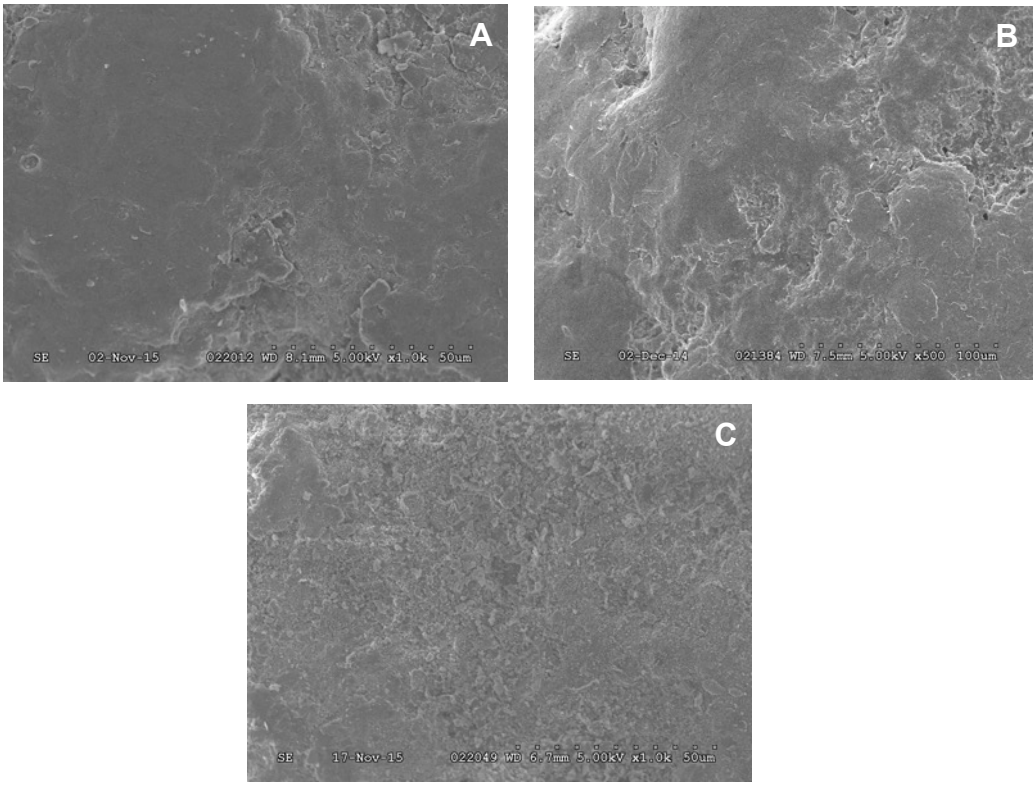

Figure 7.1 SEM micrographs of Acryl-EZE coated piroxicam pellets curing for 2 h:
(A) RFB, (B) Rotating pan coater, (C) Traditional fluidized bed

visible. Reason of this is that according to Table 7.1, the coating level and coating efficacy of the traditional fluidized bed coated pellets was relatively low. The deposition amount of the coating materials was relatively less and the thickness of the coating film was not enough to cover the pellets and form a uniform and continuous coating film. Also, since the fluidizing air introduced in the traditional fluidized bed had a large flowrate, the strong fluidizing air may have a chance to damage the surface of the pellets and this also caused the non-ideal film formation during the curing process. In contrast, the fluidizing air in the RFB was quite small and mild that would not affect the film formation, and the rotating pan coater had no fluidizing air, thus the surfaces of the pellets coated with these two coating systems performed a more uniform and smoother coating film.

Based on the results above, the RFB presented comparable film formation quality with the rotating pan coater while being superior to the traditional fluidized bed.

7.3.2. Coating of micronized microcrystalline cellulose (MCC) pellets

Today, the application of the coating of small solid dosage forms with a micronized size has become one of the popular research projects since it is very widely applied in pharmaceutical industry. For instance, some research groups are working on coating micronized pellets coating that are encapsulated in the capsule. This can help to control the action site of the API more accurately. However, since the micronized pellets have a large specific surface area and tend to agglomerate easily, the coating process is very difficult to achieve.

In this section, the three coating apparatus were attempted to coat the micronized MCC pellets (D=0.1-0.3mm) using dry powder coating technique. Compared to the piroxicam pellets whose size is 0.9-1.1mm, the tiny MCC pellets not only have a small size but also show a relatively light weight, which makes its behavior more like powders. The tiny MCC pellets are equipped with a really high specific surface area. The coating of them becomes more difficult since they are easy to get sticky and need much more coating material feeding times to avoid the sticky effect as well as longer curing time to achieve a uniform coating film compared to the larger pellets.

During the experiment, it was found that compared to the RFB and the traditional fluidized bed, the rotating pan coater has an open system, which means that the coating pan is not covered with a lid during the coating process. The tiny MCC pellets were easy to be blown away by the air generated from the plasticizer-spraying nozzle, and the pellets also dropped out all the time due to the rotation of the coating pan. These observation suggested that the rotating pan coater was not suitable for the coating of tiny pellets not only owing to the open system of the pan coater but also due to the light weight of the tiny pellets. The RFB and the traditional fluidized bed performed better in the coating of tiny MCC pellets. During the process, the RFB coated pellets were not easy to get sticky and agglomerated with each other. This is due to the fluidizing air

introduced in the system. The introduced fluidizing air helped the tiny pellets generate ‘gasless fluidized state’ with the help of the wall friction that came from the rotation. It dramatically contributed to the mixing between the coating materials and the tiny pellets and further improved the uniformity of the coated pellets.

The traditional fluidized bed also exhibited a good fluidization state with the strong fluidizing air, and the tiny pellets, during the coating process, did not show a strong sticky phenomenon apart from the wall part that near the plasticizer spraying nozzle. The reason for this is that the diameter of the plasticizer sprayed from the nozzle was larger than the size of the column of the fluidized bed, and this may lead to wetness of the wall near the outlet of the nozzle. This phenomenon more or less lowers the coating efficiency since the wet wall may be adhered to by a small portion of the pellets.

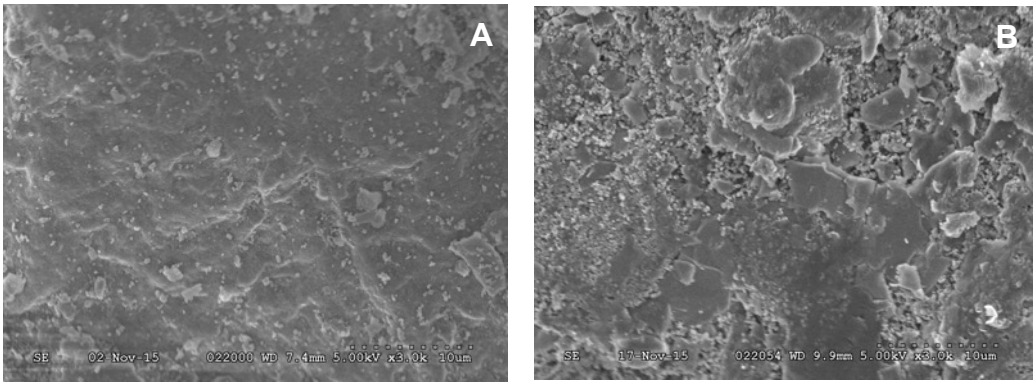

Figure 7.2 SEM micrographs of Acryl-EZE coated tiny MCC pellets curing for 2 h: (A) RFB, 50 ^{o}C, (B) Traditional fluidized bed, 40 ^{o}C

The surface of the RFB and the traditional fluidized bed coated pellets were illustrated by the SEM, as shown in Figure 7.2. It is clearly shown that the RFB coated tiny pellets had a relatively complete and continuous coating film (Figure 7.2A), while there were still come non-fused particles and additives attached on the pellets surface, and the smoothness of the coating film was not very good due to the ‘layer by layer’ phenomenon. Compared to the RFB coated tiny pellets, the SEM micrographs of the traditional fluidized bed coated pellets (Figure 7.2B) performed a non-ideal coating film. And it was

clearly illustrated that only part of the deposited coating powders were fused with voids characterized on the pellets surface, and the boundaries between the particles still existed, which indicated a non-uniform and in-complete coating film.

The photos of the RFB dry powder coated tiny MCC pellets (Figure 7.3B) further indicated the coating performance. The coated pellets showed a uniform appearance with the even color on every pellet, and the pellets were not sticky at all. Compared to the uncoated tiny MCC pellets (Figure 7.3A), it can be concluded that the pellets were covered with a thick and continuous coating film.

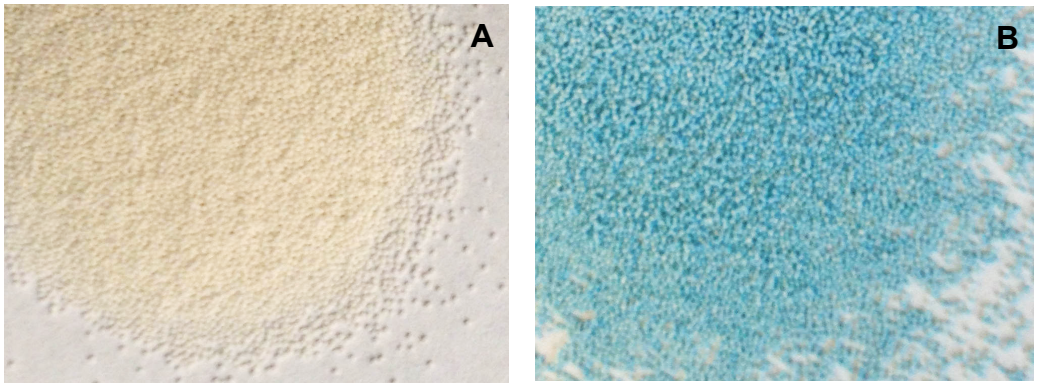

Figure 7.3 Photos of Acryl-EZE coated MCC pellets curing for 2 h, 50 ^{o}C:
(A) Uncoated MCC tiny pellets, (B) RFB coated MCC tiny pellets

As a consequence, in terms of the performance of the coating process and film formation effect of the tiny MCC pellets from the SEM micrographs, the RFB has the best coating film with the lowest loss of the coated pellets, and the traditional fluidized bed was practicable for the coating, however, the film formation of the coated tiny pellets was not as good as the RFB coated ones. The rotating pan coater was not an appropriate selection due to its open system. Moreover, it can be predicted that the RFB is more suitable for the coating of tiny pellets even workable for the coating of powders owing to the unique points of closed system and the introduce of the fluidizing air.

Chapter 8
Conclusions

A newly invented pharmaceutical coating apparatus, the rotary fluidized bed (RFB), was applied for the pellets coating with dry powder coating technique. The RFB has a unique structure where the uniform pellets coating is facilitated by the introduced fluidizing air and a rotation behavior during the process. SEM micrographs indicated the complete film formation over the entire piroxicam pellets via dry powder coating. All typical drug release types were realized, including immediate release, sustained release and delayed release with the coating materials Eudragit® EPO, Eudragit® RS/RL and Acryl-EZE, respectively.

For the immediate release coating with Eudragit® EPO, the coating level presented no influence on the drug release profiles due to the water-soluble property of Eudragit® EPO. The results were ideal for immediate release coating.

For the sustained release coating with Eudragit® RS/RL, SEM micrographs indicated that the pellets with higher coating level demonstrated better smoothness of the coating film. From the in-vitro drug release tests, the cumulative release after 12 h decreased dramatically as the coating level increased, indicating that the pellets with higher coating level (17.88%) are able to sustain for a longer time (more than 12 h), since Eudragit® RS/RL are water insoluble polymers and the drug release rate reduced with the increasing coating film thickness. In addition, the mass ratio of the Eudragit® RS to Eudragit® RL affected the drug release as well. The pellets with a higher ratio of the polymers (Eudragit® RS/RL= 2:1) showed a slower release rate compared to the pellets with a lower ratio (Eudragit® RS/RL=1:2). This is mainly because Eudragit® RS is less permeable than Eudragit® RL since it has less amount of the quaternary ammonium groups.

For the Acryl-EZE coated pellets, the in-vitro drug release tests proved that the acid resistance of the coated pellets in the first 2 h improved as the coating level increased. The pellets with a coating level higher than 13.25% were qualified to achieve 'delayed release' according to the USP <711> standard where the cumulative release should be less than 10% after the 2 h release in acid medium.

Optimization of process conditions in RFB with dry powder coating technique was investigated using Acryl-EZE as the example coating material. It was found that the RFB should be operated under moderate conditions. The curing temperature has to be maintained at 50 ^{o}C and the curing time should be no less than 2 h. This is because the film formation of the coating materials can only be achieved with a curing step and the curing temperature has to be closed to/above the T_g of the coating materials. In addition, the most appropriate rotating speed of the RFB was around 20 rpm. Below the 20 rpm range, the mixing of coating materials/pellets and the film formation were undesired. Above that, the strong tumbling of the pellets possibly damaged the coating film. Moreover, the most suitable plasticizer spraying rate and fluidizing air flowrate were around 0.25 g/min and 35 L/min, respectively. The last three factors (RFB rotating speed, plasticizer spraying rate and fluidizing air flow rate) should be matched with the pellets loadings and coating material feedings, and may vary with the change of the RFB size.

The performance of the rotating pan coater and the traditional fluidized bed were studied in comparison with the RFB. Acryl-EZE was selected as the example coating material. Under similar operating conditions, the RFB demonstrated comparable coating efficiency with the rotating pan coater while being superior to the fluidized bed. The latter is mainly because the RFB required relatively small amount of fluidizing air than the traditional fluidized bed that would not cause considerable loss of coating materials. In addition, the RFB coated piroxicam pellets achieved continuous, dense and smooth coating film as shown by the SEM micrographs, which were the same as the rotating pan coater and

much better than the fluidized bed. Furthermore, the RFB presented a potential ability of the micronized pellets coating (0.1-0.03 mm) compared to the other two apparatus. This is mainly owing to its unique closed system and the mild gasless fluidization generated by the rotation and the introduced fluidizing air. The closed system prevents the micronized pellets from being blown away and the fluidizing air helps the coating materials form a uniform coating film.

In summary, dry powder coating of pharmaceutical pellets with the RFB is a promising technique for the pharmaceutical coating industry. The coating of the pellets presented a continuous and dense film with fast release, sustained release, delayed release successfully modified. Compared to conventional aqueous coating, the operating time can be efficiently shortened from hours even days to only 2-3 h and the operating temperature is lowered as well. No organic solvent is required in contrast to the organic solvent coating avoiding the potential hazards of the organic solvent evaporation.

References

1. Cole, G., M.E. Aulton, and J.E. Hogan, *Pharmaceutical coating technology*. 1995: Taylor & Francis.

2. McGinity, J., *Aqueous polymeric coatings for pharmaceutical dosage forms*. 2008: Informa healthcare.

3. Lehmann, K.O., *Chemistry and application properties of polymethacrylate coating systems.* Drugs and the pharmaceutical sciences, 1997. **79**: p. 101-176.

4. Sakellariou, P. and R. Rowe, *Interactions in cellulose derivative films for oral drug delivery.* Progress in polymer science, 1995. **20**(5): p. 889-942.

5. Augsburger, L.L. and S.W. Hoag, *Pharmaceutical dosage forms-tablets*. 2008: CRC Press.

6. Hogan, J.E., *Film-coating materials and their properties.* Pharmaceutical coating technology, 1995: p. 27-33.

7. Rathbone, M.J., J. Hadgraft, and M.S. Roberts, *Modified-release drug delivery technology*. 2002: CRC Press.

8. O'Donnell, P.B., et al., *Aqueous pseudolatex of zein for film coating of solid dosage forms.* European journal of pharmaceutics and biopharmaceutics, 1997. **43**(1): p. 83-89.

9. Wheatley, T.A. and C.R. Steuernagel, *Latex emulsions for controlled drug delivery.* Drugs and the pharmaceutical sciences, 1997. **79**: p. 1-54.

10. Qiao, M., et al., *Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process.* International journal of pharmaceutics, 2010. **399**(1): p. 37-43.

11. Qiao, M., et al., *A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55.* European Journal of Pharmaceutics and Biopharmaceutics, 2013. **83**(2): p. 293-300.

12. Yang, Q., Y. Ma, and J. Zhu, *Applying a novel electrostatic dry powder coating technology to pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 2015. **97**: p. 118-124.

13. Maeda, Y. and D.R. Paul, *Effect of antiplasticization on gas sorption and transport. III. Free volume interpretation.* Journal of Polymer Science Part B:

Polymer Physics, 1987. **25**(5): p. 1005-1016.

14. Rowe, R.C., *Materials used in the film coating of oral dosage forms*. 1984, Blackwell Science, Cambridge, MA. p. 18-19.

15. Kablitz, C.D., M. Kappl, and N.A. Urbanetz, *Parameters influencing polymer particle layering of the dry coating process.* European Journal of Pharmaceutics and Biopharmaceutics, 2008. **69**(2): p. 760-768.

16. Obara, S., et al., *Dry coating: an innovative enteric coating method using a cellulose derivative.* European journal of pharmaceutics and biopharmaceutics, 1999. **47**(1): p. 51-59.

17. Sauer, D., et al., *Influence of processing parameters and formulation factors on the drug release from tablets powder-coated with Eudragit® L 100-55.* European journal of Pharmaceutics and Biopharmaceutics, 2007. **67**(2): p. 464-475.

18. Smikalla, M., et al., *Impact of excipients on coating efficiency in dry powder coating.* International journal of pharmaceutics, 2011. **405**(1): p. 122-131.

19. Rekhi, G.S. and S.S. Jambhekar, *Ethylcellulose-A polymer review.* Drug development and industrial pharmacy, 1995. **21**(1): p. 61-77.

20. Lippold, B. and P.R. Monells, *Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions.* Die Pharmazie, 2001. **56**(1): p. 5-17.

21. Porter, S., *In I. Ghebre-Sellassie, ed. Multiparticulate Oral Drug Delivery*. 1994, New York: Marcel Dekker.

22. Porter, S.C., *Aqueous film coating: An overview.* Pharm. Technol, 1979. **3**(9): p. 55.

23. Banker, G. and G. Peck, *The new, water-based colloidal dispersions.* Pharm. Technol, 1981. **5**(4): p. 55-61.

24. Amighi, K. and A. Möes, *Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit® RS30D film-coated sustained-release theophylline pellets.* European journal of pharmaceutics and biopharmaceutics, 1996. **42**(1): p. 29-35.

25. Bose, S. and R.H. Bogner, *Solventless pharmaceutical coating processes: a review.* Pharmaceutical development and technology, 2007. **12**(2): p. 115-131.

26. Salman, A., M. Hounslow, and J. Seville, *Handbook of Powder Technology, Vol. 11: Granulation*. 2007, Elsevier Publishing, Amsterdam.

27. Wruster, D.E., *Particle coating process*. 1966, Google Patents.

28. KuShaari, K., et al., *Monte Carlo simulations to determine coating uniformity in a Wurster fluidized bed coating process.* Powder Technology, 2006. **166**(2): p. 81-90.

29. Hampel, N., et al., *Continuous pellet coating in a Wurster fluidized bed process.* Chemical engineering science, 2013. **86**: p. 87-98.

30. Watano, S., et al., *Fine particle coating by a novel rotating fluidized bed coater.* Powder Technology, 2004. **141**(3): p. 172-176.

31. Joachim, J. and E. Cauture, *A hot-melt coating agent for controlled release.* J Pharm. Manufact Rev, 1996. **8**: p. 24-7.

32. Ozeki, Y., et al., *Evaluation of novel one-step dry-coated tablets as a platform for delayed-release tablets.* Journal of controlled release, 2004. **95**(1): p. 51-60.

33. Matsuo, M., et al., *Delayed-release tablets using hydroxyethylcellulose as a gel-forming matrix.* International journal of pharmaceutics, 1996. **138**(2): p. 225-235.

34. Ozeki, Y., et al., *Evaluation of the compression characteristics and physical properties of the newly invented one-step dry-coated tablets.* International journal of pharmaceutics, 2003. **267**(1): p. 69-78.

35. Ozeki, Y., et al., *Comparison of the compression characteristics between new one-step dry-coated tablets (OSDRC) and dry-coated tablets (DC).* International journal of pharmaceutics, 2003. **259**(1): p. 69-77.

36. Hariharan, M. and V.K. Gupta, *A novel compression-coated tablet dosage form.* Pharmac. Technol, 2001: p. 14-19.

37. Tahara, K., K. Yamamoto, and T. Nishihata, *Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910.* Journal of controlled release, 1995. **35**(1): p. 59-66.

38. Jones, D. and P. Percel, *Coating of multiparticulates using molten materials. Formulation and process considerations.* Drugs and the pharmaceutical sciences, 1994. **65**: p. 113-142.

39. Kennedy, J.P. and P.J. Niebergall, *Development and optimization of a solid dispersion hot-melt fluid bed coating method.* Pharmaceutical development and technology, 1996. **1**(1): p. 51-62.

40. Achanta, A., et al., *Development of hot melt coating methods.* Drug development and industrial pharmacy, 1997. **23**(5): p. 441-449.

41. Bose, S., B. Kelly, and R.H. Bogner, *Design space for a solventless photocurable pharmaceutical coating.* Journal of Pharmaceutical Innovation, 2006. **1**(1): p. 44-53.

42. Pappas, S.P., *UV curing by radical, cationic and concurrent radical-cationic polymerization.* Radiation Physics and Chemistry (1977), 1985. **25**(4): p. 633-641.

43. Kutal, C., P.A. Grutsch, and D.B. Yang, *A novel strategy for photoinitiated anionic polymerization.* Macromolecules, 1991. **24**(26): p. 6872-6873.

44. Otsubo, Y., T. Amari, and K. Watanabe, *Rheological behavior of epoxy acrylate prepolymer during UV curing.* Journal of applied polymer science, 1984. **29**(12): p. 4071-4080.

45. Wang, J.Z. and R.H. Bogner, *Solvent-free film coating using a novel photocurable polymer.* International journal of pharmaceutics, 1995. **119**(1): p. 81-89.

46. Bose, S., *Development and evaluation of solventless photocurable pharmaceutical film coating.* 2006.

47. Atai, M., et al., *Physical and mechanical properties of an experimental dental composite based on a new monomer.* Dental Materials, 2004. **20**(7): p. 663-668.

48. Subramaniam, B., R.A. Rajewski, and K. Snavely, *Pharmaceutical processing with supercritical carbon dioxide.* Journal of pharmaceutical sciences, 1997. **86**(8): p. 885-890.

49. Thies, C., et al., *A supercritical fluid-based coating technology 1: Process considerations.* Journal of microencapsulation, 2003. **20**(1): p. 87-96.

50. Tsutsumi, A., et al., *A novel fluidized-bed coating of fine particles by rapid expansion of supercritical fluid solutions.* Powder technology, 1995. **85**(3): p. 275-278.

51. Wang, Y., et al., *Extraction and precipitation particle coating using supercritical CO 2.* Powder technology, 2002. **127**(1): p. 32-44.

52. De Castro, M.D.L., M. Valcarcel, and M.T. Tena, *Analytical supercritical fluid extraction*. 2012: Springer Science & Business Media.

53. Benoit, J.-P., et al., *Method of coating particles and coated spherical particles.* US Patent 6087003 A, 2000.

54. Luo, Y., et al., *Dry coating, a novel coating technology for solid pharmaceutical dosage forms.* International journal of pharmaceutics, 2008. **358**(1): p. 16-22.

55. Grosvenor, M.P., *The physico-mechanical properties of electrostatically deposited polymers for use in pharmaceutical powder coating*. 1991, University of Bath.

56. Porter, S. *Principles and application of dry powder deposition coating technology*. in *AAPS Pharmaceutical Processing Conference, New Jersey*. 2003.

57. Bright, A., *SURFACE-FILMS PRODUCED BY ELECTROSTATIC POWDER DEPOSITION.* JOURNAL OF THE OIL & COLOUR CHEMISTS ASSOCIATION, 1977. **60**(1): p. 23-27.

58. Hogan, J.E., et al., *Powder coating composition for electrostatic coating of pharmaceutical substrates*. US Patent 6306738 B1, 2002.

59. Hogan, J.E., et al., *Electrostatic coating*. US Patent 7070656 B2, 2006.

60. Brown, S.R., L.A. Reeves, and J.N. Staniforth, *Method and apparatus for the coating of substrates for pharmaceutical use*. US Patent 6783768 B1, 2004.

61. Whiteman, M., et al., *Electrostatic application of powder material to solid dosage forms utilizing an electrically conductive shield*. US Patent 7144597 B2, 2006.

62. Szafran, R.G., W. Ludwig, and A. Kmiec, *New spout-fluid bed apparatus for electrostatic coating of fine particles and encapsulation.* Powder technology, 2012. **225**: p. 52-57.

63. Pearnchob, N. and R. Bodmeier, *Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique.* International journal of pharmaceutics, 2003. **268**(1): p. 1-11.

64. Pearnchob, N. and R. Bodmeier, *Dry polymer powder coating and comparison with conventional liquid-based coatings for Eudragit® RS, ethylcellulose and shellac.* European Journal of Pharmaceutics and Biopharmaceutics, 2003. **56**(3): p. 363-369.

65. Kablitz, C.D. and N.A. Urbanetz, *Characterization of the film formation of the dry*

coating process. European Journal of Pharmaceutics and Biopharmaceutics, 2007. **67**(2): p. 449-457.

66. Kablitz, C.D., K. Harder, and N.A. Urbanetz, *Dry coating in a rotary fluid bed.* European journal of pharmaceutical sciences, 2006. **27**(2): p. 212-219.

67. Pearnchob, N. and R. Bodmeier, *Dry powder coating of pellets with micronized Eudragit® RS for extended drug release.* Pharmaceutical research, 2003. **20**(12): p. 1970-1976.

68. Cerea, M., et al., *A novel powder coating process for attaining taste masking and moisture protective films applied to tablets.* International journal of pharmaceutics, 2004. **279**(1): p. 127-139.

69. Zhu, J., et al., *Direct coating solid dosage forms using powdered materials*. US Patent 7862848 B2, 2011.

70. Qiao, M., et al., *A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets.* European Journal of Pharmaceutics and Biopharmaceutics, 2010. **76**(2): p. 304-310.

71. Terebesi, I. and R. Bodmeier, *Optimised process and formulation conditions for extended release dry polymer powder-coated pellets.* European Journal of Pharmaceutics and Biopharmaceutics, 2010. **75**(1): p. 63-70.

72. Zhu, J., et al., *Apparatus for volumetric metering of small quantity of powder from fluidized beds*. US Patent 6684917 B2, 2004.

73. Schultz, P. and P. Kleinebudde, *A new multiparticulate delayed release system.: Part I: Dissolution properties and release mechanism.* Journal of controlled release, 1997. **47**(2): p. 181-189.

Appendix

Fast release

fast release					
coating lvl=8.82		release date	coating lvl=19.9		release date
		20150629			20150223
time/min	cumulative release	error bar	time/min	cumulative release	error bar
0	0	0	0	0	0
5	84.3559	1.2562	5	71.0518	4.1387
10	97.9008	2.5543	10	89.3393	2.4997
15	99.4754	0.6640	15	94.0618	1.8444
20	99.5768	1.4027	20	95.9749	1.5740
30	99.7905	1.3686	30	97.9237	1.3850
45	100.0000	1.9495	45	97.5296	0.2083
90	99.6667	1.5689	60	99.5246	0.7409

Sustained release

sustained release					
RS:RL=2:1	release date	20150707	release date	20150707	
coating lvl=8.08%			coating lvl=18.33%		
time/h	cumulative release	error bar	time/h	cumulative release	error bar
0	0	0	0	0	0
0.50	7.9078	0.8271	2	0	0
1	32.0333	4.1955	3.25	3.9321	1.2863
1.50	49.4109	2.4314	4	8.6157	0.4636
2	63.8521	1.6234	6	16.1381	2.9005
3.25	90.6562	3.7107	8	28.2446	3.8930
4	93.7357	2.4547	10	36.1675	4.2908
6	98.0565	2.3934	12	37.8441	3.7238
8	99.4165	0.8252			
10	100	2.1236E-05			
12	100	0			

RS:RL= 1:1	release date	20150723	release date	20150723		release date	20150805	
coating lvl=9.23%			coating lvl=13.13%			coating lvl=17.88%		
time/h	cumulative release	error bar	time/h	cumulative release	error bar	time/h	cumulative release	error bar
0	0	0	0	0	0	0	0	0
0.5	17.6045	4.9687	0.5	2.4552	0.4501	0.5	1.9567	0.4324
1	37.7266	6.5873	1	8.7879	1.8849	1	2.9196	0.6293
2	65.6735	4.2476	2	16.8453	1.3939	2	8.1449	2.2477
2.5	79.3958	3.2498	4	34.8817	0.4419	3	11.4910	1.9189
3	90.9481	7.7329	6	51.4929	1.3380	4	17.9959	1.2183
3.5	95.6594	7.3088	8	68.3035	3.3165	6	26.5355	1.1091
4	97.8581	3.7099	10	77.8257	1.0654	8	38.6567	0.1807
6	100	0	12	85.2255	1.4303	10	50.0663	3.5056
8	100	0	16	100	0	12	59.0139	3.5801
12	100	0				24	98.6119	1.0758
						26	100	0

RS:RL= 1:2	release date	20150730	release date	20150730		release date	20150805	
coating lvl=8.83%			coating lvl=13.99%			coating lvl=17.55%		
time/h	cumulative release	error bar	time/h	cumulative release	error bar	time/h	cumulative release	error bar
0	0	0	0	0	0	0	0	0
0.5	47.5657	8.2867	0.5	0	0	0.5	4.7158	0.4670
1	68.1650	2.5292	1	4.5278	0.4447	1	5.5086	1.2150
1.5	80.3657	0.3400	1.5	11.7631	1.2712	2	10.3782	0.8740
2	88.9337	0.8378	2	17.7672	2.7193	3	17.4083	1.1148
2.5	93.4166	1.5094	3	30.2681	3.3086	4	23.1458	0.9466
3	96.2532	0.3538	4	39.9918	2.0175	6	35.9058	0.1536
4	98.5059	1.3561	6	59.4250	2.0765	8	50.0904	0.8895
6	100.0000	0.0000	8	74.5457	2.1576	10	61.6633	2.0192
8	100	0	10	83.9905	1.7694	12	71.8944	1.6190
10	100	0	12	90.4105	1.3409	24	99.1408	1.4882
12	100	0	16	100	0	26	100	0

Delayed release

delayed release								
coating lvl=10.84%			coating lvl=13.25%			coating lvl=21.93%		
release date		20150818	release date		20150821	release date		20150619
time/min	average release	error bar	time/min	average release	error bar	time/min	average release	error bar
0	0	0	0	0	0	0	0	0
30	5.0670	1.1071	30	1.3964	0.8294	30	2.5765	1.2455
60	10.0001	0.5263	60	4.3002	1.4812	60	4.0477	1.3705
90	13.8254	1.0774	90	6.5159	0.8961	90	5.3282	1.5077
120	16.5748	0.8278	120	8.5870	0.7810	120	6.6573	1.4338
140	92.1231	2.0936	130	92.9377	1.6242	130	94.0827	1.5077
150	97.5977	1.6210	140	94.0250	0.8445	140	96.4472	1.3418
180	98.1014	0.9568	150	98.5486	1.5278	150	98.0851	0.9253
210	99.7231	0.4796	180	99.1051	1.1814	180	99.2156	0.2500
240	100	0	210	99.4444	0.9510	210	99.5961	0.6997
			240	100	0	240	100	0

Acryl-EZE, CL=14.6%, Temp=30℃, speed=20rpm								
Curing Time=1h		20150925	Curing Time=1.5h		20150925	Curing Time=2h		20150924
time/min	average release	error bar	time/min	average release	error bar	time/min	average release	error bar
0	0	0	0	0	0	0	0	0
30	41.5338	0.2949	30	35.4780	3.4935	30	17.6270	1.9756
60	63.2480	2.7458	60	50.4859	4.0293	60	22.6161	2.9929
90	76.0246	0.8621	90	61.9877	3.4341	90	27.3274	3.8709
120	85.2843	1.1918	120	69.6619	2.7096	120	30.9539	4.8890
130	92.6046	1.6760	130	90.4997	1.0241	130	93.5742	0.9248
140	100	0	140	99.0933	1.2822	140	99.9670	0.0572
150	100	0	150	100	0	150	100	0
180	100	0	180	100	0	180	100	0
210	100	0	210	100	0	210	100	0
240	100	0	240	100	0	240	100	0

Acryl-EZE, CL=14%, Temp=40℃, speed=20rpm								
Curing Time=1h		20151029	Curing Time=1.5h		20151029	Curing Time=2h		20150930
time/min	average release	error bar	time/min	average release	error bar	time/min	average release	error bar
0	0	0	0	0	0	0	0	0
30	13.128	2.534	30	5.2614	0.8283	30	3.8413	1.5514
60	19.217	2.706	60	14.4106	2.9125	60	9.8087	3.8480
90	23.810	2.588	90	20.4025	0.2695	90	11.6674	2.0208
120	28.580	2.034	120	24.0002	4.3767	120	19.4309	2.9384
130	93.379	2.519	130	95.4454	0.6299	130	85.6428	4.6927
140	97.430	0.846	140	96.5582	0.6247	140	92.4422	3.6883
150	98.697	1.523	150	96.8588	4.4423	150	99.0368	0.3621
180	99.677	0.560	180	100	0	180	100	0
210	100	0	210	100	0	210	100	0
240	100	0	240	100	0	240	100	0

Acryl-EZE, CL=14%, Temp=50℃, Ratating speed=20rpm								
Curing Time=1h		20151028	Curing Time=1.5h		20151028	Curing Time=2h		20150821
time/min	average release	error bar	time/min	average release	error bar	time/min	average release	error bar
0	0	0	0	0	0	0	0	0
30	0	0	30	0.4985	0.7050	30	1.3964	0.8294
60	6.6084	0.6320	60	1.3401	0.1672	60	4.3002	1.4812
90	11.6717	0.7558	90	7.4583	0.0985	90	6.5159	0.8961
120	15.0641	1.6503	120	9.7111	0.3925	120	8.5870	0.7810
130	94.9955	5.1313	130	88.4453	2.4891	130	92.9377	1.6242
140	100	0	140	100	0	140	94.0250	0.8445
150	100	0	150	100	0	150	98.5486	1.5278
180	100	0	180	100	0	180	99.1051	1.1814
210	100	0	210	100	0	210	99.4444	0.9510
240	100	0	240	100	0	240	100	0

Acryl-EZE, CL=14%, Temp=50°C, Ratating speed=20rpm								
Curing Time=1h		20151028	Curing Time=1.5h		20151028	Curing Time=2h		20150821
time/min	average release	error bar	time/min	average release	error bar	time/min	average release	error bar
0	0	0	0	0	0	0	0	0
30	0	0	30	0.4985	0.7050	30	1.3964	0.8294
60	6.6084	0.6320	60	1.3401	0.1672	60	4.3002	1.4812
90	11.6717	0.7558	90	7.4583	0.0985	90	6.5159	0.8961
120	15.0641	1.6503	120	9.7111	0.3925	120	8.5870	0.7810
130	94.9955	5.1313	130	88.4453	2.4891	130	92.9377	1.6242
140	100	0	140	100	0	140	94.0250	0.8445
150	100	0	150	100	0	150	98.5486	1.5278
180	100	0	180	100	0	180	99.1051	1.1814
210	100	0	210	100	0	210	99.4444	0.9510
240	100	0	240	100	0	240	100	0

Acryl-EZE coating lvl=14% Temp=50 ℃, curing time=2h, speed=6rpm		
Curing Time=2h		20151105
time/min	average release	error bar
0	0	0
30	10.2753	1.5848
60	18.0070	2.0321
90	24.6863	2.7766
120	29.7664	2.0080
130	92.3820	0.2319
140	96.8122	0.6654
150	99.5121	0.6900
180	100	0
210	100	0
240	100	0

Curriculum Vitae

Name:	Yunhan Zhang
Post-secondary Education and Degrees:	China University of Petroleum, Beijing Beijing, China 2009-2013, B.E.Sc The University of Western Ontario London, Ontario, Canada 2015-2016, M.E.Sc
Honours and Awards	Honour Undergraduate Student 2009-2013 Industrial sponsored first-class scholarship, SINOPEC 2012 Second prize in the China Chemical Process Design competition 2012 Third prize in 'Principles of Chemical Engineering' competition, sponsored by BASF 2012 Third-class scholarship of China University of Petroleum 2011 Industrial sponsored first-class scholarship, Shenhua Ltd. (China) 2010
Related Work Experience	Teaching Assistant The University of Western Ontario 2015-2016