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Preparation and Coating of 5-ASA Pellets with a Novel Rotating Fluidized Bed

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Abstract

Although Mesalazine (5-ASA) demonstrates huge popularity in treating inflammatory bowel disease (IBD) due to its local effect on intestinal and colonic mucosa, it still demands more accurate and effective delivery of 5-ASA. As pellets embrace various technological and therapeutic advantages over the single-unit dosage form, this study aims at developing and optimizing the drug-loading and coating processes of 5-ASA pellets with a novel rotating fluidized bed. Powder layering and powder coating techniques, which are the same in essence, were applied in the drug-loading and coating processes, respectively. Three different coatings of 5-ASA pellets were achieved, resulting in extended, delayed and extended-delayed release, aiming at prolonging 5-ASA release time, targeting 5-ASA to colon region and the combination of the first two, respectively. Overall, this project offers a promising approach to delivering 5-ASA to specific colon sites.

Keywords: 5-ASA pellets, drug-loading, pellet coating, rotating fluidized bed, extended release, delayed release, extended-delayed release

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Chapter 1

Introduction

1.1. Background

1.1.1. Colon-specific Drug Delivery System (CDDS)

For delivering pharmaceutical moieties, the colon has been a popular potential site, thereby among the site-specific drug delivery systems, there develops a novel oral colon-specific drug delivery system (CDDS). The CDDS is for treatment of ulcerative bowel disease, colitis, colon cancer and infectious diseases, where a high concentration level of active agent in the large intestine is necessary. [1,2]

The CDDS has the following advantages:

1). Due to relatively low proteolytic enzyme activities and extended transit time, colon optimizes the absorption for protein and polypeptide after oral administration, hence improves their bioavailability;

2). By combining one or more controlled release mechanisms, it barely releases drug in the upper part of the gastrointestinal tract (GIT), while after oral administration, it rapidly releases drug in the colon;

3). For diseases that show peak symptoms in early mornings and that have circadian rhythms, for instance, nocturnal asthma, angina and rheumatoid arthritis, CDDS can be therapeutically useful to provide a delayed absorption.[1]

Eventually, CDDS have several forms: low molecular weight prodrugs, macromolecular prodrugs, pH-dependent systems, positioned-release systems, and biodegradable polymers. [2]

These approaches utilize the pH of the GIT, the transit time of the small intestine, the luminal pressure of the colon or other physiological properties of the GIT and colon.

Among these, designing a pH-dependent CDDS is certainly quite simple and suitable, considering the different physiological and pathological conditions in GIT. [3,4] Generally, the pH of the human GIT increases progressively from stomach (pH 1.5-3.5 which climbs to 4 when digesting), small intestine (5.5-6.8) at the site of digestion, and in colon (6.8-7.0). The application of pH-sensitive polymers as coating materials on kinds of solid dosage forms can achieve an extended or delayed release. For CDDS, the polymers have to be capable of withstanding the lower pH of the stomach and the proximal part of the small intestine, while preferentially disintegrating at higher pH level of the colon.[5]

1.1.2. Mesalazine (5-ASA)

Inflammatory bowel disease (IBD), characterized as chronic inflammation of unknown etiology, refers to a group of diseases that occur in the small and large intestines. [6]

Mesalazine (5-ASA), which serves as the standard drug for treating IBD due to its local effect on intestinal and colonic mucosa, represents a cornerstone in the treatment of inflammatory bowel diseases. If administered orally, 5-ASA can be absorbed in the small intestine, rapidly and nearly completely. In this case, only a small portion of the intact drug reaches the lower gastrointestinal tract, which is the target region. This certainly leads to side effects.[7]

To realize controlled release and exact delivery to the intestinal target region, there are different ways to deliver 5-ASA. In this study, 5-ASA was prepared as CDDS, protecting it from the upper GI conditions and releasing it in the designated region.

1.2. Objectives

The main objective of the present study was to develop and characterize a powder coating process for producing (5-ASA)-layered pellets and subsequent polymer-coated pellets.

Specific aims of the study were:

• to load 5-ASA on pellets by a powder layering technique;

• to powder coat 5-ASA pellets with coatings of various release functions;

• to study the effects of key process conditions in a novel rotating fluidized bed on the drug-loading and pellets coating processes.

Chapter 2

Pellets

2.1. Introduction

In a number of industries, ‘pellets’ have been used to describe kinds of agglomerates manufactured from various raw materials and for kinds of purposes. With diversity in composition, size and shape, these agglomerates include fertilizers, animal feeds, iron ores, and pharmaceutical dosage units. Consequently, in different industries, ‘pellets’ have different meanings.

Particularly, the pharmaceutical industry defines pellets as agglomerates of fine powders or granules of bulk drugs and excipients. Composed of small, free-flowing, spherical or semi-spherical solid units, the size of agglomerates typically ranges from around 0.5 mm to 2.0 mm, applied in oral administration.[8] Besides, produced by compression from medicated masses, implants of small and sterile cylinders are also classified as pellets.[9]

2.2. History

It can be traced back to the early 1950’s that the pharmaceutical industry became keen on pelletization technology for obtaining extended release of drugs. Not until the late 1970’s, the advantages of pellets over single-unit dosage forms were realized.[10] Nowadays, developing a fast, economical and effective pelletization technique has been a promising trend.

2.3. Advantages & Limitations

2.3.1. Advantages

Technological Advantages

1). In multiple-unit systems, the total drug dose can be dispersed uniformly into desired dosage strength, with high accuracy offered by various pelletization techniques;

2). Pellets offer high degree of flexibility in the design and development of pharmaceutical solid dosage form, for instance, suspension, sachet, tablet and capsule;[11-13]

3). As spheres, they present excellent flow properties, due to which uniform and reproducible fill weight of capsules and tablets can be achieved;

4). Sometimes, they can be mixed to deliver incompatible bioactive agents simultaneously;

5). Since normally the dust explosions and respiration problems can arise from the fine powders, the pellets can improve the process safety by prevention of the dust formation; [10]

6). To stabilize the active ingredients in the pellets or to realize controlled-release of the active ingredients, coating of the pellets is extremely popular, in which case sphere is no doubt the perfect shape due to its edgeless property. Without extra coating material required to fill irregularities in pellets surface, sphere also costs the least; [14-16]

7). Porous beds or columns work as chemical reactors in some processes, the reproduction of beds with always the same void volume, surface area and permeability can be achieved by spheres. It gets easier when it comes to

calculations and predictions of the process characteristics, since a lot of equations are based on flows around the symmetrical bodies; [17]

8). The multiple-unit doses can realize various release profiles in the gastrointestinal tract. They are less likely to fail, compared to a single-unit system. This can be obvious in extended release single-unit dosage forms, where dose-dumping of the drug may result from a failure; [18]

9). For better product appearance or marketing reasons, spheronization is applied in certain consumer products. Spheronization can increase pellet hardness and reduce pellet friability, which rely on the internal cohesive forces and surface characteristics. This can lead to reduction in the quantity of fines produced during handling or transportation. [18]

Therapeutic Advantages

Formulated in the form of suspensions, capsules or disintegrating tablets, the pellets containing the active ingredient demonstrate significant therapeutic advantages over single-unit dosage forms, as well as enhance the safety and efficiency of the active ingredient.[19-22]

1). The small size permits a wide distribution along the gastrointestinal tract. This certainly enhances absorption and avoids the irritant effect on the mucosal lining, which may be caused by the single-unit systems, especially when stuck at a specific site for a prolonged period; [23]

2). When administrated orally, the pellets are released into the gastrointestinal tract and compared to the single-unit systems, the pellets depend less on gastric emptying; [24]

3). The gastro-intestinal transit time has pronounced influence on the bioavailability of an oral administrated drug that is prepared as controlled-release. No cut-off size for the gastric emptying actually exists, while it can become unsure and

greatly variable to predict the gastric emptying from the fed stomach when the size of pellet increases;[9]

4). Less intra- and inter- patient variation in the gastrointestinal transit time exists because the pellets can pass through the pyloric sphincter easily due to their small size; [25,26]

5). Researches have been conducted on the effect of pellet density on the transit time through the gastrointestinal tract, showing that higher density can prolong the gastric transit time. Through spheronization, the true and the bulk density of pellets are both increased, thus enhancing both the pellet manufacturing and pellet packaging processes.[18]

2.3.2. Limitations

1). Pelletization is costly and complicated to control, in demand of sophisticated equipment as well as loads of process and fomulation variables;

2). The size vaires among different fomulations, typically ranges from 0.5 to 2.0 mm;

3). Too rigid to compress them into tablets and subsequent film coating can be damageable. Consequently, they are normally encapsulated in hard gelatin capsule shells, which, however, can be costly; [18]

4). Dosed by volume instead of number and dispersed into single dose units as needed.

2.4. Requirements for Good Pellets

1). Spherical shape and smooth surface for achieving a subsequent uniform film coating;

2). The size should ranges from 0.6 mm to 1.0 mm;

3). The content of the active ingredient in pellets should be maximum so as to maintain the final dosage within reasonable limits. [9,10,27]

2.5. Theory of Pellet Formation and Growth

Fully understanding the fundamental mechanisms of pellet formation and growth is of great significance to advisably select and optimize any pelletization process.

In the whole process, the agglomerates exist in two forms:

(i) Moist feed or free fines: a large amount of particles or small agglomerates that are infinitesimal and not countable, contributing to the formation and growth of well-formed species;

(ii) Well-formed species or pellets: finite in size and countable, undergoing changes in size and number through various mechanisms of the agglomerate formation and growth. [28,29]

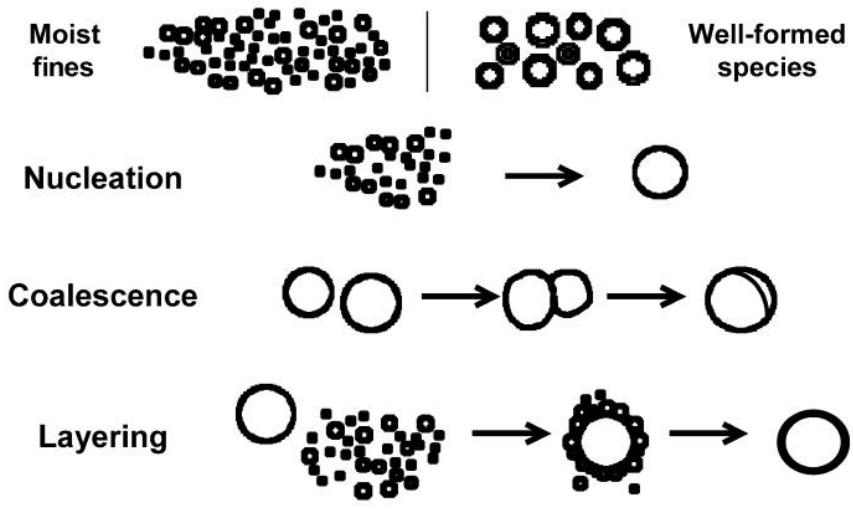


Figure 2.1. Pellet growth mechanisms

As shown in Figure 2.1[30], the first phase, nucleation, refers to the initial formation of well-formed species with the help of capillary interaction between the moist

particles. In this phase, both the number and mass of the well-formed species are on increase.

Coalescence represents the growth due to clumping of two or more colliding well-formed agglomerates. For mathematical simplifying, binary coalescence is regarded as the elementary event. This stage results in the decrease of the number of well-formed species while the mass stays constant. During this process, there exist three types of attraction forces, the Van der Waals force, the capillary force and the electrostatic force. Van der Waals force is the dominant interaction force, including both the forces between the agglomerates and between the agglomerates and the wall of the apparatus. Capillary force comes from the fluid condensation in the gap between the agglomerates in close contact, resulting in additional or liquid bridging force among agglomerates. Electrostatic force can occur by tribo-electric charging or by the formation of a potential difference when agglomerates of different work functions are brought into contact.

Layering, a growth mechanism which consumes moist fines, refers to the continuous growth of well-formed species. Thereby the number of pellets is unchanged, the mass increases.[30]

2.6. Pelletization Techniques

Generally, ‘granulation’ and ‘pelletization’ are synonymous terms, thereby there is no clarification among granules, pellets, agglomerates or spheroids, which are the products of the two processes. Some literature, however, define ‘granulation’ as a size enlargement process with products that are ‘granulates’, ranging from 0.1 mm to 2.0 mm and have high porosity (about 20-50%). Meanwhile, they define ‘pelletization’ as a size enlargement process that manufactures ‘pellets’, which possess a relatively narrow size range, normally with average size from 0.5 to 2.0 mm. Namely,

pelletization stands for an agglomeration process that converts fine powders or granules of bulk drugs and excipients into pellets.[31]

For manufacturing drug pellets, there are various techniques, among which compaction and drug layering are the most popular ones. Extrusion-spheronization is the most widely used one in compaction techniques. Other methods, such as balling, globulation and compression are also applied in the development of pharmaceutical pellets, though in a limited scale.

2.6.1. Extrusion-Spheronization

Extrusion-spheronization refers to a multistage process that produces uniform sized drug pellets from wet granules (extrudates). Especially, it shows advantages in terms of producing high drug loaded pellets with least excipients.[32] The extrusion operation, considered as specific wet granulation technique and an essential step of the overall process, refers to applying pressure to a wet mass until it passes through the calibrated openings of a screen or die plate of the extruder and then shaped into small extrudate segments. The diameter of the openings in the extruder screen determines the diameter of the segments and the final size of the spheroids. The extrudates must possess enough but excessive plasticity in order to deform, or they will stick together. [10]

Spheronization, first introduced by Nakahara in 1964, represents the manufacture of spherical particles from the small extrudates. The extrudates should not only be cohesive and firm, but also have proper plasticity because their formation determines the one of pellets.

Three steps constitute this operation (as shown in Figure 2.2[32]):

Firstly, extrudates interact with the rotating plate, stationary wall and other extrudates, thereby lead to the breaking of the cylindrical segments;

Secondly, the small fragments formed in the first breaking phase are randomly picked up by the larger granules during the smoothing phase, in this case, agglomeration happens;

Finally, during the smoothing stage, each granule rotates about its axis in the constantly changing planes, through which the spherical particles are eventually created. [33,34]

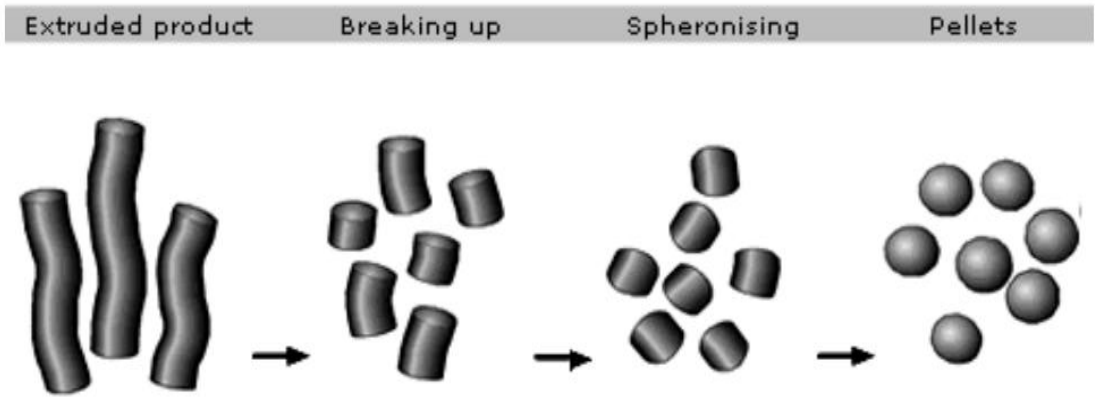


Figure 2.2. Principle of Spheronization Process

The fomulations in the process need to ensure the wet mass' capability of being extruded, besides, the extrudates must be able to undergo the rounding on the spheronizer plate, thereby limited fluid mobility is regarded as dominant in selecting fomulations used in the extrusion-spheronization process. [35]

Though as a promising technique in the area of pelletization, a major drawback of the extrusion–spheronization is its multi-step batch process. To overcome this disadvantage, the process is in need of improvement to make it more economical, technical and commercial. [8]

2.6.2. Drug Layering

As the most well-controlled and straight forward pelletization technique, layering process refers to deposition of successive layers of drug entities from solution,

suspension or dry powder on nuclei, which may be in the form of crystals or granules of the same material or inert starter seeds. In terms of the form of the drug, there are two types: solution/suspension layering and powder layering.

Solution/suspension Layering

In solution/suspension layering, the drug particles are dissolved or suspended in the binding liquid, with or without a hardening binder. The droplets spread out on the nuclei once the formation is sprayed. The crystallization of the dissolved substances happens with the liquid evaporating. On further evaporation, through capillary forces, the crystals and particles are drawn toward each other and the starter seeds. The solid bridges among the particles are created in this case, of which the strength is determined by the properties of the binder, other additives in the fomulation and the active ingredient. The above-mentioned spraying, drying and solid bridges formation happen repeatedly until the desired size of pellet is eventually achieved. (Figure 2.3[32])

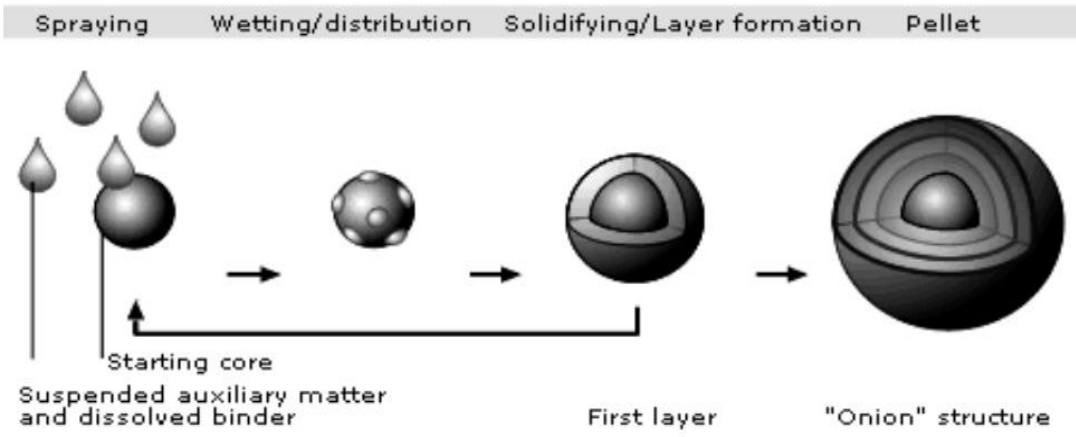


Figure 2.3. Principle of solution and suspension layering

Powder Layering

In the powder layering technology, normally by loading the micronized powders on the solid cores, pellets are thus prepared. Tumbling in the rotating pan or disc, the moist nuclei picks up the powder particles, which adhere to each other and the nuclei

through capillary forces formed in the liquid phase, hereby the layers are developed. As extra binding liquid is sprayed, layering of more powders on the nuclei furthers until the desired pellet size is realized. Once dried, the binder and other dissolved substances crystallize out and the solid bridges take place of the liquid ones partially. [18] As shown below, Figure 2.4[32] depicts the principle of the powder layering process.

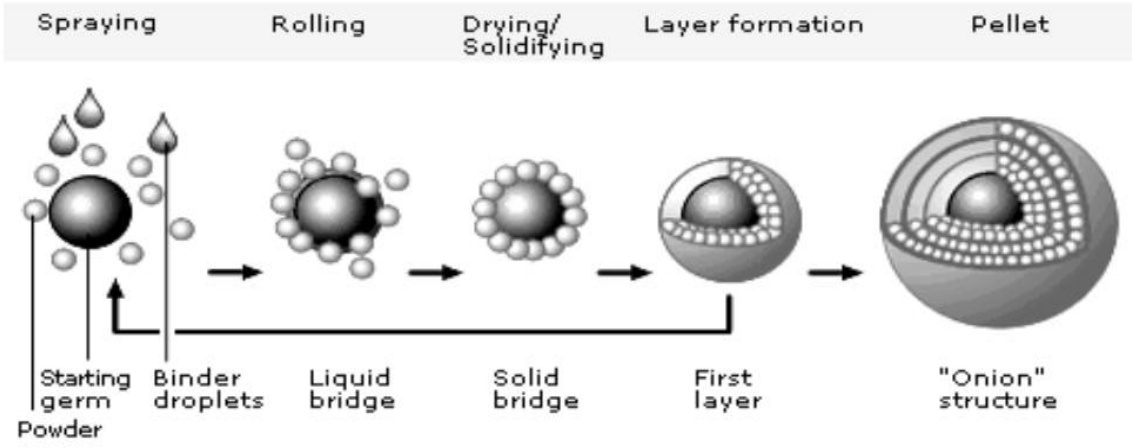


Figure 2.4. Principle of Powder Layering

Due to the greater consolidation resulted from tumbling and colliding of pellets, the pellets manufactured from powder layering process demonstrate higher density and smoother surface, compared to the ones produced from suspension layering process. [36]

The powder layering technique enlarges inert substrates, such as sugar spheres, by intermittently spraying a binder solution and applying the powders that contain drug in a rotating coating pan or in a fluidized bed.[37] Particularly, the centrifugal granulator has been proved to be a successful and efficient pelletization equipment. Centrifugal granulation is an advanced method of producing drug-layered pellets. It has numerous advantages such as, lower manufacturing costs, flexibility in operation and ease of automation over other pelletisation techniques. Besides, rotation of the apparatus circulates the involved air and powders, both of which enhance the quality

of gas-solid contact. Likewise, a rotating fluidized bed is selected in this study due to the following advantages:

1). Operational feasibility: uniform distribution of the binder solution and continuous drug layering can be achieved; [38]

2). Ease of handling and variable controlling parameters: layering and drying take place in one single machine, a rotating fluidized bed;[39]

3). The layering process and the filling and emptying of the machine can be implemented in complete isolation, without any product spread into the environment, thus reduces total contaminant;

4). Protecting the pellets from moisture, light and air;[40]

5). Specific manipulation of the pellet surface characteristics as well as the way in which the pellet dissolves the decomposition or the release of active pharmaceutical ingredients (APIs).

Overall, for pellets that require a delayed or extended release profile, powder layering in a rotating fluidized bed is desirable.

Despite of the advantages mentioned above, the method certainly shows some drawbacks:

1). Time consuming due to repeated wetting and powdering operations;

2). Existence of unexpected agglomeration and pellets adhering to the wall of the coating equipment;

3). Specialized equipment like a rotating fluidized bed or modified rotating pans are required;

4). No sufficient evidence showing the relationship between the fomulation and process parameters and the physical, technological, and biopharmaceutical properties of the pellets. [41,42]

During the preparation of pellets, the inert starter cores over which the drug is layered serve as the primary materials, as a consequence, their physico-chemical properties have rather pronounced influence on the quality of the drug loaded pellets. [9]

The properties involve:

1). Suitable density, size and distribution as required by the layering process;

2). Nearly spherical shape in order to flow and roll well in the layering equipment;

3). Proper compaction, impaction, and attrition strengths in case of ruptures in the layering process. [41]

The characteristics mentioned above can promise good quality of drug loaded pellets: uniform film disposition and formation during layering, proper film thickness, non-segregation during capsule filling, desired rate of drug release and easy packing properties.

Non-pareils were once applied as cores in the layering process, while its initial component, sucrose, was found to be harmful to diabetics and potential cariogenicity. At present, microcrystalline cellulose (MCC) has taken place of them and shows great feasibility.

2.6.3. Other Pelletization Methods

1). Balling refers to a continuous rolling and tumbling motion in pans, discs, drums or mixers. With addition of certain liquid, the finely divided particles are converted into spherical particles in this process.

2). Globulation, also called droplet formation, has two stages: firstly, spray drying, during which suspension or solution with drug but excipient is sprayed into a hot stream, hence dry and spherical particles are created. This can enhance the dissolution rate, or bioavailability of poorly soluble drugs. Secondly, spray congealing, through which drug is melted, dispersed or dissolved in hot melts of gums, waxes or fatty acids and then sprayed into an air chamber to manufacture spherical congealed pellets.[10]

3). As one of the compaction techniques, compression refers to compact blends of active ingredients and excipients to create pellets of desired sizes and shapes.

4). CPS (Complex Perfect Spheres) Pelletization Technology, as a proprietary, direct pelletization method, mixes the drug with an excipient, such as MCC and water, in a mixer to create a damp mass, which is to be processed into spheres in the CPS fluid bed unit. Through air suspension and other mechanical means, the loose agglomerates in the damp mass are densified and spheronized by an orbital motion in the CPS unit. Small, uniform spheres are initially produced during the densification process, through applying mechanical forces or adding water, the smaller spheres coalesce and create larger, smooth spheres stepwise. The process ends until the desired particle size is achieved with the acquired wet spheres to be dried in a fluid bed dryer. [43]

Chapter 3

Pellet Coating

3.1. Introduction

For the solid oral dosage forms, coating is quite essential, it is a process where layers of coating materials are deposited on the pellet surfaces. Pellets are usually film-coated with one or more layers of polymer film [44] for various purposes: aesthetic appearance improvement; protection from environmental factors like moisture, acid oxygen and light; enhancement of API (active pharmaceutical ingredient) physico-chemical stability; physical property improvement, namely, moisture content, flowability, density modification. Particularly, coating helps realize desired release profiles for the pharmaceutical pellets, resulting in proper drug fluctuations in the patient blood and more patient compliance.[45] Specifically, drug release refers to the conversion of the drug into forms that are subjected to absorption, distribution, metabolism, and excretion (ADME), thereby showing the pharmacological activity.[46]

3.2. Coating Types

In terms of polymer-based coatings, the polymer properties and the fomulation (polymers, plasticizers and dye) parameters have certain influence on the properties and performance of coatings. According to specific use, the polymers differentiate as protective or functional coating.

3.2.1. Protective Coating

Protective coating, also called ‘plain coating’, according to to USP XXII, is applied for enhancing aesthetic appearance, masking taste and odor as well as protecting the

pellets from the detrimental effects, namely, light and moisture. This type of coating allows the drugs to dissolve immediately, without any delayed or prolonged dissolution or absorption, which is certainly useful when a fast onset of action is required therapeutically.[47]

Commonly, water-soluble polymers constitute the coating polymers for this coating type, guaranteeing a immediate dissolution. Among the water-soluble polymers, methacrylate-based polymer developed by Evonik (trade name: Eudragit® E) is no doubt an excellent option. Composed of dimethyl-laminoethyl methacrylate, butyl methacrylate and methyl methacrylate with a ratio of 2:1:1, Eudragit® E (shown in Figure 3.1) is a cationic copolymer. It has three categories: Eudragit® E100, Eudragit® E12,5 and Eudragit® EPO, applied in the granules, organic solutions and powders, respectively. They are capable of dissolving in the gastric solutions with pH up to 5.5, indicating a rapid dissolution in the stomach while being insoluble in the saliva.[48]

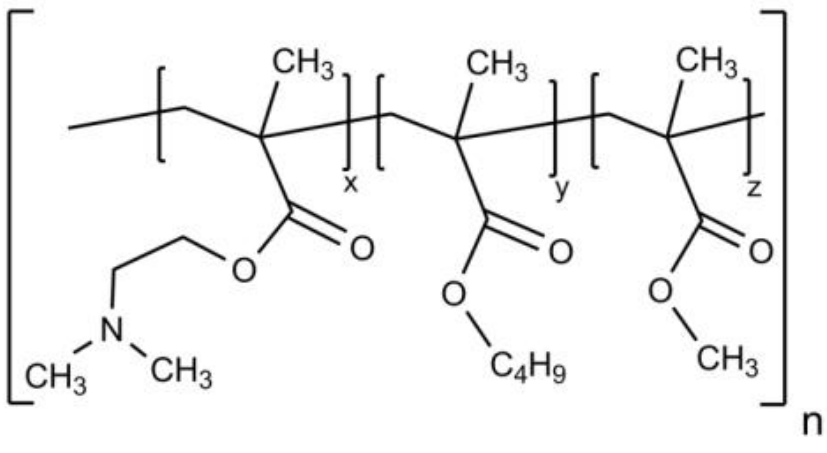


Figure 3.1. Eudragit® E monomer structure

3.2.2. Functional Coating

Functional coating, known as modified-release coating, aims at releasing the incorporated drug as desired: for a prolonged period, or at certain point after the initial administration or towards a specific area in human body.

Extended-release Coating

Extended-release coating helps control the release of the drug over a prolonged period after administration. It reduces dosing frequency by extending the release profile of a drug, which can be especially essential when patients need to take the drug for a quite long time, namely, the rest of their life for treating chronic diseases. Thus this kind of coating is regarded as time-controlled, where the drug concerned is released during the gastrointestinal transit period.[49]

The polymers employed in extended release, which are insoluble in water as well as independent of pH along the gastrointestinal tract, can greatly improve the therapeutic effect and the compliance of patients.[50] Ethyl cellulose (EC), Eudragit® RL and Eudragit® RS (shown as Figure 3.2) have gained their popularity for such mentioned purposes.

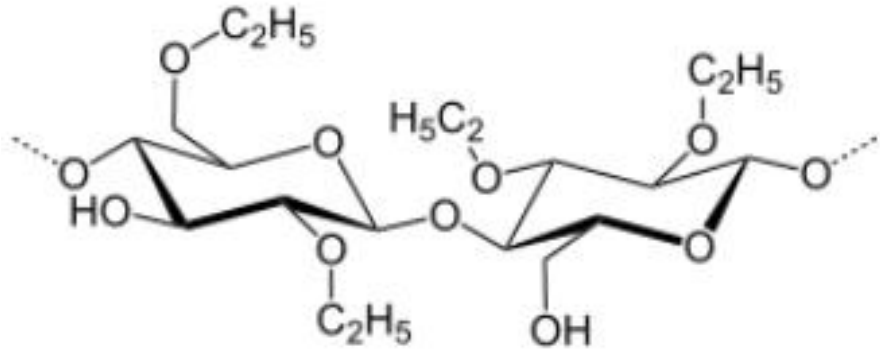


Figure 3.2. Ethyl cellulose molecular structure

Eudragit® RL and Eudragit® RS are composed of ethyl acrylate, methyl methacrylate and a small quantity of methacrylic acid ester with quaternary ammonium groups (trimethyl-ammonioethyl methacrylate chloride), which function as salts that help achieving desired permeability of the coating. Once contacting the solution, the quaternary ammonium groups can be ionized, resulting in the swelling and opening pores of the coating. The only character that differentiates these two

polymers is the content of quaternary ammonium groups. The molar ratio between the quaternary ammonium groups to neutral methacrylic acid ester groups of Eudragit® RL and Eudragit® RS are 1:20 and 1:40, respectively. Compared to Eudragit® RS, Eudragit® RL has double content of quaternary ammonium groups, hence shows a higher permeability. Through adjusting the thickness of the coating and modifying the ratio of the two polymers in the fomulation, different drug release rates can be achieved.[51]

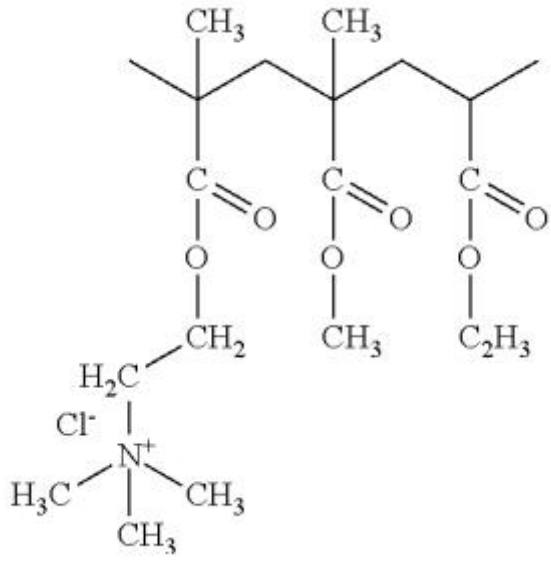


Figure 3.3. Chemical structure of Eudragit® RL and Eudragit® RS

Delayed-release Coating

Other than immediately released after administration, this type of coating delays the release of drug at a certain point. Intended to protect the drug from the gastric environment or to protect the stomach from irritation by the drug, delayed-release coating is also called enteric coating. The polymer coating dissolves when travelling from low-pH environment to higher-pH environment, hence the drug can be released immediately, leading to a similar plasma concentration versus time curve to the one with immediate-release coating.

For delayed-release coating, the polymers protect the API from being damaged in the stomach, which offers an acid condition. Additionally, they need to demonstrate easy dissolution in the environment which possesses high pH value, for instance, the colon. Specifically, cellulose-based and methacrylate-based polymers represent the most popular ones for delayed-release coating.

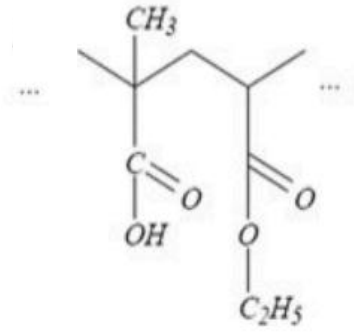


Figure 3.4. Chemical structure of Eudragit® L 100-55

Eudragit® L100-55, also known as Acryl-EZE MP, is capable of dissolving in the solution with high pH, due to the molecular structure which has carboxylic acid groups, it can protect the API from low pH conditions.

3.3. Coating Techniques

The modern pharmaceutical coating technology witnesses the evolution from sugar coating to organic and aqueous-based film coating. While for organic-based film coating technique, it has drawbacks like toxicity, environmental, economic and safety problems; for aqueous-based coating technique that uses water as solvent, it shows disadvantages like slow drying, high energy demand and microbial contamination.[52]

In order to overcome these limitations of the solvent coating techniques, efforts have been made to realize solventless coating, for instance, hot-melt coating, supercritical fluid spray coating, photo curing coating and powder coating. [53]

Among the methods mentioned above, dry powder coating technique is selected in this study. In the pharmaceutical industry, among the solventless coating techniques, it gains the most popularity, recognized to further develop the coating technology and as a promising alternative to overcome the limitations that solvent coating techniques bring about.

Its development can be traced back to the late 1990s, in which process the dry powders are directly deposited onto the surface of pellets with a liquid plasticizer being sprayed simultaneously. At elevated temperature, the film is created in the following curing step.[52] Particularly, the curing temperature must be over the glass transition temperature (T_g) of the coating materials. Hereby T_g refers to the temperature range where a thermosetting polymer transforms from a hard, rigid or 'glassy' state to a pliable, compliant or 'rubbery' state.

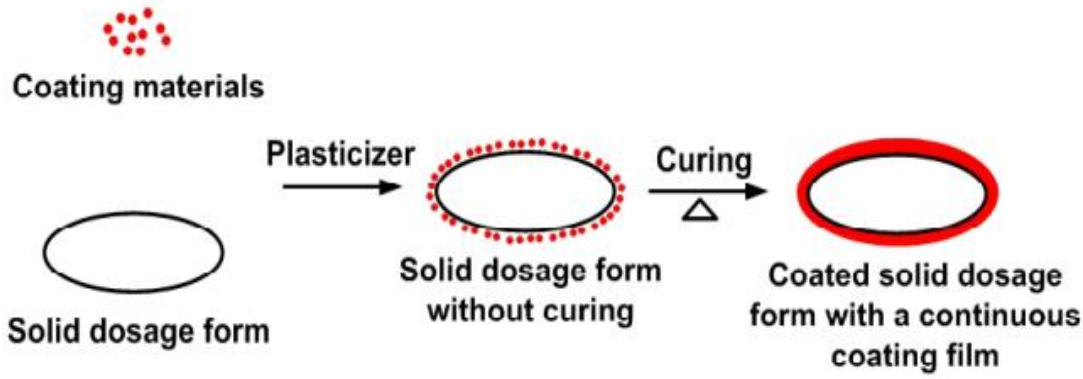


Figure 3.5. Schematic of plasticizer powder coating

During the coating process, through incorporating themselves between the polymers chains, the plasticizers can increase the free volume, resulting in a considerable reduction in T_g [54-56]. The damage of API can be avoided due to the decrease of the coating temperature.[57,58] Plus, the plasticizers improve the adhesion between the coating powders and the pellets. This benefits the film formation by improving viscous flow and particle deformation.[59] Furthermore, before the plasticizer immerse into the pellets, capillary forces will generate, consequently, the deformation

in the interstitial capillary system and the film formation can be enhanced as well.[59,60]

Due to the absence of solvents, it not only greatly saves processing time in solvent evaporation but also becomes environmental friendly and safe. Furthermore, for drugs that are solvent or moisture sensitive, dry powder coating is an advisable choice. However, the dry powder coating shows less coating efficiency than conventional coating procedures, demands more time and energy because film formation becomes more difficult without solvent involved in the process.[61]

For absorption in the GIT, dissolution of the active pharmaceutical ingredient (API) from the pellet is rate-limiting. For oral administrated drugs, it is common to modify the mass transport from the drug carrier system into physiological dissolution media. Particularly, dissolution testing is essential to develop appropriate excipients and optimize the manufacture techniques. During the dissolution testing, the content of dissolved drug is analyzed as a a function of time. For multiple-unit systems such as pellets, the dose of API is released by individual subunits, the quality if subunits determine the functionality of the entire dose.[62]

In terms of the coated pellets in this study, when the pellets contact the dissolution media, a hydrostatic pressure is generated inside the pellets, when the mechanical stability of the coating films cannot withstand the hydrostatic pressure, the coating film cracks and then the release of the API is no longer controlled by the coating film, instead it is dominated by the diffusion of API through the dissolution media, which releases the API at a considerably faster rate.

Chapter 4

Materials, Apparatus and Methods

4.1. Materials

4.1.1. Powders

Eudragit® EPO, Eudragit® RS, Eudragit® RL, Eudragit® L100-55 and Colloidal silicon dioxide (AEROSIL® 200 Pharma) were supplied by Evonik Degussa Corporation (Germany). Acryl-EZE was developed by Colorcon, Inc. (US). Eudragit® EPO was applied as the immediate release coating polymer, and Eudragit® RS, Eudragit® RL were used as the extended release coating polymers. Acryl-EZE and Eudragit® L100-55 serve as the delayed release coating polymers. Talc powder was purchased from Mallinckrodt Baker Inc. (Canada), used as the anti-adherent agent together with colloidal silicon dioxide, with the aim of facilitating the coating process. Red dye (FD&C RED NO.40), blue dye (BLUE#1 LAKE) and yellow dye (FD&C YELLOW NO.6) were supplied by Food Ingredient Solutions LLC (UK).

4.1.2. Plasticizers

Polyethylene glycol 400 (PEG 400) was supplied by EMD Chemicals Inc. (Ontario Canada). Triethyl citrate (TEC) was purchased from Caledon Laboratories Ltd. (Ontario Canada). The selections of liquid plasticizers were according to their ability of decreasing the glass transition temperature (T_g) of the coating polymers. Therefore, PEG 400 was chosen as the liquid plasticizer for Eudragit® EPO, Eudragit® L100-55 as well as Acryl-EZE, and TEC selected as the one for Eudragit® RS and Eudragit® RL[54].

4.1.3. MCC Pellets

The microcrystalline cellulose (MCC) pellets were provided by Asahi Kasei Chemicals Cooperation. The pellet applied were of two sizes, 0.1-0.3 mm and 0.5-0.7mm.

4.2. Apparatus

Originated from the fluidized bed, rotating fluidized bed (RFB), a novel apparatus was created by our research group to realize dry powder coating of small dosage forms. [63]

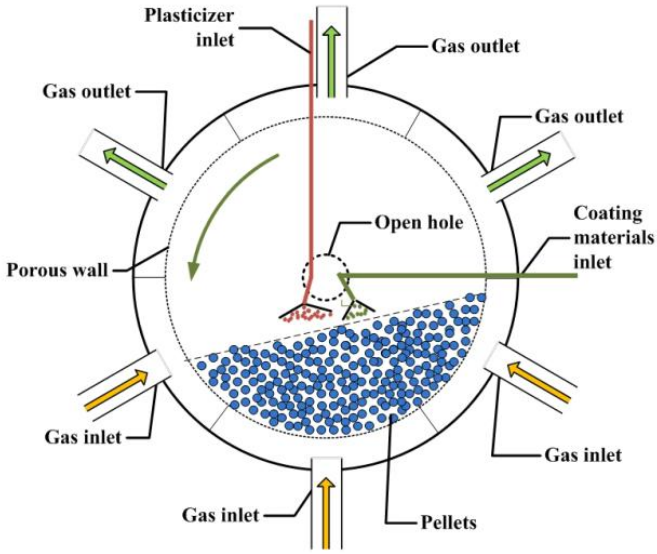


Figure 4.1. Schematic of the RFB

Figure 4.1 reveals the horizontal schematic of the rotating fluidized bed along with the rotating axis. Lying horizontally, the rotating part of the RFB is a cylindrical tank (diameter = 12 cm, depth = 10 cm), of which the cover is removable for material loading. In the center of the cover, there locates an open hole (2 cm) that acts as the inlet of coating powders and plasticizers. Two layers compose the cylindrical tank, the outer one being made of acrylic and inner one being covered with porous material, mesh (size 100 μm, made of stainless steel). Between the two layers, there exist six

chambers, three serving as the inlet of fluidizing air and three as the outlet, when rotating, they work as inlet and outlet alternately. The rotation speed and temperature of the tank can be controlled, the latter one depends on the fluidizing air, which is introduced through the backside of the rotating tank and then circulates in the tank.

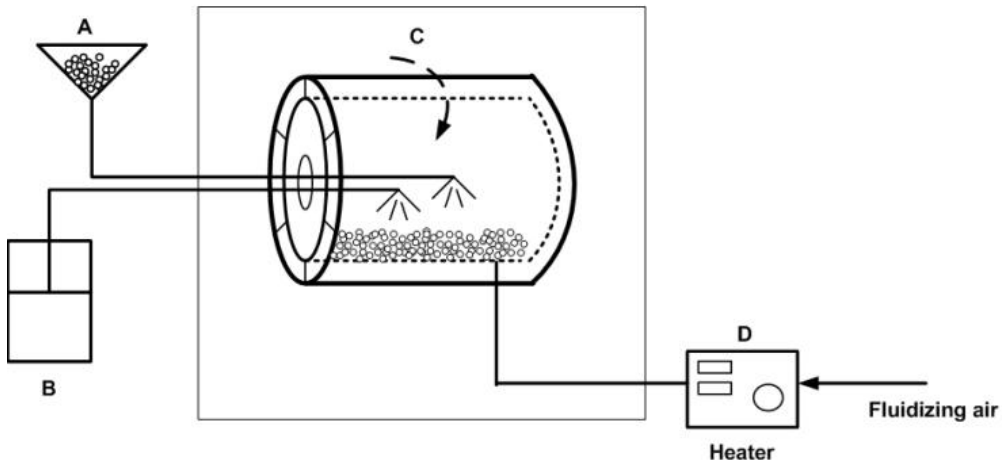


Figure 4.2. Schematic of the RFB system:

(A) Coating materials feeder, (B) Liquid plasticizer spraying system, (C) Rotating fluidized bed, (D) Fluidizing air heating and introducing system

As Figure 4.2 shows, four major parts constitute the RFB: the coating materials feeder, the liquid plasticizer spraying system, the fluidizing air heating and introducing system.

As an innovative apparatus, the RFB has various advantages:

1). The processing time can be saved to only 2-3 hours, while conventional solvent-based coating methods normally take 10-20 hours, given the the same coating level.

2). The processing temperature is largely reduced, compared to the conventional solvent-based coating methods.

3). The flow rate of fluidizing air in the RFB is greatly decreased, compared to that of liquid-based coating in the fluidized bed coater.

4). Due to the porous material (mesh) that covers the inner layer of the rotating tank, the moisture can be released efficiently.

5). Combining the rotation and the fluidizing air can eliminate the agglomeration of pellets.

6). The smoothness of pellets surface can be improved due to the ability of the fluidizing air to blow the unattached coating powders away from the surface of the pellets.

Overall, the drug loading or coating procedure comprises five steps:

1). Preparation of fomulation

This preparation phase refers to blending the polymers (Eudragit® EPO, Eudragit® RS, Eudragit® RL, Eudragit® L100-55 and Acryl-EZE) with the drug or additives (talc, colloidal silicon dioxide and dye) to get a homogeneous fomulation for drug loading or coating.

2). Preheating of the equipment and pellets

During this stage, 35 g pellets (MCC pellets or drug loaded pellets) were loaded into the rotating cylindrical tank and to warm up the equipment and pellets, the fluidizing air was introduced at a flowrate of 20 L/min, temperature was set to be 40 ℃. Additionally, the rotating speed of the RFB was 50 rpm.

3). Liquid plasticizer spraying

Once the temperature of the pellets achieved the given temperature, 40 ℃, the liquid plasticizer was sprayed onto the pellets at a given flow rate from an atomizing nozzle (internal diameter: 1 mm, channel length 3.0 cm). This step takes about 30 to 40 seconds based on polymers that are to be applied. What is worth mentioning is that pellets tend to get sticky when spraying liquid plasticizers, hence increasing the rotating speed to around 70 rpm before

spraying can effectively avoid the agglomeration. Furthermore, to avoid the blow-away of coating materials, the fluidizing air was stopped before the spraying step.

4). Coating materials feeding

Immediately after the spraying step, a certain amount of coating materials (usually 1.5-2.5 g) was delivered into the cylindrical tank. Normally, the spraying and feeding steps are repeated for several times until enough powders are deposited on the pellets. The interval is usually 10 min, during which the fluidized air is reintroduced at the temperature of 40 ℃ and at a flowrate of 20L/min. Besides, the rotating speed of the RFB was 50 rpm.

5). Curing

This refers to the formation of a uniform and stable coating film, during which the fluidized air is introduced at the temperature of 50℃ or 60℃ (for delayed-release polymers) and at a flowrate of 35L/min. Besides, the rotating speed of the RFB was 50 rpm.

Eventually, the coating level (%) was defined as the weight gain of coated pellets over that of uncoated ones, as illustrated in the equation below:

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

4.3. Particle Size Reduction and Analysis

During the drug loading and coating fomulation preparation, it is of vital importance to reduce particle size for the polymer powders so as to achieve a uniform film

coating. A blade grind mill was used as the particle size reduction apparatus, and an ultrasonic sieving (HK Technologies Ultrasonics Rugby, United Kingdom) was employed in selection of the powders with ideal size.

A particle size analyzer (TSI Corporation, Model 3603, Shoreview, MN, USA) was employed to validate the particle size of powders after size reduced. The volume average diameter D[4,3] was used as the mean particle size. The calculation equation is as below:

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

The particle size tests were implemented three times. The mean particle sizes of powders were revealed in Table 4.1.

Table 4.1. Particle size of polymers and additives

Powders	Average particle size, D[4,3] (μm)
Eudragit® EPO	13.3
Eudragit® RS	47.7
Eudragit® RL	40.8
Acryl-EZE	20.5
Eudragit® L100-55	23.0
Talc	28.9

4.4. Glass Transition Temperature

Differential scanning calorimetry (DSC) analysis (Mettler Toledo, DSC822, Mississauga, Canada) was employed to study the glass transition temperature (T_g) of both raw polymers and polymers with liquid plasticizers. Each sample (10 mg) was heated at the rate of 2°C /min under a nitrogen atmosphere with the range from 20 °C to 200 °C. For each sample, the test was validated twice[64]. The DSC results are shown in Table 4.2. As T_g is normally a temperature range, hereby the midpoint data is shown.

Table 4.2. T_g of polymers with and without plasticizer

Polymers	Plasticizer	T_g without plasticizer (°C)	T_g with plasticizer (°C)
Eudragit® EPO	PEG400	58	50
Eudragit® RS	TEC	62	45
Eudragit® RL	TEC	59	46.5
Acryl-EZE	PEG400	85	55
Eudragit® L100-55	PEG400	85	55

4.5. SEM Characterization

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

4.6. In-vitro Drug Release Testing

The release of 5-ASA from coated pellets was determined by the standard paddle dissolution method, using the United States Pharmacopeia (USP) apparatus (Apparatus 2, paddle; Huanghai Rcz-6c2, Shanghai, China).

For Eudragit® EPO coated pellets, the drug release media was 900 mL of 0.1 N HCl solution under the temperature of 37 ^{o}C and the rotation speed of the paddle was 100 rpm. For Eudragit® RS and Eudragit® RL coated pellets, the drug release media was 900 mL of pH 7.2 phosphate buffer solution under the temperature of 37 ^{o}C and the rotation speed of the paddle was 50 rpm. For Acryl-EZE or Eudragit® L100-55 coated pellets, the dissolution test was specially performed with a change in the dissolution media: starting with 0.1 N HCl (pH 1.0) for 2 h followed by phosphate buffer (pH 7.2) at 37 ^{o}C, the rotation speeds of the paddle were 100 rpm and 50 rpm, respectively.

During the process, samples were collected by a 10 mL syringe at predetermined intervals and followed by the replacement of 10 mL of fresh release media. After filtered, 5-ASA content of the samples were analyzed with an 8453 UV-Visible Spectrophotometer (Agilent Technologies, Mississauga, Canada) at wavelengths of 300 nm for pH 1.0 HCl solution (0.1 N) and 330 nm for pH 7.2 phosphate buffer solution.

4.6.1. Standard Curve

The drug release standard curves of 5-ASA at the wavelengths of 300 nm and 330 nm are demonstrated in Figure 4.3 and Figure 4.4, respectively. Data for known concentrations of 5-ASA are used to make the standard curve, plotting concentration on the X axis, and the assay measurement on the Y axis. The same assay is then performed with samples of unknown concentration. To analyze the data, one locates the measurement on the Y-axis that corresponds to the assay measurement of the

unknown 5-ASA and follows a line to intersect the standard curve. The corresponding value on the X-axis is the concentration of 5-ASA in the unknown sample. The curves help calculating unknown concentrations of 5-ASA samples collected from the in-vitro drug release testing.

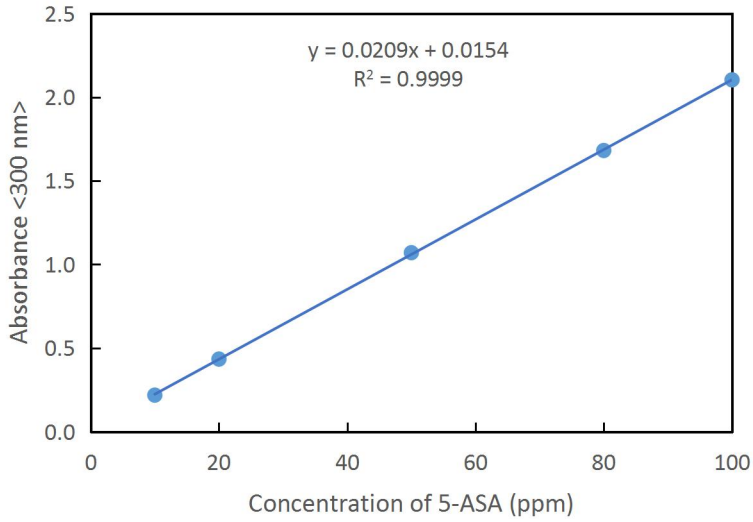


Figure 4.3. Standard curve of 5-ASA (wavelength=300 nm)

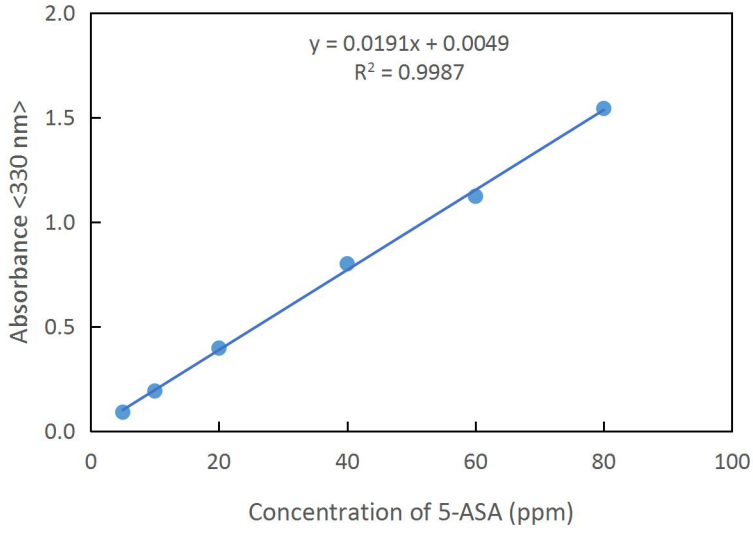


Figure 4.4. Standard curve of 5-ASA (wavelength=330 nm)

4.6.2. UV-Vis Spectrophotometer Validation

UV-vis spectrophotometer was applied for measuring and analyzing the drug release from 5-ASA pellets, thus its acceptability validation of application requires precision test, accuracy (recovery) test and stability test.

To ensure the maximum absorbency wavelength, two buffer solutions containing 5-ASA were scanned by the UV-vis spectrophotometer, as a result, for the release media of pH 1.0 HCl solution (0.1 N) and pH 7.2 phosphate buffer solution, the wavelengths are 300 nm and 330 nm, respectively.

With the maximum absorbency wavelength of different release media with known concentration confirmed, the three mentioned tests were implemented for both the two release media.

1). Precision test

Three same solution samples with known concentration of 5-ASA (less than the maximum absorbency concentration of the standard curve) were prepared. Then scanned a defined amount of each sample. The standard error among the three samples that collected from the UV-vis spectrophotometer output determines the standard of the precision test. The precision test is regarded as successful when the standard error is smaller than 1%.

The equation for the calculation of standard error is:

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

2). Accuracy (recovery) test

Samples of three different known 5-ASA concentrations were prepared, which were low, medium and high. Then scanned a defined amount of each sample. The accuracy test is defined as the difference between the true value and the mean experimental value of the release data within a confidence interval. Each of the three concentration samples requires the accuracy test, thus the tests give an overall accuracy of the UV-vis spectrophotometer.

The calculation equation of percentage difference is:

$$\text{Percentage Difference} = \frac{\text{True value - Mean experimental value}}{\text{True value}} * 100\%$$

3). Stability test

In the stability test, a solution sample of known 5-ASA concentration (less than the maximum absorbency concentration of the standard curve) was prepared and put into a chamber of the dissolution tester under the temperature of 37°C. Each sample was collected with a 10 mL syringe at predetermined intervals (0 h, 1 h, 2 h, 6 h, 12 h) and then scanned. The sample of 0 h was regarded as the basis. If the experimental values of the samples throughout 12 hours stayed constant within a very tiny error, compared to the 0 h basis, the accuracy test succeeded.

Chapter 5

(5-ASA)-Loading of MCC Pellets

5.1. Introduction

To achieve pellets containing 5-ASA, powder-layering technique in RFB (rotary fluidized bed) was applied in this study. The powder-layering process comprises two stages: applying loading materials which contain 5-ASA and curing. The critical stage with respect to the loading efficiency is the first phase whereas the curing phase is decisive for the film formation. Particularly, the first phase is implemented repeatedly, the reason for this is as follows: a high loading efficiency can be achieved when a low feeding/spraying rate is used during the layering phase[61], which means that breaking the whole process into repeated loading steps can enhance the powders' cohesion and adhesion on pellets and prevent the entrainment of loading materials by the air stream passing through the fluidized bed. Besides, the repeated application also prolongs the coating phase: since the penetration of the plasticizer into the polymer requires certain time, the improved plasticizing effect of the plasticizer arises from several intervals among per application, thus increase the stickness of the polymer.

During the development, microcrystalline cellulose (MCC) was selected as the core, different loading materials were used to mix with 5-ASA for reaching desired drug-loading efficiency.

In the powder-layering technique, loading efficiency refers to the amount of 5-ASA actually loaded on pellets compared to the feeding amount. The actual amount was evaluated by dissolution test implemented in pH 7.2 phosphate buffer solution under the temperature of 37 ^{o}C and the rotation speed of the paddle was 50 rpm, given 5-ASA is determined to take effect in the environment of pH around 7.2. In terms of

optimization of the layering process, a high loading efficiency, on which other properties like film thickness depend, can be regarded as the most significant for an efficient layering process.

To improve the loading efficiency, factors like loading material content, pellet size, excipient, plasticizer flowrate, curing time and process temperature were also taken into consideration. The aim of this chapter is the investigation of the parameters mentioned above with respect to the loading efficiency.

5.2. Improvement of the (5-ASA)-Loading Process

5.2.1. Loading Material

To load pellets with 5-ASA, polymers work as carrier, blended with 5-ASA of certain ratio (2% of total loading material mass). Three polymers were applied to investigate the proper loading material: Eudragit® EPO, Eudragit® RS and Eudragit® RL mixture (1:1) and Acryl-EZE. The detailed fomulations were as shown in Table 5.1, 5.2 and 5.3, among which the talc and colloidal silicon dioxide serve as the anti-adherent agent and the dye is aiming at a better observation of film formation.

Table 5.1. Loading fomulation of Eudragit® EPO

Fomulation	Composition (wt%)
Eudragit® EPO	19.6 (or 39.0)
Talc	77.4 (or 58.0)
Colloidal silicon dioxide	0.5
Dye	0.5
5-ASA	2.0

Table 5.2. Loading fomulation of Eudragit® RS and Eudragit® RL

Fomulation	Composition (wt%)
Eudragit® RS	39.0
Eudragit® RL	39.0
Talc	19.0
Colloidal silicon dioxide	0.5
Dye	0.5
5-ASA	2.0

Table 5.3. Loading fomulation of Acryl-EZE

Fomulation	Composition (wt%)
Acryl-EZE	97.5
Dye	0.5
5-ASA	2.0

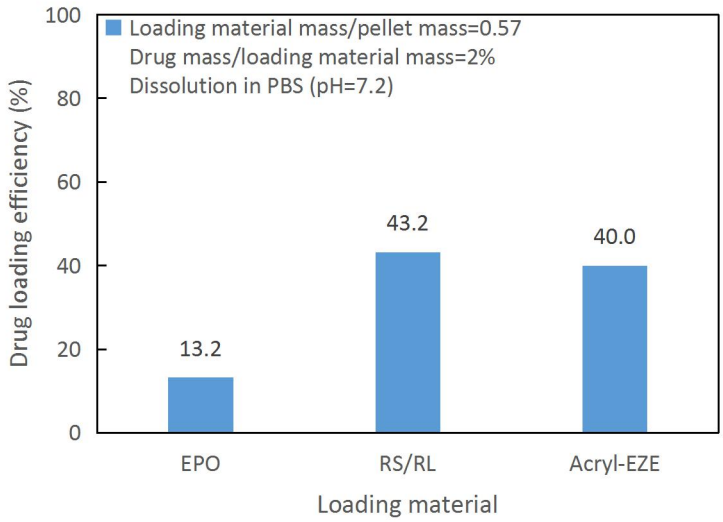


Figure 5.1. The effect of loading material on drug loading efficiency

As shown in Figure 5.1, with same amount of loading material (57.0% compared to pellet mass) used to load 5-ASA on pellets, three fomulations demonstrated different loading efficiencies, among which Eudragit® RS and Eudragit® RL mixture (1:1) were preferred (43.2%), while Eudragit® EPO only reached 13.2%, attributed to the fact that it dissolves in solutions with pH up to 5.5. Besides, Acryl-EZE showed a slightly lower loading efficiency (40.0%) compared to Eudragit® RS and Eudragit® RL mixture (1:1) since Acryl-EZE normally serves as a polymer that helps delaying drug release. These phenomena can be illustrated by that the loading materials help loading 5-ASA on the pellet due to their well-known capability of being layered onto MCC pellets and the correspondence with plasticizers. This helps dispensing the API uniformly into polymer powders to make the layering more even onto MCC pellet surfaces. Considering the loading polymers' solubility and majority in the loading fomulation compared to the 5-ASA content, they can be obstacles of drug release when released in the dissolution media.

5.2.2. EPO Content

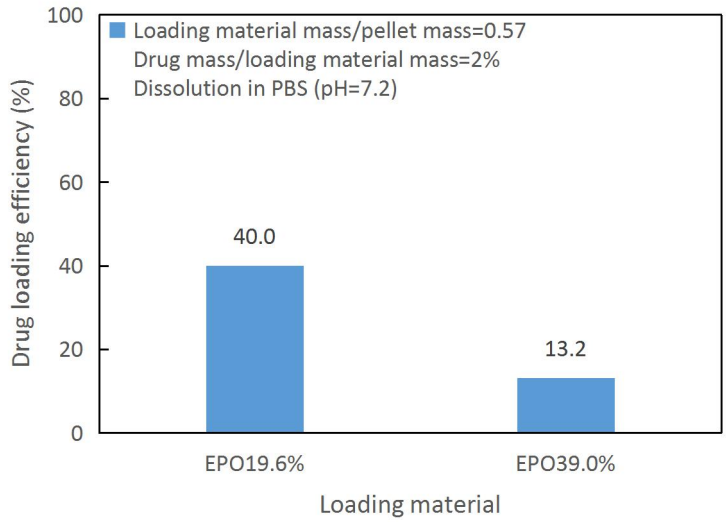


Figure 5.2. The effect of Eudragit® EPO on drug loading efficiency

To further confirm the phenomenon mentioned above, two different ratios of Eudragit® EPO compared to total loading material were studied (19.6% and 39.0%). As seen in Figure 5.2, the fomulation containing lower content of Eudragit® EPO (19.6%) improved the loading efficiency, from 13.2% to 40.0%. This again proved that Eudragit® EPO was not a sensible option for facilitating the loading of 5-ASA due to its insolubility in media that has pH higher than 5.5.

5.2.3. Pellet Size

To investigate the effect of pellet size on loading efficiency, two sizes (100-300 μm and 500-700 μm) of MCC pellets were used as the cores of loading. Two different loading fomulations, Eudragit® RS and Eudragit® RL mixture (1:1) and Eudragit® EPO (39.0%) were applied respectively to achieve a convincing result.

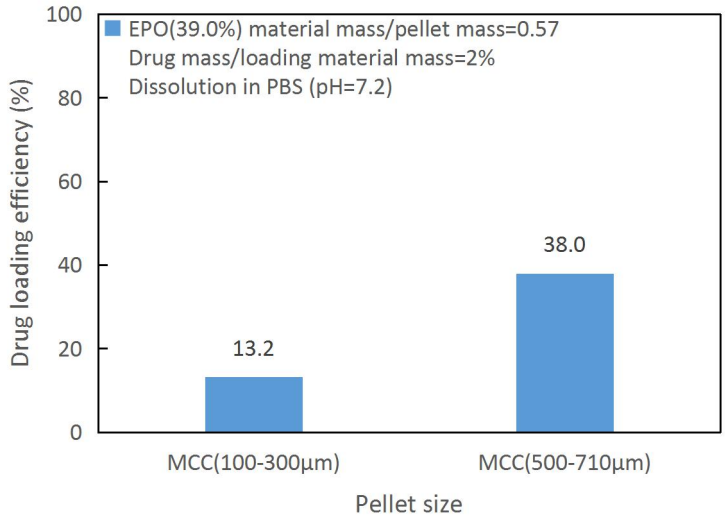


Figure 5.3. The effect of pellet size on drug loading efficiency

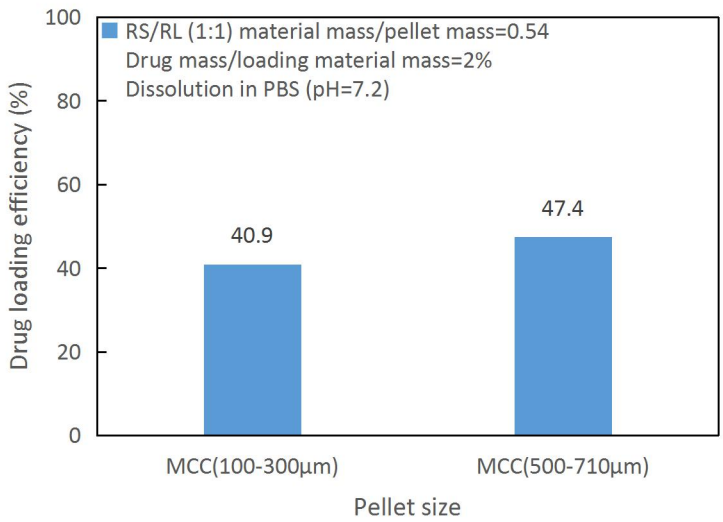


Figure 5.4. The effect of pellet size on drug loading efficiency

From Figure 5.3 and Figure 5.4, it is obvious that MCC pellets of larger size (500-700 µm) demonstrated better loading performance, regardless of loading material. Furthermore, as can be seen Figure 5.5, apparently, for the pellets of size 500-700 µm (Figure 5.5, B), loading materials were layered more evenly on the pellet surface. This can be illustrated as that given the same total pellet mass in a batch, the

larger the pellet diameter, the less pellet amount in total, the smaller surface area in total, which certainly resulted in more drug powders distributed on each pellet when the loading materials of the same amount were applied.

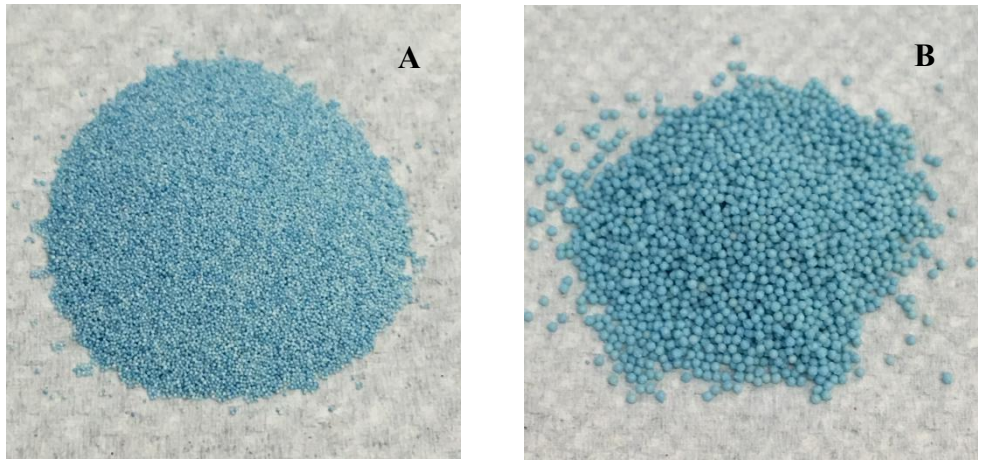


Figure 5.5. Photos of 5-ASA loaded pellets of different sizes:
(A) size: 100-300 μm (B) size: 500-700 μm

5.2.4. Excipient

During the drug loading process, there are some excipients involved in the fomulation, among which dye was applied to make the observation of the process easier. Dye should be simply making the observation of pellets easier, without any interference with loading materials on the loading efficiency. Thus the following investigation is to make sure that the applied dye doesn't have obvious influence on the loading efficiency.

In this study, three different dyes were used to see whether they had influence on the loading efficiency or not. For Eudragit® EPO (39.0%) loaded pellets, red dye (FD&C RED NO.40) and blue dye (BLUE#1 LAKE) were applied, compared with a blank sample (no dye). Theoretically, the data of the ones with dye are expected to be the same with the blank sample. From Figure 5.6, the pellets loaded with blue dye demonstrated a lower loading efficiency than the blank one, this was resulted from

the fact that the applied blue dye is insoluble, thus inhibiting the release of 5-ASA in the dissolution media.

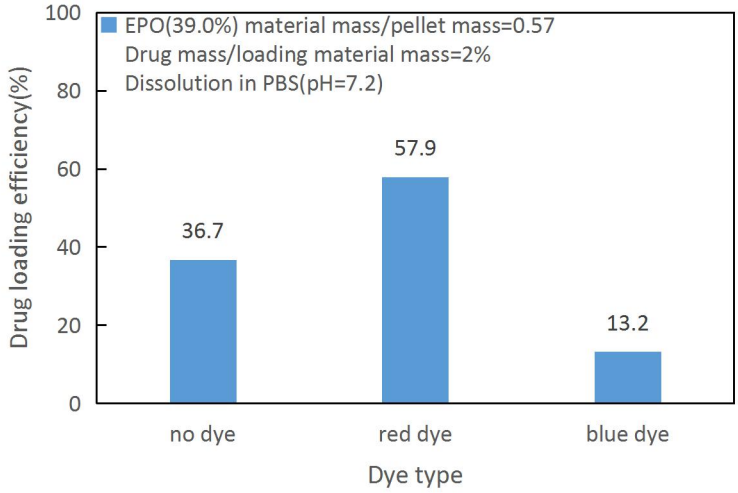


Figure 5.6. The effect of dye on drug loading efficiency

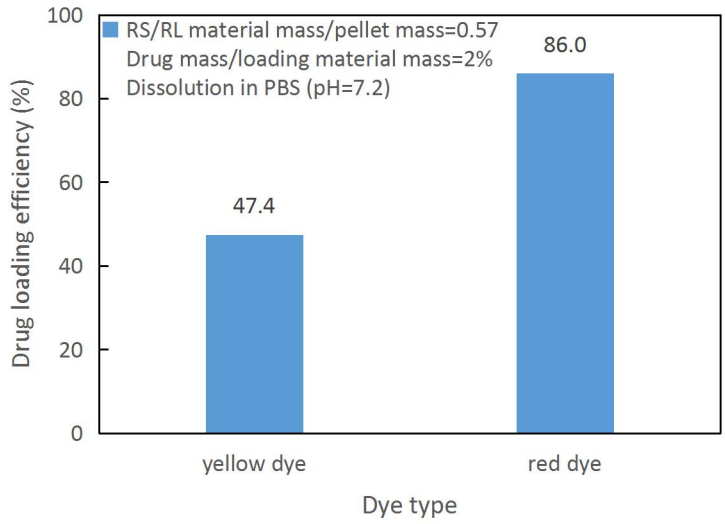


Figure 5.7. The effect of dye on drug loading efficiency

From both Figure 5.6 and Figure 5.7, it can be seen that the pellets loaded with red dye possessed evidently higher loading efficiency, even compared to the blank one, while this is actually due to that the applied red dye has certain absorption at the wavelength of 330 nm, which interferes with 5-ASA when the content was tested by

UV-vis spectrophotometer. Namely, the unexpected absorption of red dye adds to the one of 5-ASA, thus this data acquired from UV-vis spectrophotometer cannot represent the practical 5-ASA content. Therefore, for the preferred Eudragit® RS and Eudragit® RL mixture (1:1) loaded pellets, the applied yellow dye (FD&C YELLOW NO.6) was selected as the proper one.

5.2.5. Plasticizer Flowrate

As discussed in Chapter 3.3, in the powder coating technique, the plasticizers' addition can help avoid the generation of the brittle coating film from pure coating polymers. Thus, advisedly selecting an accurate addition amount can be quite critical. The plasticizer addition amount is composed of two factors: spraying time and flowrate, of which the former one needs to match the loading material amount and plasticizer flowrate, therefore, the latter one can be a key point of the coating process in the RFB. On one side, small spraying flowrate leads to a poor powder adhesion and results in an uncompleted film formation, producing a brittle, discontinuous coating film. On the other side, large flowrate means excessive amount of liquid plasticizer addition immediately and may lead to a sticky problem. Overall, an appropriate spraying flowrate can generate a uniform and strong coating film without the sticky problem.

For Eudragit® RS and Eudragit® RL, Triethyl citrate (TEC) serves as a suitable liquid plasticizer. The feeding amount of MCC pellets was 35 g/batch. With constant spraying time (40 s) of the plasticizer, the amount of plasticizer was varied through modifying the flowrates.

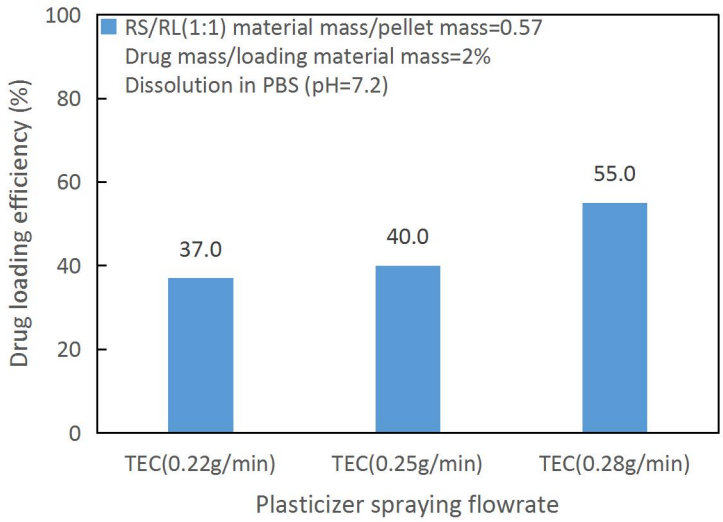
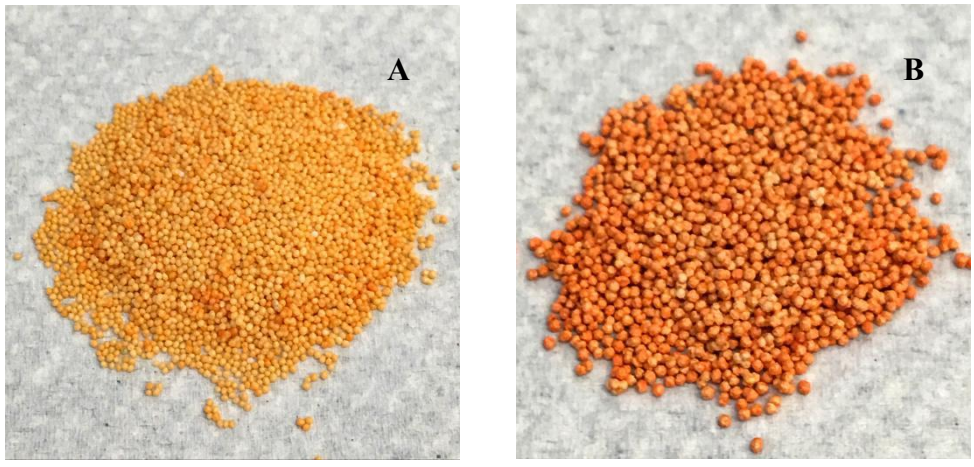


Figure 5.8. The effect of plasticizer flowrate on drug loading efficiency

As shown in Figure 5.8, three spraying flowrates of TEC were applied, including a relatively low one at 0.22 g/min, a medium one at 0.25 g/min and a relatively high one at 0.28 g/min (spraying was performed right before feeding the loading materials). It turned out that a plasticizer flowrate as high as 0.28 g/min can be appropriate for increasing the loading efficiency.



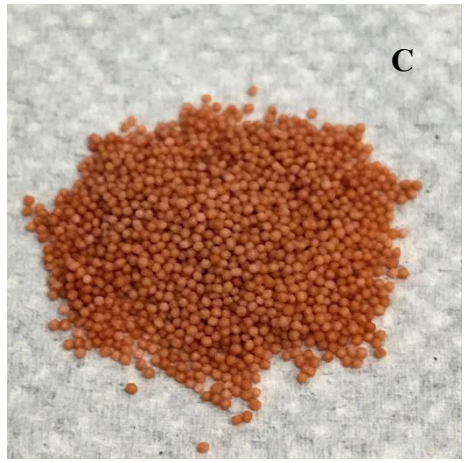


Figure 5.9. Photos of 5-ASA loaded pellets of different plasticizer flowrates: (A) 0.22 g/min (B) 0.25 g/min (C) 0.28 g/min

Also as shown in Figure 5.9, among the three samples with different plasticizer flowrates, the increasing plasticizer flowrate resulted in a more uniform drug layering on pellets.

What is worth noticing though is that a high plasticizer flowrate and high rotating speed of the RFB can decrease the loading efficiency, since both of them facilitate the entrainment of loading materials with the air passing the fluidized bed, in which case the entrained materials are captured in the filter of the RFB.

5.2.6. Curing Time

Curing is a vital step in the whole layering process, when the curing temperature is above the glass transition temperature (T_g) of the coating polymers, there occurs the deformation and viscous flow of the loading polymer particles, thereby the film is created. As the temperature increases, the viscosity of the loading materials goes up and the particles are deformed.

Additionally, the coalescence of the coating particles needs enough time. As seen in Figure 5.10, curing time of 2 h and 3 h were conducted in this study, from which the 3 h-curing turned out to result in a higher loading efficiency (62.0%).

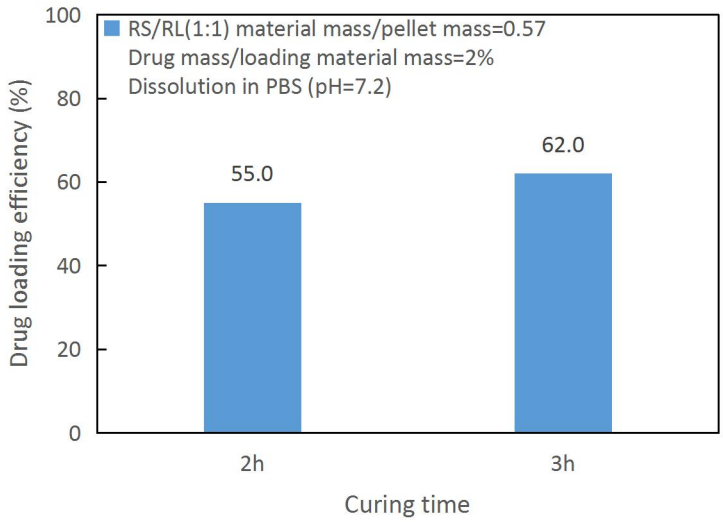


Figure 5.10. The effect of curing time on drug loading efficiency

As the film formation requires a period of time, consequently, increasing the curing time can help strengthen the solution resistance of the pellets effectively when the curing temperature is around or above the T_g of the loading polymers.

5.2.7. Processing Temperature

Apart from the curing time, the temperature, including preheat temperature and curing temperature, also have significant influence on the film formation of the loading materials. The effect of the processing temperature was investigated at the preheat and curing temperature of 30 ℃ and 40 ℃, 40 ℃ and 50 ℃, respectively.

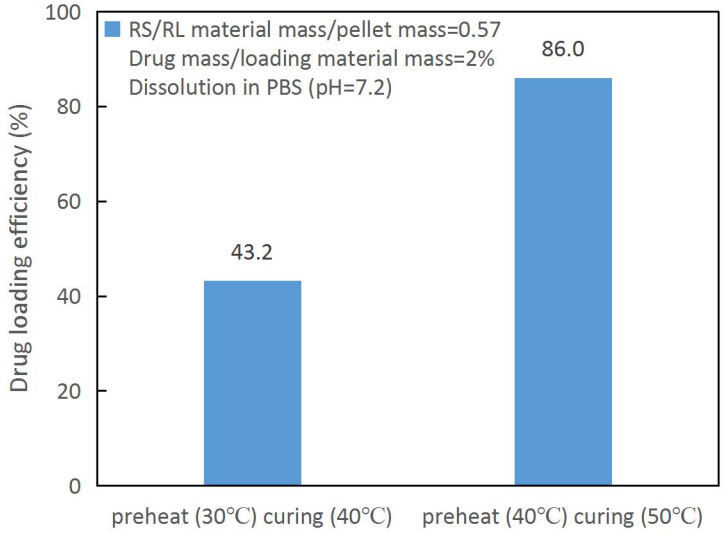


Figure 5.11. The effect of processing temperature on drug loading efficiency

Figure 5.11 indicates that under the condition of preheating at 40 ℃ and curing at 50 ℃, 5-ASA was more likely to be loaded on pellets (loading efficiency: 86.0%), instead of being wasted when preheated at 30 ℃ and cured at 40 ℃ (loading efficiency: 48.2%). This is largely attributed to the difference between curing temperature and T_g of the loading polymer, the deformation and viscous flow of the loading particles tend to happen when the curing temperature is closed to or above the T_g, this can be explained by the fact that at elevated temperatures, the stickier surface of the loading materials facilitates the particle attachment. Furthermore, the enhanced spreading of the plasticizer also promotes particle attachment. Besides, a certain preheat temperature is also essential to warm up the pellets to predetermined condition, which promises a better following loading performance. Additionally, at low processing temperature, the entrainment of loading materials with the air passing the fluidized bed happens more frequently due to the weak adhesion of the loading materials to the cores.

The distinct layering performances at different processing temperatures can be clearly seen in Figure 5.12, of which the product with higher temperature (Figure 5.12, B) show darker color than the other one, indicating better film formation.

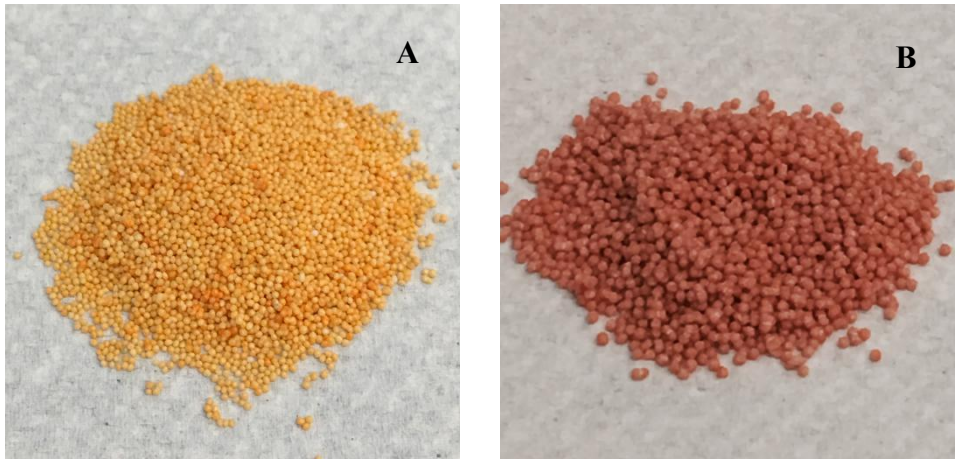


Figure 5.12. Photos of 5-ASA loaded pellets of different processing temperatures:

(A) preheated at 30 ℃ and cured at 40 ℃

(B) preheated at 40 ℃ and cured at 50 ℃

Eventually, various factors contribute differently to the loading efficiency. Interestingly, the air flow rate has reversed effects in the two stages: a low air flow rate reduces the loss of loading materials during the layering phase while favors sticking and deposition of loading materials on the surfaces of the rotatory fluidized bed during the curing phase. Thereby, a low air flow rate increases and reduces the loading efficiency in the two phases, respectively.

Overall, the proper 5-ASA loading condition is as follows: using the fomulation of Eudragit® RS and Eudragit® RL mixture (1:1) with a yellow dye, TEC sprayed with the flowrate of 0.28 g/min, applied on MCC pellets with size of 500-710 μm, preheated at 40 ℃ and cured at 50 ℃ for 3 h. Under the condition above, when 20g loading materials (containing 2% 5-ASA) are applied on 35 g MCC pellets, a loading efficiency of as high as 86.0% can be achieved.

Chapter 6

Extended-release Coating of 5-ASA Pellets

6.1. Introduction

The definition of extended release is to release drug over a prolonged period of time so as to achieve extended therapeutic effect after oral administration. An ideal coating film for a pellet is supposed to be strong and tough, possessing an optimal permeability for water. Besides, sufficient strain and resistance to rupture under high forces are also expected. To fulfill all the above requirements, Eudragit® RL was the most promising polymer, while the disadvantage of its application is too rapid release of the drug from the Eudragit® RL coated pellets, where an extended-release pattern should be observed instead.[65]

In this study, Eudragit® RS and Eudragit® RL were combined to be the coating polymers. Both of them have quaternary groups which are conjugated with the chloride ion in their structures, responsible for hydration and swelling of polymer. Because of the presence of the extra chloride ion, less ion exchange are needed for hydration. [66] Due to the molecular structural characteristics that compared to Eudragit® RS, Eudragit® RL has double content of quaternary ammonium groups, hence shows a higher permeability. Once contacting the solution, the quaternary ammonium groups can be ionized, resulting in the swelling and opening pores of the coating. Namely, given more amounts of ammonium groups exist in Eudragit® RL, by adding Eudragit® RL in the fomulations, swelling in the dissolution media could be increased. Consequently, increasing the ratio of Eudragit® RS can improve the extended effect. Accordingly, Triethyl citrate (TEC) was selected as the liquid plasticizer to reduce the glass transition temperature (T_g) of the coating polymers.

6.2. Development

Table 6.1 demonstrates the overall composition of the extended-release coating fomulations, where the sum of Eudragit® RS and Eudragit® RL was 80.0%, additives including talc, colloidal silicon dioxide and a yellow dye make up the remaining 20%. The talc and colloidal silicon dioxide serve as the anti-adherent agent and the dye is aiming at a better observation of film formation.

Table 6.1. Coating fomulation of Eudragit® RS and Eudragit® RL

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

To develop a perfect coating fomulation, four different ratios (1:1, 2:1, 4:1 and 1:0) of Eudragit® RS and Eudragit® RL were investigated in this study, with various coating levels, respectively.

The results were evaluated by the dissolution test implemented in pH 7.2 phosphate buffer solution under the temperature of 37 ^{o}C, and the rotation speed of the paddle was 50 rpm. The created cumulative release profiles indicated the coating performances.

What is noticeable is that different coating levels were achieved subsequently, which is to say, the coating and curing process were implemented for several times until desired release profiles were reached. Consequently, the higher coating level, the

more coating films on the pellets, namely, multi-coated pellets are the study object in this investigation.

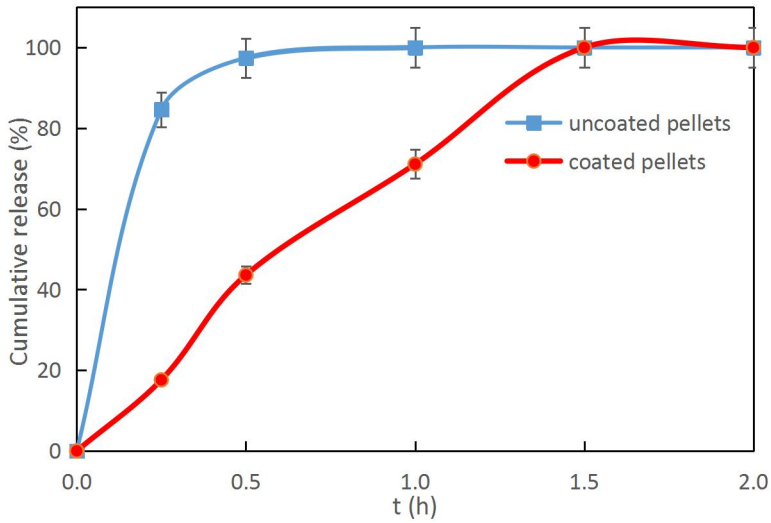


Figure 6.1. The effect of coating on drug release profiles

As Figure 6.1 shows, when dissolved in pH 7.2 phosphate buffer solution, the uncoated pellets behave as an immediate release dosage form. This phenomenon can be illustrated as no excipient in the composition with features that modify drug release. On the contrary, the Eudragit® RS/RL coated pellets demonstrate an obvious extended effect on drug release profiles.

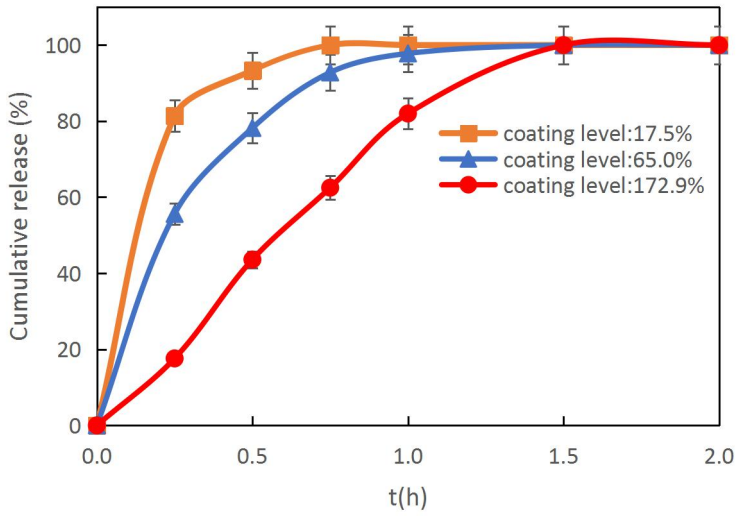


Figure 6.2. The effect of Eudragit® RS/RL (1:1) on drug release profiles

For the pellets with coating levels of 17.5%, 65.0% and 172.9%, all the drug release profiles in the pH 7.2 phosphate buffer solution reveal an extended drug release which is due to the action of time-dependent swelling of Eudragit® RS and Eudragit® RL in coating films.

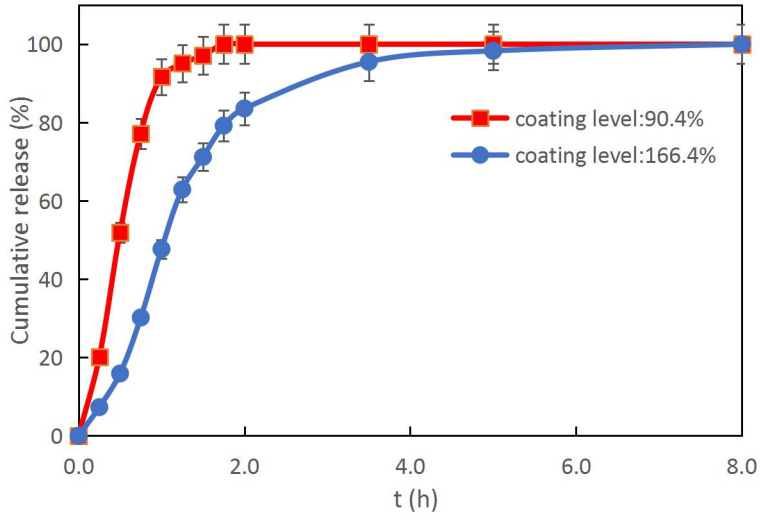


Figure 6.3. The effect of Eudragit® RS/RL (2:1) on drug release profiles

As the ratio of Eudragit® RS/RL in the fomulation increased to 2:1, it can be seen that compared to the former fomulation (Eudragit® RS/RL 1:1), with similar coating

level (172.9% in the former and 166.4% in the latter), the latter one reached a plateau (5.5 h) 4 hours later than the former one (1.5 h), which indicates a better extended release profile. Apparently, the lower permeability of the coating film with the fomulation of more Eudragit® RS was responsible for the phenomenon.

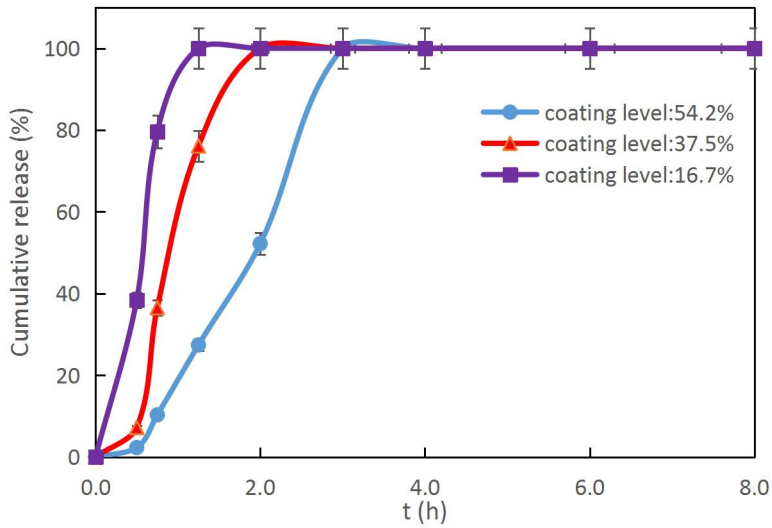


Figure 6.4. The effect of Eudragit® RS/RL (4:1) on drug release profiles

As can be seen in Figure 6.4, the lag time of drug release was obviously extended with an increasing coating level. In theory, a hydrostatic pressure can be created in the coated pellets once contacted with the release medium. And the cracking of coating film occurs when the hydrostatic pressure is over its mechanical stability. Therefore, the release profiles of lower coating levels performed faster film cracking behavior, where the coating films cannot withstand the hydrostatic pressure generated inside the pellets. With the film cracking, the drug release was mainly dominated by the diffusion through water and thereby led to faster release rate. Eventually, through higher coating level, namely, more layers of coating film, the stronger capability of withstanding the dissolution media can be achieved.

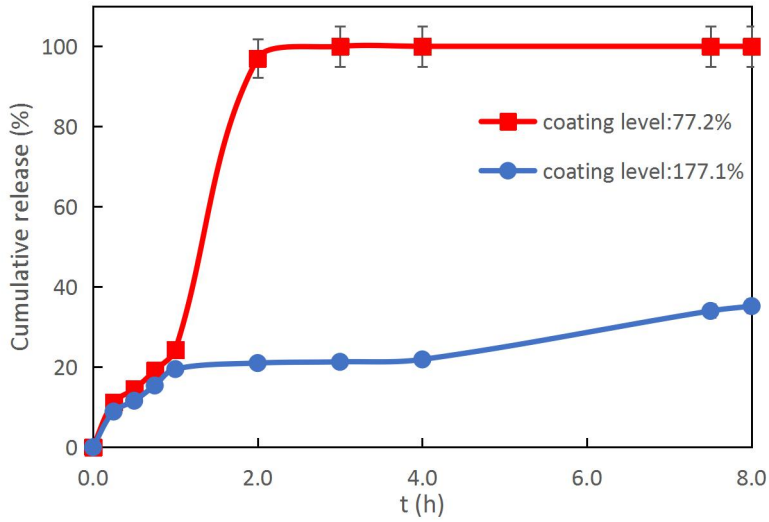


Figure 6.5. The effect of Eudragit® RS/RL (1:0) on drug release profiles

Particularly in Figure 6.5, when the coating level reached 177.1%, the film could not crack completely even if in 8 hours, which meant the pellets were over-coated so that 5-ASA could not be released in a proper period of time. This certainly indicates that when Eudragit® RS was used alone, low permeability of the coating film could be more likely to be achieved, thus the coating level had to be controlled under specific limitation.

6.3. Optimization Attempt

To investigate a proper fomulation for extended-release coating, other than the one with barely Eudragit® RS, the other three were compared.

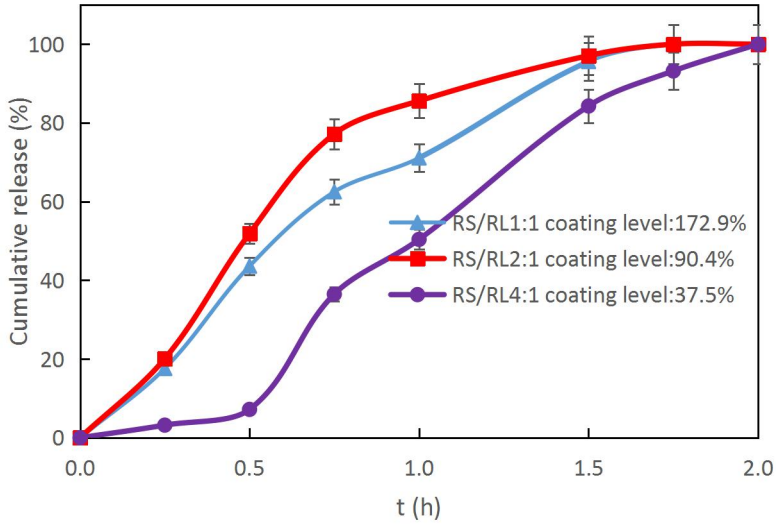


Figure 6.6. The effect of Eudragit® RS/RL ratio on drug release profiles

As demonstrated in Figure 6.6, to release 5-ASA in 2 hours, different coating levels were implemented for coating fomulations with different ratios of Eudragit® RS and Eudragit® RL: 172.%, 90.4% and 37.5% for 1:1, 2:1 and 4:1, respectively. The higher content of Eudragit® RS in fomulation, the lower coating level was required. Namely, the drug release at pH 7.2 was slowed by the addition of Eudragit® RS in the coating fomulation, this confirms that Eudragit® RS had lower water permeability and the pellets coated with higher content of it is correspondingly expected to decrease the drug-release rate. Evidently, Eudragit® RS and Eudragit® RL with ratio of 4:1 can be an appropriate fomulation to improve the extended-release coating for 5-ASA pellets.

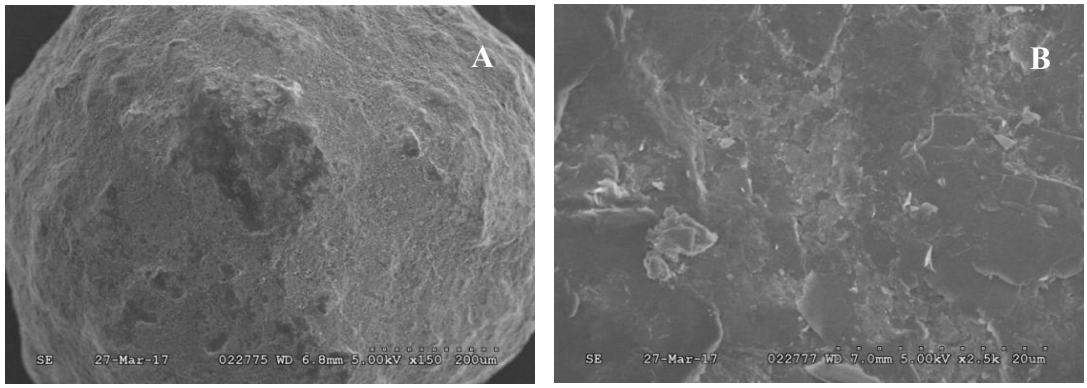


Figure 6.7. SEM micrographs of Eudragit® RS/RL (4:1) coated 5-ASA pellets

Scanning electron microscope (SEM) was employed to observe the film formation of the Eudragit® RS/RL (4:1) coated pellets with a coating level of 54.2%. The surface were shown in Figure 6.7, in two magnifications, 150 and 2500, respectively. It can be seen that the coating fomulation helped form a continuous and dense coating film, where even though exists scaly structure, indicating a desirable film formation as a whole.

Overall, the ratio of Eudragit® RS and Eudragit® RL in the coating fomulation plays a significant role in regulating the release behavior of 5-ASA coated pellets. Accordingly, the fomulation with Eudragit® RS/RL ratio being 4:1 and the coating level being 54.2% would be a promising candidate for desired extended-release 5-ASA pellets.

6.4. Evaluation

In pharmaceutical industry, stability of a product refers to its ability of maintaining physical, chemical, microbiological, toxicological, protective and informational characteristics in a specific container/closure system. Various factors have to be taken into consideration in the stability test, for instance, stability of the active ingredients, interaction between active ingredients and excipients, dosage form types as well as manufacturing, packaging and shipping conditions which involve light, heat and moisture. Since the stability test evaluates environmental influence on

pharmaceutical products, it certainly can be informative to predict shelf life and determine proper storage conditions, thereby providing advisable requirement for regulatory approval of the product.[67]

Similarly in this study, the interest of testing the stability of coating film arose, thus a so-called accelerated stability test was performed according to the United States Pharmacopoeia (USP). 2 g of samples were put into plastic bottles and sealed with parafilm at the cap. The bottles were put into a vacuum dryer, of which the RH (relative humidity) was controlled to be 75% by using saturated NaCl solution and then in an oven, of which the temperature was set to be 45 ℃. Under such condition, the products were stored for a month, and after this, they were retested for dissolution. Therefore, the release profiles of the same sample before and after the one-month storage mentioned above were compared to determine whether the coating film was stable or not. If the two curves were similar, the film was regarded as stable, which meant a qualified coating, and vice versa.

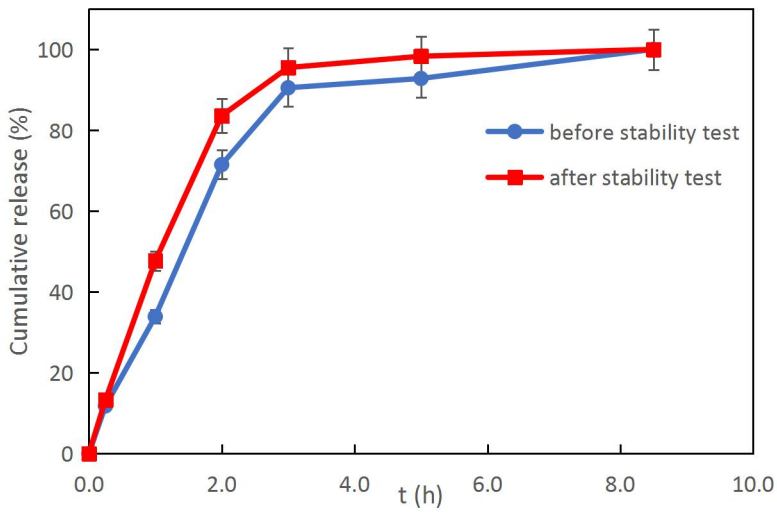


Figure 6.8. The effect of Eudragit® RS/RL (4:1) on drug release profiles (coating level: 54.2%)

From Figure 6.8, when the coating level reached 54.2%, the fomulation of Eudragit® RS and Eudragit® RL (4:1) resulted in a qualified coating as the release of 5-ASA was slightly accelerated, which stayed within the tolerance.

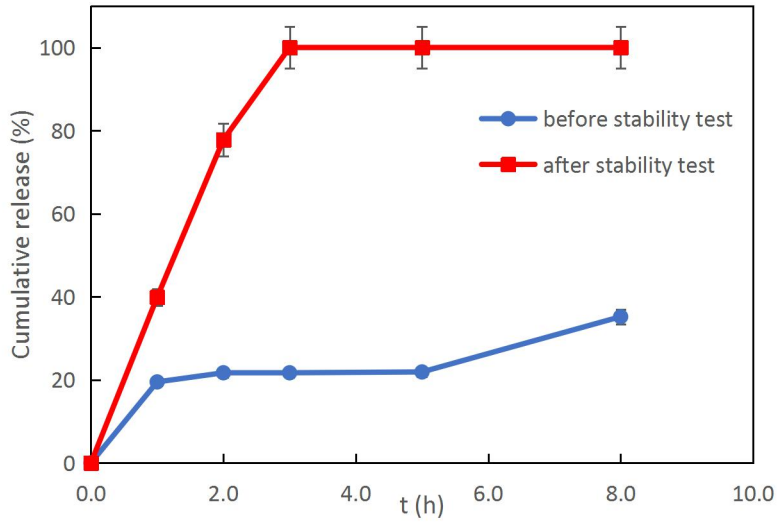


Figure 6.9. The effect of Eudragit® RS/RL (1:0) on drug release profiles (coating level: 177.1%)

Meanwhile, for the one with ratio of 1:0, when the coating level was 177.1%, the product which had undergone accelerated stability storage demonstrated a distinct release profile, as can be seen in Figure 6.9. This phenomenon indicated that the coating failed and again proved that a too high coating level of only Eudragit® RS would prevent 5-ASA from releasing in a proper period of time.

Admittedly, Eudragit® RS/RL (4:1) turns out to be a appropriate fomulation, which not only reaches a desirable extended release profile, but also helps form a stable coating for 5-ASA pellets.

Chapter 7

Delayed-release Coating of 5-ASA Pellets

7.1. Introduction

Compared to any other region of the gastroinstestinal tract (GI tract), the colon has the highest pH, thereby a dosage form that disintegrates preferentially at high pH levels can be an excellent candidate for site-specific delivery into this region. Consequently, such pH dependent systems enjoy great popularity in colon targeting. To design a pH dependent multiparticulate colon specific delivery system, one of the simplest approaches is equipping pellets with enteric coatings, which are also known as delayed-release coatings.[68]

Delayed release can be defined as delaying release until specific regions of the GI tract are reached, for instance, the colon. Through reducing the penetration rate of water into pellets, these delayed-release coatings can facilitate delaying the onset of release without possibly impacting on the mechanism involved. [69]

In this study, Acryl-EZE and Eudragit® L100-55 were selected as coating polymers, of which the latter one was the main component of the former one. As mentioned in section 3.2.2, they are capable of dissolving in the solution with pH above 5.5, due to the pH-sensitive property of them, they were selected to avoid the rapid dissolution of 5-ASA during the initial transit of the pellets through the gastric cavity. Accordingly, Polyethylene glycol 400 (PEG 400) was chosen to be the liquid plasticizer to reduce the glass transition temperature (T_g) of the coating polymers.

7.2. Development

In this study, a fomulation comprising Acryl-EZE was used to investigate delayed-release coating. Table 7.1 depicts the composition, where Acryl-EZE takes up 99.0% as it is a full-fomulation coating material, a yellow dye makes up the remaining 1.0%, aiming at a better observation of film formation.

Table 7.1. Coating fomulation of Acryl-EZE

Fomulation	Composition (wt%)
Acryl-EZE	99.0
Yellow dye	1.0

For delayed-release coating, the acid resistance test is of vital significance to determine whether the coating is qualified or not, and it is characterized by the cumulative drug release percentage in 0.1 N 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.

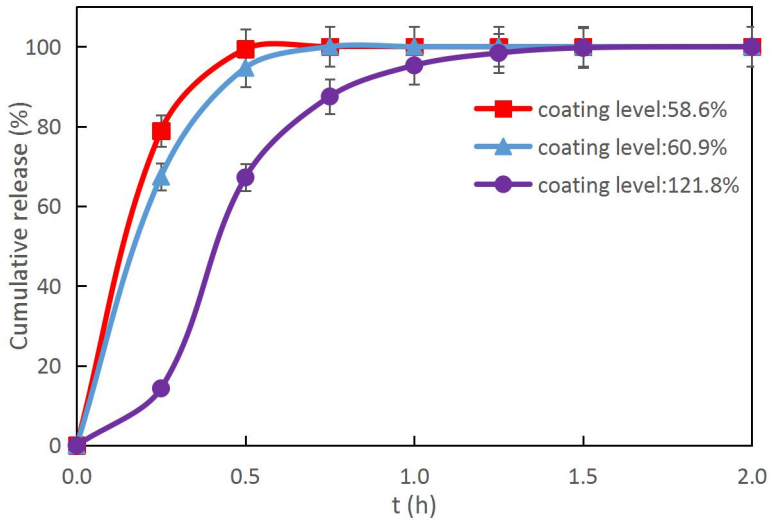


Figure 7.1. The effect of Acryl-EZE on drug release profiles

As shown in Figure 7.1, as the coating level of the coating film increased, the acid-resistant property of coating film was enhanced, while the coating of this fomulation failed in reaching delayed release for all the three coating levels: 58.6%, 60.9%, 121.8%. This may be attributed to the fact that the applied Acryl-EZE was beyond its expiration date. Thereby the investigation of Acryl-EZE coated pellets was suspended.

7.3. Optimization Attempt

Enteric coating polymers have been reported to be used as both binders and as coating materials for pellets.[68] In our study, it is investigated to delay drug release in a novel approach, through both preparing and coating the drug-loaded pellets with officially accepted enteric polymers. Initially, the practicability of using enteric polymers as loading materials was tested. In a subsequent step an enteric coating was added to the pellets.

In this case, the 5-ASA pellets used in this chapter were produced using a different loading fomulation, compared with the ones in chapter 6 and chapter 8. Particularly, Eudragit® L100-55 were selected as the polymer instead of Acryl-EZE since it is the

main component of the latter one, namely, the application of Eudragit® L100-55 can manipulate the fomulation more flexibly.

To load pellets with 5-ASA, polymers work as carrier, blended with 5-ASA of certain ratio (4% of total loading material mass). The detailed fomulation is as shown in Table 7.2, among which the talc and colloidal silicon dioxide serve as the anti-adherent agent and the dye is aiming at a better observation of film formation.

Table 7.2. Loading fomulation of Eudragit® L 100-55

Fomulation	Composition (wt%)
Eudragit® L 100-55	76.8
Talc	18.2
Colloidal silicon dioxide	0.5
Yellow dye	0.5
5-ASA	4.0

To fix the problem mentioned in section 7.2 and also increase the ratio of effective component (Eudragit® L 100-55), the second coating fomulation of Eudragit® L 100-55 was created. Table 7.3 shows the fomulation that contains Eudragit® L 100-55, where it occupies 80.0%, additives including talc, colloidal silicon dioxide and a yellow dye make up the remaining 20.0% among which the talc and colloidal silicon dioxide serve as the anti-adherent agent.

Table 7.3. Coating fomulation of Eudragit® L 100-55

Fomulation	Composition (wt%)
Eudragit® L 100-55	80.0

Talc	19.0
Colloidal silicon dioxide	0.5
Yellow dye	0.5

The results were evaluated by the dissolution test which was implemented under the temperature of 37 ºC, dissolution media, pH 1.0 (stomach) for a period of 2 h, and pH 7.2 (colon) for the remaining duration of the study were sequentially used so as to simulate the pH changes along the GI tract, this method is normally referred to as the sequential pH change method. Besides, the rotation speed of the paddle were 100 rpm and 50 rpm for media of pH 1.0 and pH 7.2, respectively. The created cumulative release profiles indicated the coating performance. It is commonly assumed that colon targeted drug delivery succeeds when it achieves minimum drug release during its transit in the stomach but maximum drug release in the colon.[70]

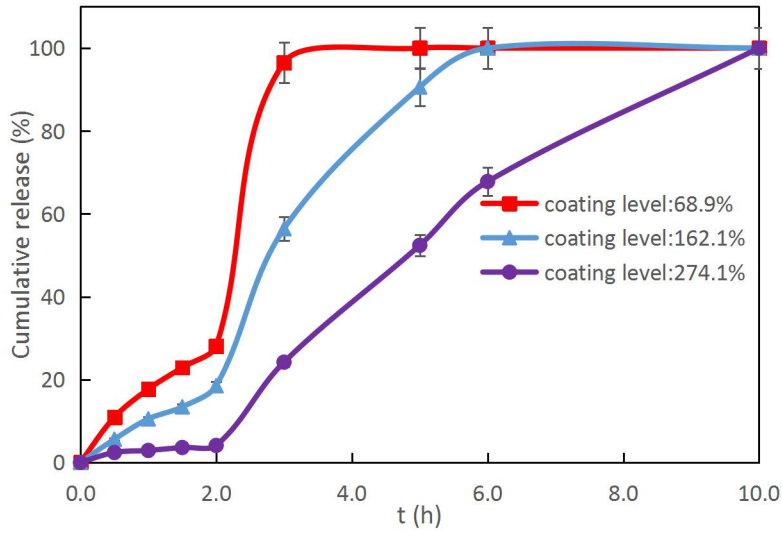


Figure 7.2. The effect of Eudragit® L 100-55 on drug release profiles

The effect of Eudragit® L 100-55 coating level on drug release profiles was clearly revealed in Figure 7.2, where three different coating levels, 68.9%, 162.1% and 274.1%, were investigated. As can be seen, all of the release profiles of the coated

pellets showed a ‘delayed release’, which is to say, 5-ASA came out very few within the first 2 h.

With higher coating level, the retardation in drug release became more significant. An increased diffusion pathlength resulted from thicker coating films can explain this phenomenon. Furthermore, at lower coating level, smaller pellets were formed, leading to larger surface area exposed to dissolution medium, and consequently demonstrating faster drug release. In this case, the lowest coating level (68.9%) performed an acid resistance of 28.1% cumulative release after the first 2 h, and the pellets with higher coating levels of 162.1% and 274.1% showed acid resistance of 18.5% and 4.1% cumulative release, respectively. Thereby the pellets with the first two coating levels (68.9% and 162.1%) were unqualified according to the standard of USP <711>, which released more than 10% after 2 h in pH 1.2 acid media, meanwhile, the pellets with the highest coating level (274.1%) could meet the pharmaceutical standard.

All of the coated pellets of three coating levels released immediately after adjusting the release media from pH 1.0 to pH 7.2 through the addition of 0.2M tribasic sodium phosphate solution. Interestingly, as the coating level increases, the release profile in dissolution of pH 7.2 behaves more like an extended profile, this indicates that the pellets were coated unevenly. To be more specific, even though the pellets were thought to be coated to a certain level generally, the immature technique cannot promise each pellet in a batch was coated equally, so some pellets with higher individual coating level took more time to dissolve in media, while the ones with lower individual coating level dissolved much more quickly. Namely, the general coating level is based on the whole batch, rather than each pellet.

This phenomenon can be more obvious as the general coating level increases, where the variety of individual coating levels increases. Thereby when the general coating level was as high as 274.1%, the drug release was perpetuated until the end of the test, generating a release profile which resembled an extended release form.

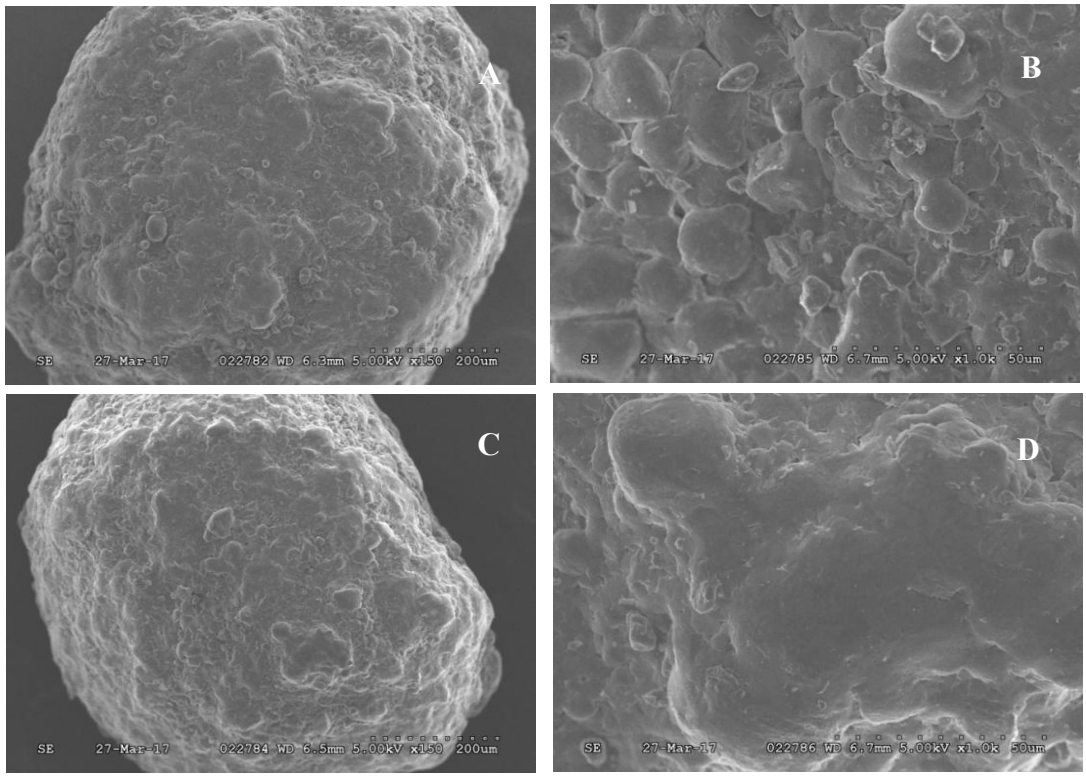


Figure 7.3. SEM micrographs of Eudragit® L 100-55 coated 5-ASA pellets

(A,B) Sample 1 in magnification of 150 and 1000

(C,D) Sample 2 in magnification of 150 and 1000

Scanning electron microscope (SEM) was employed to observe the film formation of the Eudragit® L 100-55 coated pellets with a coating level of 274.1%. The surfaces of two samples were shown in Figure 7.3, both in two magnifications, 150 and 1000, respectively. It can be seen that despite of the same general coating level, significant difference exists among their surfaces, indicating distinct coating performances, where Sample 1 shows rather non-uniform coating film while Sample 2 demonstrates a relatively continuous and dense one.

Obviously, increasing the coating level resulted in a more desired release profile, which is because that compared to pellets with higher coating levels, the amount of the coating materials attached onto the lower coating level pellets surface, were not enough to form dense and continuous coating films. This certainly leads to weakness of coalescence between polymer molecules during curing procedure and also reduces

the coating film intensity, eventually, the cracking effect of the coating film occurs. In contrast, for the higher coating level coated pellets, strong coating films could be achieved, which nicely acquired delayed release.

Admittedly, the Eudragit® L 100-55 loaded and coated pellets gave negligible release in the simulated gastric fluid and maximum release in the colonic environment. Consequently, the Eudragit® L 100-55 loaded and coated pellets can be regarded as quite promising carriers for the colon-targeted delivery of 5-ASA, reaching a desired delayed-release profile when the pellet coating level is high enough (274.1% in this study).

7.4. Evaluation

In this chapter, the accelerated stability test mentioned in section 6.4 was performed to evaluate the product quality. 2 g of Eudragit® L 100-55 coated pellets were put into plastic bottles and sealed with parafilm at the cap. The bottles were put into a vacuum dryer, of which the RH (relative humidity) was controlled to be 75% by using saturated NaCl solution and then in an oven, of which the temperature was set to be 45 ℃. Under such condition, the sample was stored for a month and then retested for dissolution. Therefore, the release profiles of the same sample before and after the one-month storage were compared to determine whether the coating film was stable or not. If the two curves were similar, the film was regarded as stable, which meant a qualified coating, and vice versa.

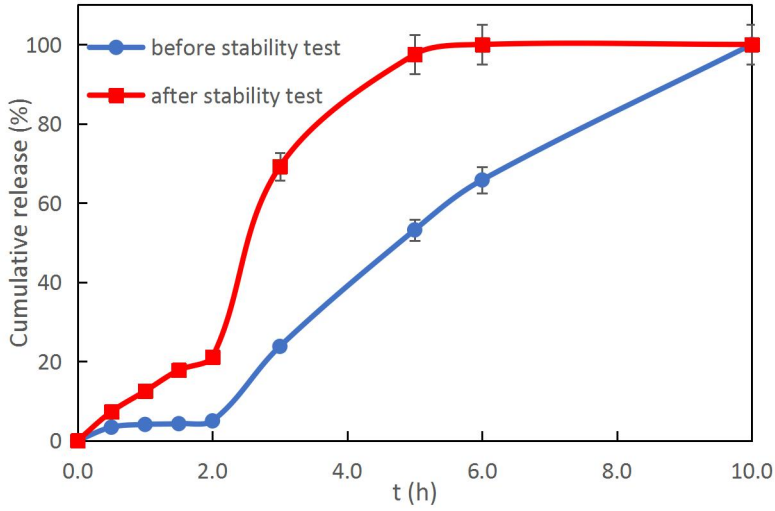


Figure 7.4. The effect of Eudragit® L 100-55 on drug release profiles (coating level: 274.1%)

From Figure 7.4, when the coating level reached 274.1%, the fomulation of Eudragit® L 100-55 resulted in a unqualified coating as after the accelerated stability test, the release of 5-ASA was largely accelerated, which failed in the first 2 h acid resistance test.

Above all, although Eudragit® L 100-55 coated pellets have achieved a desirable delayed release profile in this chapter, demonstrated an unsatisfactory stability, which may be due to the unstable properties of polymers or excipients, under the stability test conditions, the pellet surface gets a little sticky, leading to the breakage of coating film and subsequent faster drug release.

Chapter 8

(Extended-Delayed)-release Coating of 5-ASA Pellets

8.1. Introduction

In the pharmaceutical industry, delayed release is witnessing more and more popularity due to its capability of treating pathologies with night or early-morning symptoms in the form of chronotherapy. [69] While the enteric coated dosage forms serve as a simple and practical approach to deliver colon-specific drug, they lack sufficient site specificity. [71] As commonly accepted, a colonic delivery system cannot fulfill therapeutic requirements when it only depends on either of GI transit time or GI tract pH. This can be illustrated by the inherent variability of pH and emptying times from the GI tract. [68]

Consequently, the integration of time-dependent and pH-dependent functions into a single dosage form is believed to fix the problem, given the physiological characteristics of the GI environment in human body.

The time-dependent concept is normally realized by extended-release coating, which release the drug over a period of time. Additionally, the application of delayed-release polymers advantageously localize the drug to the target tissue, thereby achieving the pH-dependent effect.[72]

This chapter aims at combining pH based dissolution characteristics of delayed-release polymers and constant transit time in the GI tract to achieve pellets that can release 5-ASA mainly in the colon and also demonstrate a lasting release profile over a prolonged period, which can be a reliable multiparticulate colonic delivery system.

Overall, the product is expected to have a drug-loaded core, inner extended-release coating and outer delayed-release coating. Upon interaction with biological fluids, the delayed-release polymers protect 5-ASA from dissolving in acidic media that mimics the stomach environment and in subsequent colonic solutions, the extended-release polymers sustain the drug release for a period of time that is programmable as a function of the polymer characteristics and coating level.

Since this product has two different coatings, various coating materials were applied accordingly. For the inner layer on drug-loaded pellets, Eudragit® RS and Eudragit® RL were chosen to be coating polymers, as the coating condition has been optimized in Chapter 6.3, a ratio of 4:1 was applied in this study. Accordingly, Triethyl citrate (TEC) was selected as the liquid plasticizer to reduce the glass transition temperature (T_g) of the coating polymers. For the outer layer, Eudragit® L100-55 was selected as the coating polymer, as mentioned in section 7.3. Correspondingly, Polyethylene glycol 400 (PEG 400) was chosen to be the liquid plasticizer.

8.2. Development

Table 8.1 demonstrates the inner layer coating fomulation, where the sum of Eudragit® RS and Eudragit® RL (ratio 4:1) was 80.0%, additives including talc, colloidal silicon dioxide and a yellow dye make up the remaining 20%. The talc and colloidal silicon dioxide serve as the anti-adherent agent and the dye is aiming at a better observation of film formation.

Table 8.1. Coating fomulation of the inner layer

Fomulation	Composition (wt%)
Eudragit® RS and Eudragit® RL	80.0
Talc	19.0

Colloidal silicon dioxide	0.5
Yellow dye	0.5

Table 8.2 shows the fomulation for the outer layer, it contains Eudragit® L 100-55, which occupies 80.0%, additives including talc, colloidal silicon dioxide and a yellow dye make up the remaining 20%.

Table 8.2. Coating fomulation of the outer layer

Fomulation	Composition (wt%)
Eudragit® L 100-55	80.0
Talc	19.0
Colloidal silicon dioxide	0.5
Yellow dye	0.5

The results were evaluated by the dissolution test implemented in pH 7.2 phosphate buffer solution under the temperature of 37 ^{o}C, and the rotation speed of the paddle was 50 rpm. The created cumulative release profiles indicated the coating performances.

As discussed in Chapter 6.3, Eudragit® RS and Eudragit® RL with ratio of 4:1 is an optimal fomulation in terms of extended-release coating for 5-ASA pellets. In this study, 3 different coating levels (16.7%, 37.5% and 54.2%) were implemented, as shown in Figure 8.1, as the coating level increased, the release could be further prolonged. Especially when the coating level reached 54.2%, 5-ASA was completely released in up to 3 h.

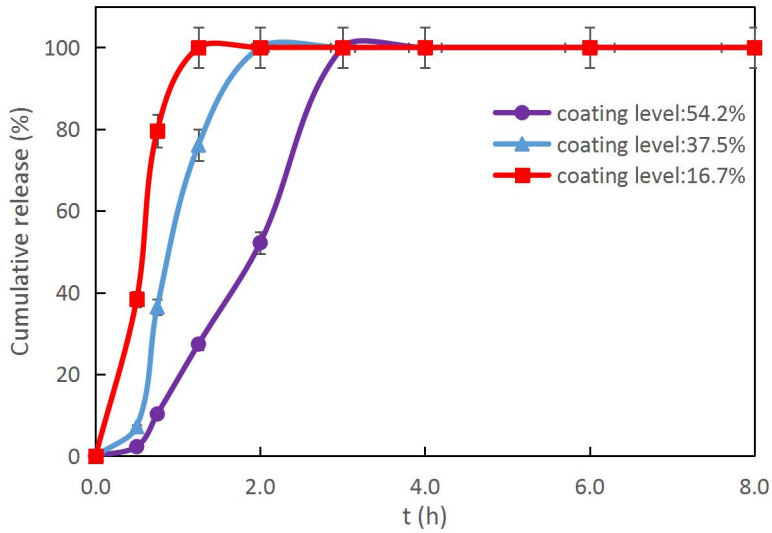


Figure 8.1. The effect of Eudragit® RS/RL (4:1) on drug release profiles

Although the fomulation of Eudragit® RS/RL (ratio 4:1) can effectively sustain 5-ASA release from pellets, it cannot retard the release of 5-ASA in the environment with pH over 5.5 due to the pH-independent characteristics of the polymers. Delayed-release coating with Eudragit® L 100-55 as outer coating film can fix the problem. Therefore, Eudragit® RS/RL (4:1) coated pellets were further coated with outer layer using Eudragit® L 100-55. Besides, due to the best extended-release effect that has been achieved, the pellets with the highest coating level (54.2%) were selected as the cores for the next-step coating. In this case, the coating level in the following discussion is only about the Eudragit® L 100-55, rather than the one together with existing Eudragit® RS/RL (54.2%).

The results were evaluated by the dissolution test which was implemented under the temperature of 37 ^{o}C, dissolution media, pH 1.0 (stomach) for a period of 2 h, and pH 7.2 (colon) for the remaining duration of the study were sequentially used so as to simulate the pH changes along the GI tract. Besides, the rotation speed of the paddle were 100 rpm and 50 rpm for media of pH 1.0 and pH 7.2, respectively. The created cumulative release profiles indicate the coating performance. A colon targeted drug delivery succeeds when it achieves minimum drug release during its transit in the stomach but maximum drug release in the colon.

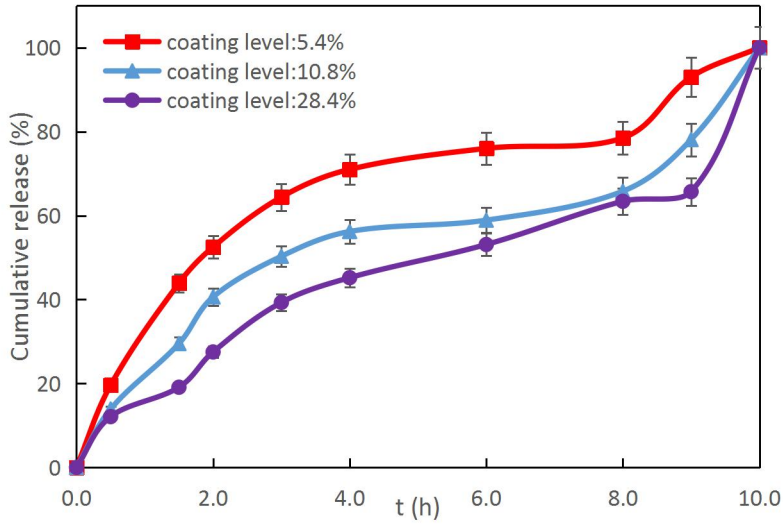


Figure 8.2. The effect of Eudragit® L 100-55 (combined with Eudragit® RS/RL 4:1 coating level 54.2%) on drug release profiles

As shown in Figure 8.2, the three coating levels: 5.4%, 10.8% and 28.4% of Eudragit® L 100-55 did not achieve desired delayed-release profiles within the first 2h, where all the three released 5-ASA more than 10% in the acidic media. While they demonstrated certain delayed effect, namely, pH-dependent property. Besides, as the coating level increased, the acid resistance became more evident: no more than 30% released in the acidic media when the coating level reached 28.4%, thereby indicating the need of higher coating level.

Despite of the unqualified delayed-release effect, following the 2 h-stomach setting simulation, extended-release profiles, which are attributed to the cooperation of Eudragit® L 100-55 and Eudragit® RS/RL (4:1), were demonstrated obviously. An prolonged period of up to 8 h was achieved. The drug release was much more quickly in the last 2 h, which can be attributed to that the mechanical stability of the coating film cannot withstand the hydrostatic pressure generated inside the pellets, thus diffusion through water leads to a faster release rate.

After all, the results above again indicated that Eudragit® L 100-55 outer coating could inhibite the 5-ASA release in the upper digestive tract and increase the

localization in colon region. Also, the combination of Eudragit® L 100-55 and Eudragit® RS/RL (4:1) can be promisingly further implemented.

8.3. Optimization Attempt

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.

In order to meet the standard, more Eudragit® L 100-55 were further coated on the Eudragit® RS/RL (4:1) coated pellets, accordingly, the coating levels were: 45.9%, 71.6%, 89.2% and 121.6%.

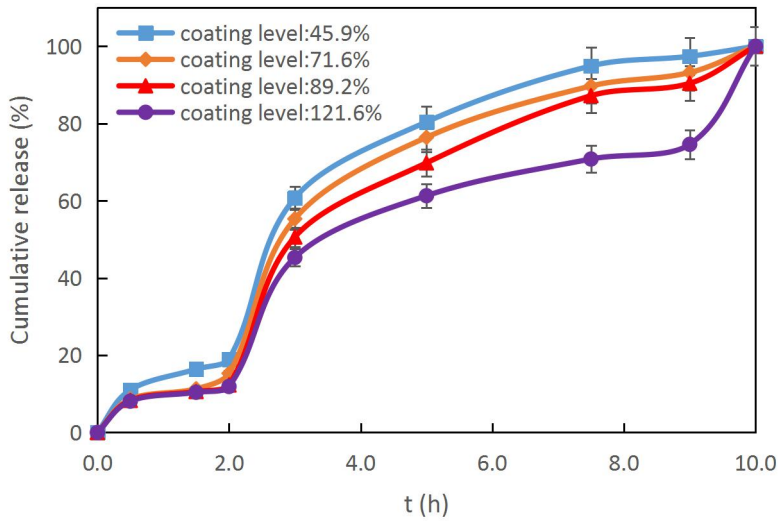


Figure 8.3. The effect of Eudragit® L 100-55 (combined with Eudragit® RS/RL 4:1 coating level 54.2%) on drug release profiles

From Figure 8.3, obvious pH-sensitive release behaviors were shown: all of the release profiles of the coated pellets showed a 'delayed release', in which 5-ASA came out very few within the first 2 h while released quickly in the following colonic environment. As the coating level reached 121.6%, around 10% of 5-ASA were released within the first 2 h, once the pellets contacted the media with pH 7.2, 44% of

5-ASA were suddenly dissolved and then pellets showed a gradual release over the subsequent 8 h. Complete drug release was achieved within 10 h.

As can be seen, with increasing coating level, both the delayed and extended effect can be improved since through higher coating level, namely, more layers of coating film, the stronger capability of withstanding the dissolution media can be achieved.

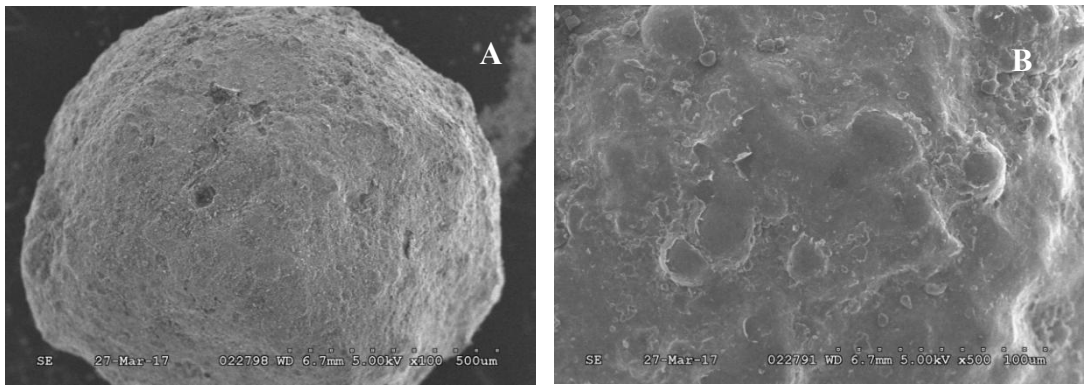


Figure 8.4. SEM micrographs of Eudragit® L 100-55 (combined with Eudragit® RS/RL 4:1 coating level 54.2%) coated 5-ASA pellets

Scanning electron microscope (SEM) was employed to observe the film formation of the Eudragit® L 100-55 (combined with Eudragit® RS/RL 4:1 coating level 54.2%) coated pellets with a coating level of 121.6%. The surface were shown in Figure 8.4, in two magnifications, 100 and 500, respectively. It can be seen that the coating fomulation helped form a continuous and dense coating film, where the smooth surface denotes an elegant coating performance.

8.4. Evaluation

As mentioned in section 7.3, a delayed and extended release profile could be obtained using only Eudragit® L 100-55, while the issue of relatively high amount of coating polymers needed to achieve lag time suitable for chronotherapy and colon targeting have to be faced. The resulting coating thickness might not comply with the dimensional constraints of pellets and the coating stage may need too much processing time.

In such case, the advantage of the system developed in this chapter becomes more significant, as shown in Figure 8.5, to obtain similar coating effect, it took coating level as high as 162.1% when Eudragit® L 100-55 was applied alone, while only 45.9% in the novel system, where even taking consideration of the total coating level (54.2% for Eudragit® RS/RL 4:1 added) only leads to 100.1%. Comparatively, this novel system saves coating level greatly.

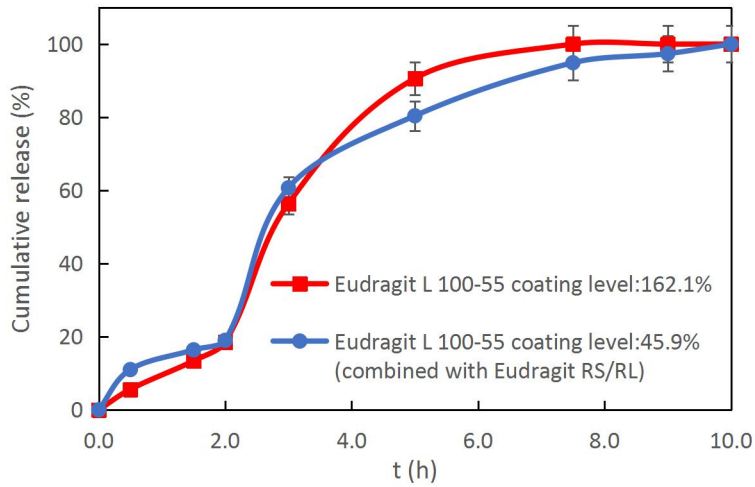


Figure 8.5. Comparison of the effects of two fomulations on drug release profiles

Eventually, a promising colonic drug delivery system of 5-ASA was developed: 5-ASA loaded pellets were coated with Eudragit® RS/RL as inner layer for prolonging action time and Eudragit® L 100-55 as the outer layer for colon targeting.

Chapter 9

Conclusions

With the application of the rotating fuidized bed, the (5-ASA)-loading and coating of pellets were successfully achieved in this study.

The technique of pelletization by powder layering resulted in the realization of 5-ASA loaded pellets. During the development and improvement of the pelletization process, the influence of loading material content, pellet size, excipient, plasticizer flowrate, curing time and process temperature were investigated on the drug loading efficiency. The eventual processing conditions were improved to be using the fomulation of Eudragit® RS and Eudragit® RL mixture (1:1) with a yellow dye, TEC sprayed with the flowrate of 0.28 g/min, applied on MCC pellets with size of 500-710 μm, preheated at 40 ℃ and cured at 50 ℃ for 3 h. Under the condition above, when 20 g loading materials (containing 2% 5-ASA) are applied on 35 g MCC pellets, a loading efficiency of as high as 86.0% can be achieved.

Three different coatings aiming at specific release profiles were successfully achieved:

For extended release, the ratio of the Eudragit® RS to Eudragit® RL plays an important role in regulating drug release. The pellets coated with a higher ratio of Eudragit® RS showed a slower release rate compared to the pellets coated with a lower one. This is mainly because that Eudragit® RS, which has less amount of quaternary ammonium groups, is less permeable than Eudragit® RL. While when Eudragit® RS was used alone, the pellets cannot be over-coated (coating level reached 177.1% in this study), or 5-ASA cannot be released in a proper period of time. Eventually, the fomulation with Eudragit® RS/RL ratio being 4:1 and the coating level being 54.2% would be a promising candidate, gradually releasing 5-ASA in up to 9 h.

For delayed release, the Eudragit® L 100-55 loaded and coated pellets can be regarded as proper carriers for colon-targeted delivery of 5-ASA. The in-vitro drug release tests proved that the acid resistance of the coated pellets in the first 2 h enhanced as the coating level increased. According to the USP <711> standard, the cumulative release should be less than 10% after the 2 h release in acid medium, when the coating level is high enough (274.1% in this study), the coated pellets were qualified to achieve delayed release.

For extended-delayed release, when 5-ASA loaded pellets were coated with Eudragit® RS/RL (4:1) as inner layer with a coating level of 54.2% and Eudragit® L 100-55 as outer layer with a coating level of 121.6%, desired release patterns could be reached: around 10% of 5-ASA were released within the first 2 h, once the pellets contacted the media with pH 7.2, they showed a gradual release over the subsequent 8h. Complete drug release was achieved within 10 h.

Overall, 5-ASA pellets coated with multiple layers of polymers which may possess the same or different functions in terms of dissolution, represent a feasible strategy to achieve effective delivery systems for drug release targeting at the colon.

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