7-24-2019 2:30 PM

Application of Electrostatic Dry Powder Coating Technology on Hard Capsules

Zhehao Jing, *The University of Western Ontario*

Supervisor: Jesse Zhu, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Chemical and Biochemical Engineering

Abstract

This project applied electrostatic dry powder coating technology on hard gelatin and HPMC capsules using Eudragit® RS/RL and Eudragit® L 100-55 to achieve sustained release and enteric release respectively. Dry powder coating eliminated the difficulties associated with conventional liquid coating processes such as poor adhesion and stickiness for capsules. Additionally, through optimizing sprayed plasticizer volume, the coating powders deposited on the capsules could be efficiently maximized. The weight gain of coating and the formulation of coating materials were important parameters which controlled the release profiles of coated capsules. The release mechanism of coated capsules was quite different from tablets owing to the existence of capsule shells.

Enteric release aspirin capsules were developed and compared with aspirin tablets. The investigation showed that enteric release capsules could be an alternative form to deliver aspirin. The capsules eliminated the migration of the drug from cores to the coating films, a problem observed with aspirin tablets. It was also found that enteric coating film would not protect aspirin from hydrolysis for both tablets and capsules. And an important factor that caused hydrolysis of aspirin could be the moisture in the environment that penetrated the film.

Finally, the dry powder coating process was scaled up and optimized successfully with tablets. Compared to the conventional aqueous coating process, the dry powder coating process had shorter processing time, lower energy consumption and comparable coating efficiency. And the coated aspirin tablets had similar release profiles as aqueous coated. Additionally, due to the absence of water, less hydrolysis occurred for aspirin coated by the dry powder coating process.

Key words: Electrostatic dry powder coating technology, Hard gelatin capsule, Hard HPMC capsule, Sustained release, Release mechanism, Enteric release, Aspirin, Hydrolysis of aspirin, Scale up, Aqueous coating process

Summary for Lay Audience

In pharmaceutical manufacturing process, drugs and excipients are mixed first. And then, the mixture is compressed into tablets or filled into capsules, two of the most common oral solid dosage forms. After tablets and capsules are manufactured, thin polymer films can be applied on their surface to achieve different functions like enhancing stability, modifying drug release profiles etc. which process is called coating process.

Currently, the coating process is based on organic solvent or water. The polymers are dissolved or dispersed into organic solvent or water and sprayed onto tablets or capsules. After evaporation, the polymers are left on the surface and form films. However, this process is not suitable for capsules owing to their smooth surface and moisture sensitivity. Additionally, the organic solvent coating process would cause pollution and safety issues while the aqueous coating process would require high energy consumption and long processing time.

The electrostatic dry powder coating process was developed to coat pharmaceutical oral solid dosage forms. This process avoids the use of organic solvent and water. Thus, organic solvent and water related issues mentioned above were eliminated. The dry powder coating process was successfully applied on capsule coating and showed its benefits. Capsules were coated directly to achieve modified release profiles like enteric release and sustained release. The coating process and the parameters that would influence the release profiles like weight gain after coating, formulation of the coating materials, etc. were investigated to have a better understanding of this process.

Aspirin is normally made into tablets and coated to achieve enteric release. However, there are some problems for aspirin tablets such as drug migration. Thus, enteric release aspirin capsule was first developed to prevent aspirin migration. It provided a new dosage form for aspirin. The differences of these two dosage forms were investigated which indicated that the capsule would be a better form to deliver aspirin.

In addition, electrostatic dry powder coating process was scaled up and optimized for commercialization. This process proved to be more energy saving and less time consuming than aqueous coating process. And it caused less degradation for moisture sensitive drugs like aspirin.

Co-Authorship Statement

Chapter 3 Application of dry powder coating technology on sustained release capsules

Authors: Zhehao Jing, Yingliang Ma, Jesse Zhu

Zhehao Jing designed and performed all experiment and carried out data analysis under the guidance of Dr. Jesse Zhu and Ms. Yingliang Ma. All drafts of this manuscript were written and revised by Zhehao Jing under close supervision of advisor Dr. Jesse Zhu. The final version of this article will be submitted to "International Journal of Pharmaceutics".

Chapter 4 Application of dry powder coating technology on enteric release capsules

Authors: Zhehao Jing, Yingliang Ma, Jesse Zhu

Zhehao Jing designed and performed all experiment and carried out data analysis under the guidance of Dr. Jesse Zhu and Ms. Yingliang Ma. All drafts of this manuscript were written and revised by Zhehao Jing under close supervision of advisor Dr. Jesse Zhu. The final version of this article will be submitted to "International Journal of Pharmaceutics".

Chapter 5 Enteric release aspirin capsules and tablets, a comparison

Authors: Zhehao Jing, Yingliang Ma, Jesse Zhu

Zhehao Jing designed and performed all experiment and carried out data analysis under the guidance of Dr. Jesse Zhu and Ms. Yingliang Ma. All drafts of this manuscript were written and revised by Zhehao Jing under close supervision of advisor Dr. Jesse Zhu. The final version of this article will be submitted to "International Journal of Pharmaceutics".

Chapter 6 Scale up of dry powder tablets coating process in comparison to aqueous coating process

Authors: Zhehao Jing, Yingliang Ma, Jesse Zhu

Zhehao Jing designed and performed all experiment and carried out data analysis under the guidance of Dr. Jesse Zhu and Ms. Yingliang Ma. All drafts of this manuscript were written and revised by Zhehao Jing under close supervision of advisor Dr. Jesse Zhu. The final version of this article will be submitted to "International Journal of Pharmaceutics".

Acknowledgement

First of all, I would like to send my sincere gratitude to my supervisor, Dr. Jesse Zhu, for his kindly support and encouragement during my 4 years PhD study. His guidance helped me to finish this project and improve my knowledge not only on academic but also on other fields which would be a tremendous treasure for my future without doubt.

I also sincerely appreciate Ms. Ying Ma for her great help on my research, without whom this project may not be able to fulfill. She provided important advices when I came to some problems on my experiments. In addition, her optimism helped me pass many difficulties in the last four years, it is my great pleasure to work with her.

Also, I want to thank my oral defense committee members: Dr. Wankei Wan, Dr. Dimitre Karamanev, Dr. Chao Zhang and Dr. Arturo Macchi, for their helpful suggestions.

I want to thank Qingliang Yang, a senior PhD who worked with me in the first year. He helped me at the beginning to be aware of what is research and give me a lot of suggestions and instructions about how to do experiments. And I would like to thank Dr. Tang Li, Yuqing Ye who assist me to use SEM and HPLC. I also want to thank Zachary Gouveia who help me to revise the thesis.

I was funded by Mitacs for the first 3 years and I am very grateful for this that made it possible for me to pursue PhD.

Finally, I would like to express my deepest love to my mother who is the most respectable woman and to my father who will always live in my heart. Their endless support brought me to today. I also want to appreciate my aunt Jinhua Qian and other relatives who provided me and my family kindly support and gave me courage to move forward.

Table of Contents

List of Figures

List of Tables

List of Abbreviations, Symbols, Nomenclature

M_t	Amount of drug released at different time after putting in the solution (mg)
t	Time (minute)
M_∞	Total amount of drug in a solid dosage form (mg)
K	Kinetic constant (dimensionless)
n	Diffusion exponent (dimensionless)
R^2	Coefficient of Determination (dimensionless)
WG	Weight gain, weight increased/surface area (mg/cm^2)
RH	Relative humidity (%)

SEM	Scanning electron microscopy
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
PEG	Polyethylene glycol
TEC	Triethyl citrate
ASA	Acetylsalicylic acid
SA	Salicylic acid

Chapter 1

1 Introduction

1.1 Background

In the pharmaceutical industry, a long process is required for a drug in solid dosage form to be developed. First, an active pharmaceutical ingredient (API) was founded from nature or synthesized in a lab, then it is developed to have high curative effect, low toxicity and relatively high stability at the same time. Second, the dosage form of the drug is determined and go through pre-clinical stage. In this stage, safety and efficacy of the drug will be tested on animals. Third, the drug will be tested on human body to evaluate its effectiveness, safety (short term and long term) etc. If the drug satisfies all the requirements, it will be manufactured and sold on market after regulatory approval.

As for determining the solid dosage forms, there are many options. Tablet, pellet, capsule (showed in Figure 1.1, 1.2 &1.3) and so on are normally used. They all have their own advantages and disadvantages. For tablet, it is simple, cheap and convenient to use. It can also provide protection for medicament and prolong its stability. For pellet, it can provide enhancement of drug dissolution, uniform packing, ease of capsule filling because of better flow properties and even distribution in the GI tract (Sirisha et al., 2013). For capsule, it is tasteless, odorless, easily administered and suitable for drugs with low compressibility (Hoag, 2017). With the development of capsule, it is becoming more and more popular in the market.

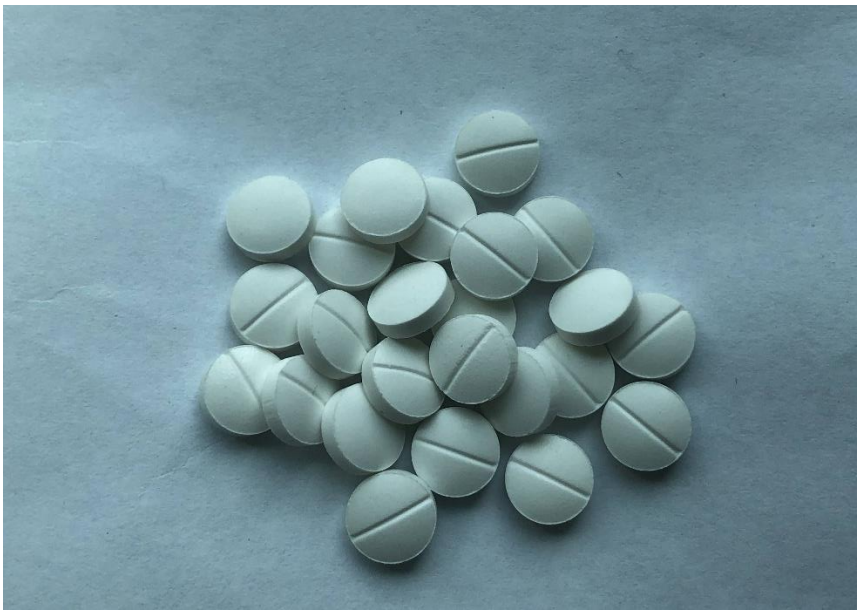


Figure 1.1 Picture of tablets

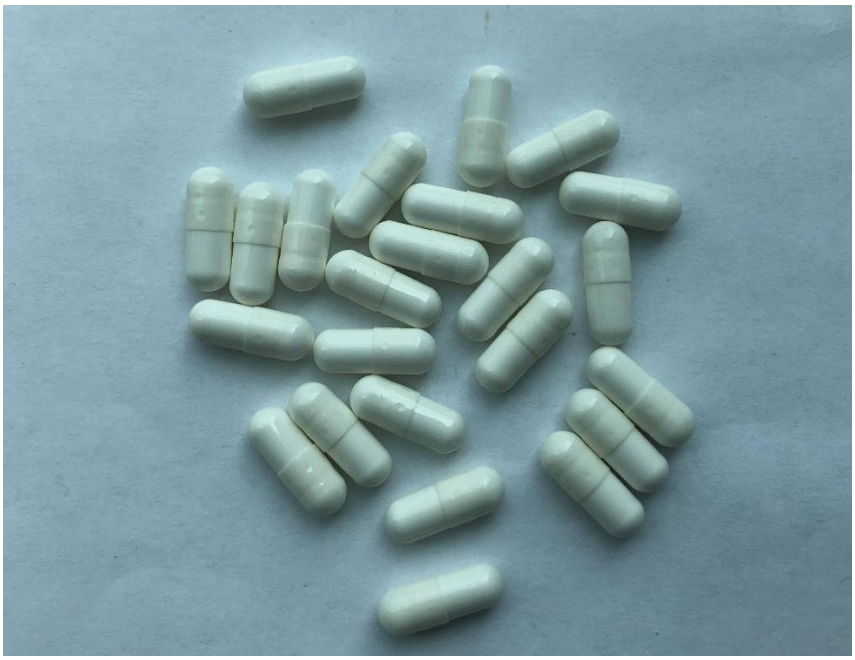


Figure 1.2 Picture of capsules

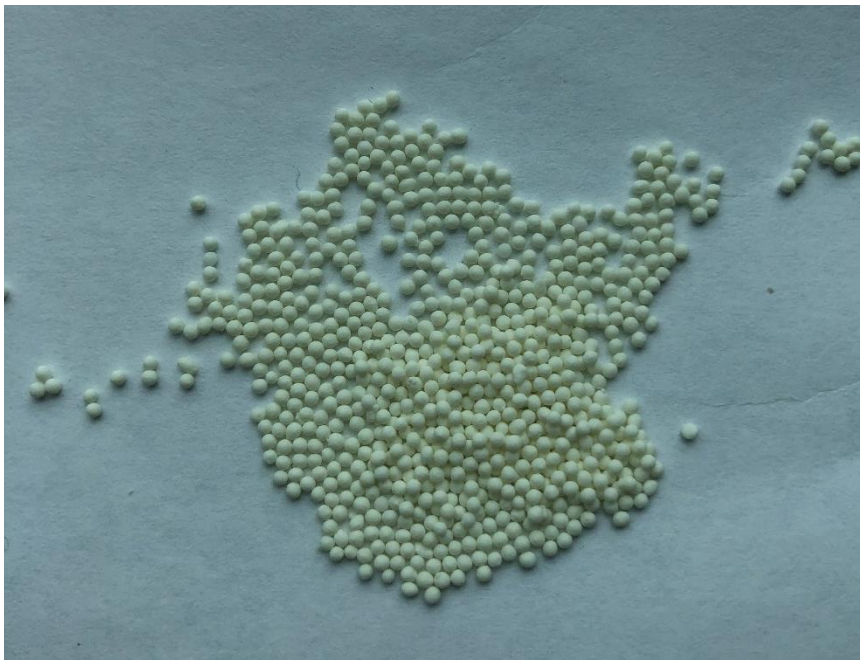


Figure 1.3 Picture of pellets

Film coating is normally required for oral solid dosage forms to provide protection from moisture or light and to modify release properties. Conventionally, solid dosage forms are coated by using either organic solvent coating or aqueous coating process to achieve immediate release, delayed release or extended release. However, organic solvent coating causes toxicity, pollution and safety issues (Aulton et al., 1995), while aqueous coating requires longer processing time, higher energy consumption. Also, aqueous coating process is not suitable for moisture sensitive drugs.

Electrostatic dry powder coating technology (Zhu et al., 2011, 2012) eliminates use of organic solvent and water in the coating process. Coating powders are sprayed on the substrates directly and coalesce to form the films with the assistance of plasticizers. Thus, it is more environmentally friendly, safe and economical. Also, the dry powder coating technology is suitable for moisture sensitive drugs. This technology has been successfully applied on tablets and pellets coating (Qiao et al., 2010; Qiao et al., 2010; Qiao et al., 2013; Yang et al., 2018; Yang et al., 2015; Yang et al., 2016).

Capsules can also be coated by the dry powder coating process like tablets and pellets to achieve modified release profiles, such as sustained release which can decrease frequency of taking drugs and decrease side effects and enteric release which can protect drug or stomach and achieve target release. For capsule coating, poor adhesion of coating materials would happen because of smooth

surface of capsules (Murthy et al. 1986), and stickiness and shell embrittlement would appear because capsules would be partially dissolved (Thoma & Bechtold, 1992). Thus, the dry powder coating process would be a good alternative method to coat capsules. In addition, some drugs like aspirin may interact with coating films and cause some drawbacks (Wang et al. 2017). Thus, capsules can be used to deliver these drugs because the drugs and the coating films are separated by capsule shells.

And for now, the dry powder coating technology is still in lab scale. It is important for it to be carried out in a larger scale before commercialization, thus, scale up of this process is necessary. To scale up the dry powder coating process, some parameters need to be adjusted to optimize the process. And after scaling up, the energy consumption, processing time of this technology and the quality of the final product can be investigated and compared with aqueous coating process.

1.2 Objectives

- Coat gelatin capsules and HPMC (hydroxypropyl methylcellulose) capsules directly by using electrostatic dry powder coating technology to achieve sustained release, and compare sustained release capsules with tablets.
- Coat gelatin capsules and HPMC capsules by electrostatic dry powder coating technology to achieve enteric release, and compare enteric release capsules with tablets.
- Apply the dry powder coating technology on aspirin capsules, aspirin tablets enteric coating process, and compare the difference.
- Scale up and optimize the electrostatic dry powder coating process, and compare the dry powder coating process with aqueous coating process in terms of energy, process time, efficiency and product quality.

1.3 Thesis structure

This thesis contains seven chapters as follows.

- Chapter 1 gives a brief background to specify the needs for this study. Objectives, thesis structure and major contributions are also given.

- Chapter 2 provides detailed introduction and literature review. Information about capsule properties, different drug release process, conventional coating technology, electrostatic dry powder coating process and aspirin properties are included.
- Chapter 3 discusses the application of the electrostatic dry powder coating process on coating capsules directly to achieve sustained release. Influence of weight gain and formulation of coating materials are examined. Also, the dissolving processes and mechanisms of sustained release gelatin capsules, HPMC capsules and tablets are investigated.
- Chapter 4 discusses the application of the electrostatic dry powder coating process on capsule coating to achieve enteric release and compares enteric release capsules with tablets. Influence of weight gain and plasticizer are investigated. Also, the dissolving processes of enteric release gelatin capsules, HPMC capsules and tablets are investigated
- Chapter 5 compares enteric release aspirin tablets and capsules coated by dry powder coating process and mainly focuses on degradation of aspirin and its influence on the coating film.
- Chapter 6 includes the scale up and optimization of the dry powder aspirin tablets coating process. Conventional aqueous coating process and dry powder coating process are compared in terms of processing time, energy, efficiency, film properties after coating and influence on aspirin degradation.
- Chapter 7 summarizes this study and provides some recommendations for future work.

1.4 Major contributions

This project successfully coated hard gelatin capsules and HPMC capsules to achieve enteric release and sustained release by applying the electrostatic dry powder coating technology. The coating process was investigated. Release mechanism of coated gelatin and HPMC capsules were also examined.

Enteric release aspirin capsule, as an alternative solid dosage form to deliver aspirin, was developed. The capsule can prevent migration of aspirin to coating films. In addition, by comparing different dosage forms, the reason why enteric coated aspirin would be hydrolyzed was investigated.

The electrostatic dry powder coating process was scaled up and optimized. Comparison of the dry powder coating and aqueous coating process was also carried out.

Bibliography

Aulton, M., Cole, G., & Hogan, J. (1995). *Pharmaceutical coating technology*. Taylor & Francis.

Hoag, S. W. (2017). Capsules dosage form: formulation and manufacturing considerations. *Developing Solid Oral Dosage Forms* (pp. 723–747). Elsevier.

Murthy, K. S., Enders, N. A., Mahjour, M., & Fawzi, M. B. (1986). A comparative evaluation of aqueous enteric polymers in capsule coating. *Pharm. Technol*, *10*(10), 36–46.

Qiao, M., Luo, Y., Zhang, L., Ma, Y., Stephenson, T. S., & Zhu, J. (2010). Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process. *International Journal of Pharmaceutics*, *399*(1), 37–43.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Chow, K. (2010). A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *76*(2), 304–310.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Xiao, W. (2013). A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. *European Journal of Pharmaceutics and Biopharmaceutics*, *83*(2), 293–300.

Sirisha, V. R. K., Sri, K. V., Suresh, K., Reddy, G. K., & Devanna, N. (2013). A review of pellets and pelletization process-a multiparticulate drug delivery system. *International Journal of Pharmaceutical Sciences and Research*, *4*(6), 2145.

Thoma, K., & Bechtold, K. (1992). *Enteric coated hard gelatin capsules*. Capsugel Library.

Wang, X., Wang, P., Huang, C., Lin, X., Gong, H., He, H., & Cai, C. (2017). Hot-melt sub- and outercoating combined with enteric aqueous coating to improve the stability of aspirin tablets. *Asian Journal of Pharmaceutical Sciences*, *12*(3), 266–278.

Yang, Q., Ma, Y., Shi, K., Yang, G., & Zhu, J. (2018). Electrostatic coated controlled porosity osmotic pump with ultrafine powders. *Powder Technology*, *333*, 71–77.

Yang, Q., Ma, Y., & Zhu, J. (2015). Applying a novel electrostatic dry powder coating technology to pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, *97*, 118–124.

Yang, Q., Ma, Y., & Zhu, J. (2016). Sustained drug release from electrostatic powder coated tablets with ultrafine ethylcellulose powders. *Advanced Powder Technology*, *27*(5), 2145–2152.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2011). *U.S. Patent No. 7,862,848*. Washington, DC: U.S. Patent and Trademark Office.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2012). *U.S. Patent No. 8,161,904*. Washington, DC: U.S. Patent and Trademark Office.

Chapter 2

2 Literature review

2.1 Capsules

2.1.1 Categories and materials of capsules

Capsule, as a common solid dosage form, was first patented in 1834 (Stegemann & Bornem, 2002), and has been wildly used today to deliver drugs. There are mainly two types of capsule: Hard-shelled capsule and soft-shelled capsule.

Hard-shell capsules are made of two parts: a cap with a larger diameter and a body with a smaller diameter. Figure 2.1 shows the structure of hard capsules. Normally, it is filled with dry powdered ingredients or pellets. However, it can also be used to deliver liquid or semi-solid medicament (Cole et al., 2008). According to different volumes of the dosage, different sizes of the capsule can be selected. In the beginning, gelatin (molecular structure showed in Figure 2.2) derived from collagen of animal skin or bone was used to manufacture capsule shells. The molecular bonds between collagen strands break down into a form that can be easily rearranged by different curing, acid and alkali process. The gelatin melts when heated up and solidifies when cooled down. Gelatin capsule is non-toxic, readily soluble after taken. In addition, gelatin has excellent characteristics as gelatinizer and capability to form strong flexible shells. However, since it is derived from animals, it has a risk of bovine spongiform encephalopathy (BSE)/transmissible spongiform encephalopathies (TSE) (Rabadiya & Rabadiya, 2013). Besides, gelatin may have crosslink reaction when contact aldehydes. So, an alternative material, hydroxypropyl methylcellulose (HPMC) (molecular structure showed in Figure 2.3), was developed to produce hard capsules. Since it is a no animal derived material, BSE/TSE are no longer a problem. Compared with gelatin capsules, HPMC capsules are more stable under extreme storage conditions and have no risk of capsule crosslinking. However, unlike gelatin capsules which will dissolved rapidly in hot water, HPMC capsules are insoluble in hot water but dissolved in cold water. And compared with gelatin capsules, HPMC capsules will take a slightly longer time to dissolve in water at 37 ℃ (Chiwele et al., 2000). Nowadays, although there are some other materials are used to manufacture capsules

like polyvinyl alcohol (PVA) (Brown, 1996), starch (Menard, 1999), in the market, gelatin and HPMC are the mainly materials to make hard capsules.

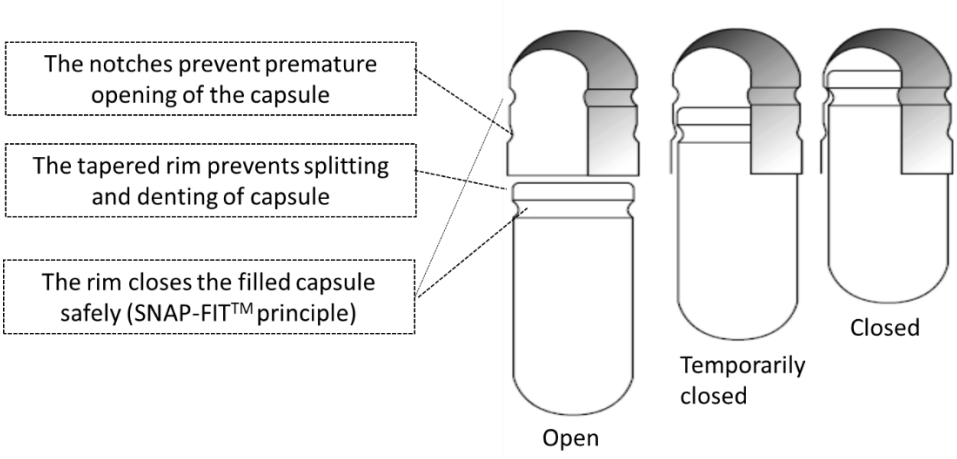


Figure 2.1 Hard gelatin capsule with features (notches or dimples) for pre-closing; closing features e.g. SNAP-FIT™) and tapered rim (e.g. CONI-SNAP™) (Reprinted from Stegemann & Bornem, 2002)

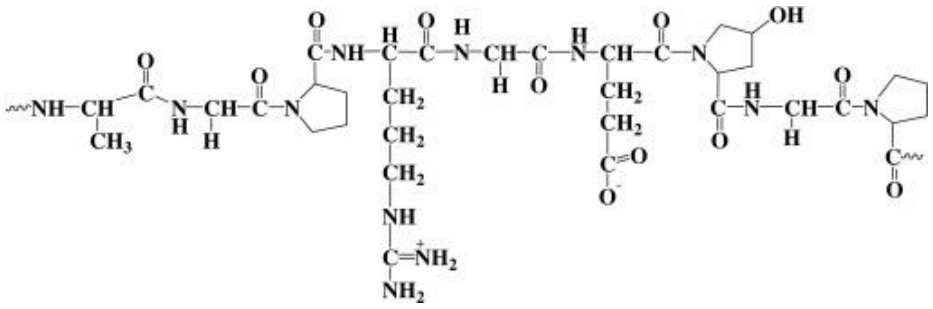
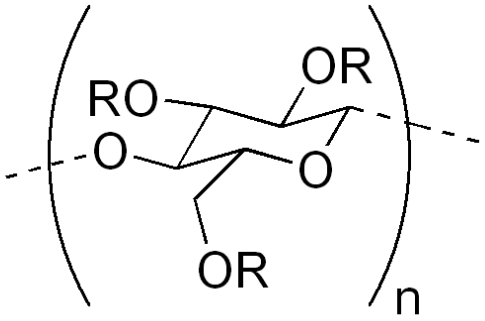


Figure 2.2 Molecular structure of HPMC



$$R = H \text{ or } CH_3 \text{ or } CH_2CH(OH)CH_3$$

Figure 2.3 Molecular structure of gelatin

Soft-shell capsules are made of only one part and is mainly used to fill liquid or semi solid medicament. Soft capsules can be made in various shapes like spherical, elliptical, etc. Soft capsule are mainly made from gelatin, but there are still a few soft capsules are HPMC based, like Vegicaps®. Compared with hard capsules, soft capsules are more suitable to enclose liquid or semi-solid medicament since they are integrated but not separated into two parts. However, soft capsules require special manufacturing equipment and not suitable for drugs that are sensitive to water because of high water concentration in soft capsule shells.

This study focused on hard capsules, so the soft capsules would not be discussed in detail.

2.1.2 Manufacturing of hard capsules

For gelatin capsule, pin shape molds at 22℃ are lubricated and dipped in gelatin solutions which are at 45-55℃ (Al-Tabakha, 2010). The gelatin solution will form films on pins because of the lower temperature of the pins. Then, the pins are slowly withdrawn from the solution and keep rotating to maintain the uniformity of the films. Afterwards, the films will go through drying process at a controlled temperature and humidity to let the film solidify. Finally, the formed films are stripped of the pins and cut to desired length. These films are capsule shells, two pieces of the films (cap and body) are jointed together and become a whole capsule.

Preservatives and surfactants are normally added in the gelatin capsule manufacturing process. Since gelatin solutions below 55℃ are ideal medium for bacteria to grow, preservatives are used to control the growth of these microorganism. And surfactants are used as wetting agent to ensure gelatin solution can cover metal moulds uniformly during manufacturing process.

For HPMC capsule, the manufacturing process is similar as gelatin capsule but with some modification. Gelatin solutions would gel and form films when temperature is decreased, but HPMC solutions would gel when the temperature is raised. The temperature of the pins is higher (70℃) to let the film form in the dipping process. Then, they will maintain the temperature until the film is dried and form the capsules. Because HPMC capsules are weaker than gelatin capsules mechanically, gelling agents are normally added to increase the strength of HPMC capsules which include tamarind seed polysaccharide, carrageenan, pectin, curdlan, gellan gum and furcellaran (Al-Tabakha, 2010).

According to different dosages of drugs required to be delivered, different sizes of capsules can be used as Table 2.1 showed.

Table 2.1 Size of hard gelatin capsules (Source from Remington, 2006)

Size	Outer Diameter (mm)	Height or Locked Length (mm)	Actual Volume (mL)	Typical Fill Weights (mg) 0.70 Powder Density
000	9.91	26.14	1.37	960
00	8.53	23.30	0.95	665
0	7.65	21.70	0.68	475
1	6.91	19.40	0.50	350
2	6.35	18.00	0.37	260
3	5.82	15.90	0.30	210
4	5.31	14.30	0.21	145
5	4.91	11.10	0.13	90

2.1.3 Difference of gelatin and HPMC capsules

Although gelatin capsules and HPMC capsules can both be used to deliver drugs, their properties are different. For structure, gelatin capsules and HPMC capsules have a gap at the joint of the cap and the body where the capsules are closed. But compared to gelatin capsules, the gap of HPMC

capsules is slightly larger than gelatin capsules (Ku et al. 2010). For mechanical strength, Ku et al. (2010) tested the resistance to breakage by dropping 100g weight from 8 cm height. It is found that gelatin capsules and HPMC capsules have similar resistance to breakage at high relatively humidity. But at low humidity, gelatin capsules would be affected because loss of water at low humidity which affected its elasticity while HPMC capsule would not. For moisture content, HPMC shell has 2–7% moisture content corresponding to RH 10–60% and gelatin capsule has 13–16% corresponding to storage at RH 35– 65% (Al-Tabakha, 2010). For *in vitro* dissolution properties, it is reported that gelatin capsule would disintegrate rapidly and faster than HPMC after put in dissolution media at 37℃ (Al-Tabakha, 2010).

2.1.4 Advantages of capsules

Capsule, different from other solid dosage forms like tablet or pellet, it has its own unique advantages. First, capsules are odorless and tasteless, so they can cover unpleasant odor and taste of medicament to improve patient compliance. Second, capsules can be easily swallowed owing to their smooth surface. And their colorful and glossy appearance increase the attraction of capsules. Third, capsule can also be administrated easily and be digested fast. Forth, the formulation requirement of capsule is minimal compared to tablet because the compression step in tablet manufacturing process was avoided. Thus, formulation development process can be speeded up especially for drugs with low compressibility (Hoag, 2017). Fifth, production of capsules has higher material cost compared to tablets because capsule shell needs to be produced first, but if the total manufacturing cost including total production time, process equipment, formulation development and so on, the cost to manufacture capsules is lower than tablets (Cole, 1998).

However, nothing is perfect, there are also disadvantages of capsules. First, hygroscopic drugs are not suitable for gelatin capsules because they would absorb water from the capsules and make the capsules brittle. But HPMC capsules can be used to fill this type of drugs owing to its lower water content. Second, the concentrated solutions which required previous dilution are not suitable for capsules, or they would cause irritation to stomach after taken.

2.2 Film coating

2.2.1 Purpose of film coating

In pharmacy, a film coating is a thin polymer-based coat applied to a solid dosage form like tablet or capsule. It is frequently applied for the following reasons: First, the film can protect drugs from moisture and/or light, enhance the stability of the drugs and give drugs a long shelf time. Second, for drugs with unpleasant odor and/or taste which make them hard to be taken especially for elder people and younger children, coating film can be used to achieve odor and/or taste masking and improve patient compliance. Third, some functional films can produce film-controlled drug delivery systems which is becoming more popular in the last few decades. These films can modify the drug release profiles, achieving extended drug release or delayed drug release.

2.2.2 Extended release

For extended release, it can be mainly divided into sustained release and controlled release. Sustained release can maintain drug release over a sustained period but not at a constant rate. While controlled release can maintain drug release over a sustained period at a nearly constant rate (Perrie & Rades, 2012). Extended release can decrease dosing frequency and enhance patient adherence. Sometimes people may forget to take drugs if they need to take them frequently, which will cause low curative efficiency of drugs, extend release coating will be able to solve this problem. In addition, extended release solid dosage forms would reduce or eliminate the side effects associated with high peak plasma concentration (Savage & Rhodes, 1995).

Figure 2.4 shows the plasma drug concentration after uncoated (or immediate release) drug and extended release coated drug are taken. For uncoated drug, plasma drug concentration will increase after a drug is taken and reach minimum effect concentration soon. Then the concentration will keep increasing and may be higher than the maximum safe concentration which will be toxic for human body and cause some other side effects. Afterwards, due to metabolism of human body, plasma drug concentration will decrease and when it is lower than minimum effect concentration, patient will need to take another dose of the drug. However, after coating a sustained release film on the drug, the plasma drug concentration will increase slowly and stay between the minimum effect concentration and maximum safe concentration for a longer time compared to uncoated (or

immediate release) drug. And because the drug is released with a slow rate, the plasma drug concentration would not exceed maximum safe concentration leading to less side effects.

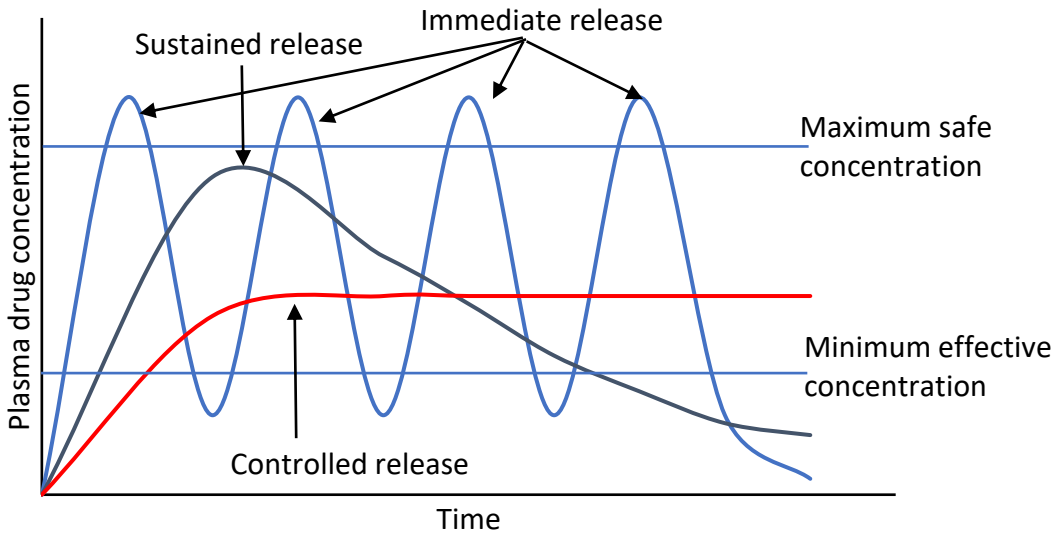


Figure 2.4 Plasma drug concentration after taken extended release drug and immediate release drug

Extended release can be achieved by matrix systems which include reservoir matrix system, monolithic matrix system and osmotic pump system (Nokhodchi et al., 2012).

For reservoir system, the drug was loaded in non-degradable polymeric systems. The drug would be released driven by concentration gradient after dissolved. Figure 2.5 is the reservoir system where a non-degradable porous polymer membrane surrounded the enclosed drugs. When the system was put into water, it would absorb water and the drug would be dissolved. Owing to the different concentration between the inside of membrane and the outside of the membrane, the drug will be released.

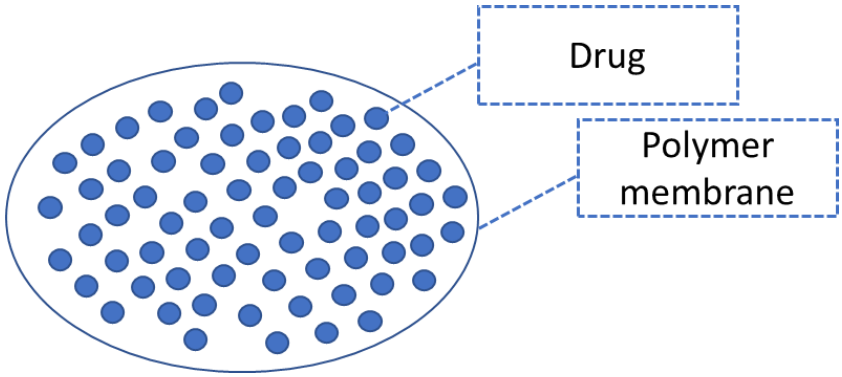


Figure 2.5 Schematic of reservoir system

For monolithic matrix systems, drug is encapsulated or dispersed in a matrix as Figure 2.6 shows. The matrix system where drug is homogeneously distributed is either an insoluble polymer matrix or a soluble matrix. For insoluble matrix, after uptake water, the drug would dissolve and release through the porous polymer matrix driven by concentration gradient in the polymer matrix. For soluble matrix, after merged in water, the matrix will either swell or be eroded and release drug.

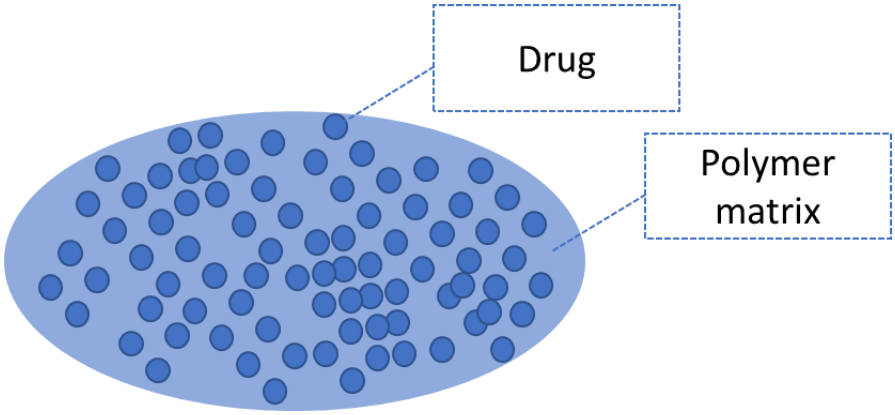


Figure 2.6 Schematic of matrix system

For osmotic pump system, the drugs are loaded with osmotic agents, such as sodium carboxy methyl cellulose, HPMC, crosslinked PVP, in a semipermeable membrane with delivery orifices. The semipermeable membrane is permeable to water but not to particular solutes. After absorb water, the drugs are released at a controlled rate which follows zero-order transport.

Most polymers used for extended release are water-insoluble like Eudragit® RS/RL (copolymers of ethyl acrylate, methyl methacrylate and a low content of trimethylammonioethyl methacrylate chloride), ethyl cellulose, polyvinyl acetate and so on. The molecular structure of Eudragit® RS/RL which is used to achieve sustained release in this study is shown in Figure 2.7. For Eudragit® RS/RL, The molar ratio of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate is approx. 1:2:0.2 in Eudragit® RL and approx. 1:2:0.1 in Eudragit® RS.

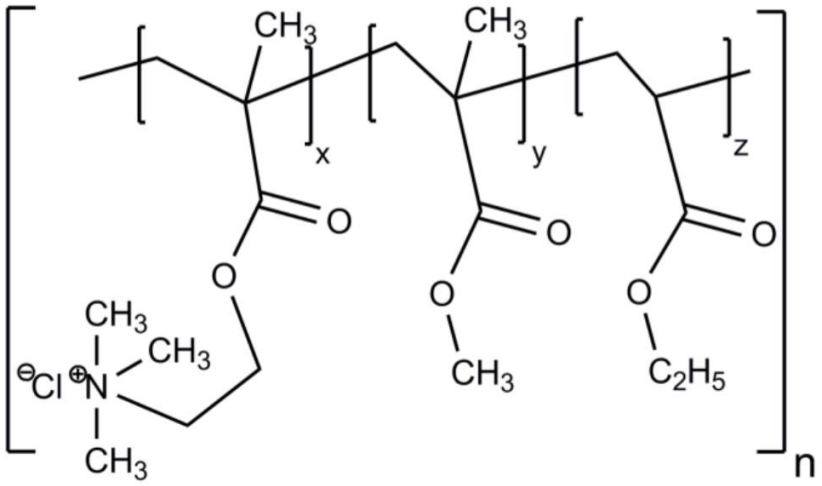


Figure 2.7 Molecular structure of Eudragit® RL and Eudragit® RS ("EUDRAGIT RL 100, EUDRAGIT RL PO, EUDRAGIT RS 100 and EUDRAGIT® RS PO product specification, 2019")

2.2.3 Delayed release

For delayed drug release, it is a release type that prevent drug from releasing after taken until the drug reaches target place in gastrointestinal tract. The films used to achieve delayed release are either time dependent or pH dependent. Enteric release is one type of delayed release which allows the drug to be passed through the stomach and be released in the upper tract of the intestine. The most popular enteric release film is pH dependent. Owing to different pH value at different parts of human's gastrointestinal tract, the coated drug will not dissolve in stomach with low pH value but release after exposed to an environment with a higher pH value like small intestine (Juliano, 1980). This type of release profile has some advantages: First, the coating film can protect the drug from gastric acid and enzymes in the stomach. Because some drugs are acid sensitive and will

degrade when contact with acid or be digested by enzymes in the stomach, enteric release coating becomes necessary. Second, the coating film can also protect stomach from irritation caused by some drugs like aspirin and potassium chloride. These drugs may damage stomach mucosa and cause nausea or stomach bleeding. Third, enteric coating can also be used to obtain drug targeting. Some drugs, like anthelmintics, target intestine where enteric coating can ensure drug will only dissolve and have a high concentration in intestine.

Aside from enteric coating, there are also other delayed release coatings to make drugs release in different position of the digestive tract like colon. Figure 2.8 is the release profiles of immediate release drugs and delayed release drugs. After taken, the immediate release drugs will dissolve and be absorbed by human body rapidly resulting in the plasma drug concentration increasing shortly. However, for delayed release coated drugs, they will not release any drug until they reach certain part of gastrointestinal tract or after certain time. Then the drug can be released, absorbed and increase plasma drug concentration.

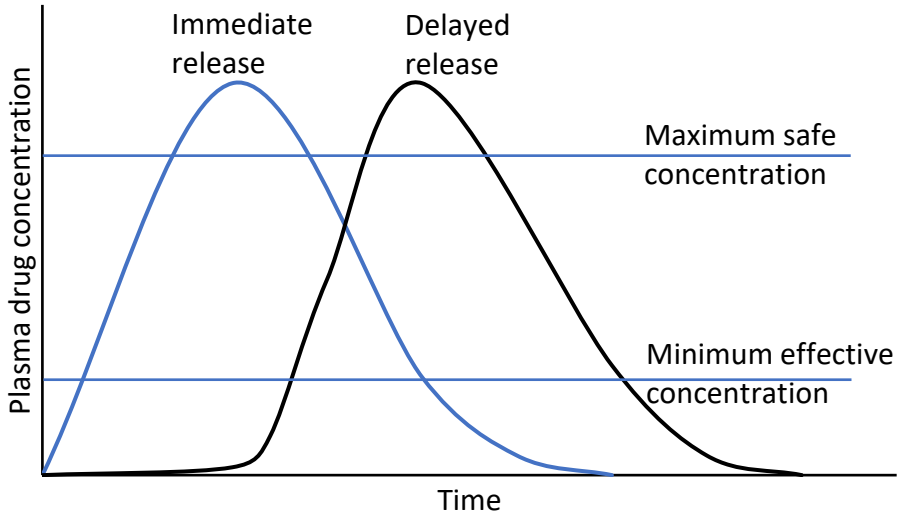


Figure 2.8 Plasma drug concentration after taken delayed release drug and immediate release drug

The polymers used for enteric coating are either nature polymers like shellac or synthetic polymers like Eudragit® L 100-55 (Methacrylic Acid - Ethyl Acrylate Copolymer), Hydroxypropyl methyl cellulose phthalate (HPMCP), Polyvinyl acetate phthalate (PVAP) and so on. Figure 2.9 is the

molecular of Eudragit® L 100-55 which is the polymer used in this study to achieve enteric release. For Eudragit® L 100-55, the ratio of the free carboxyl groups to the ester groups is approx. 1:1 and the monomers are randomly distributed along the copolymer chain.

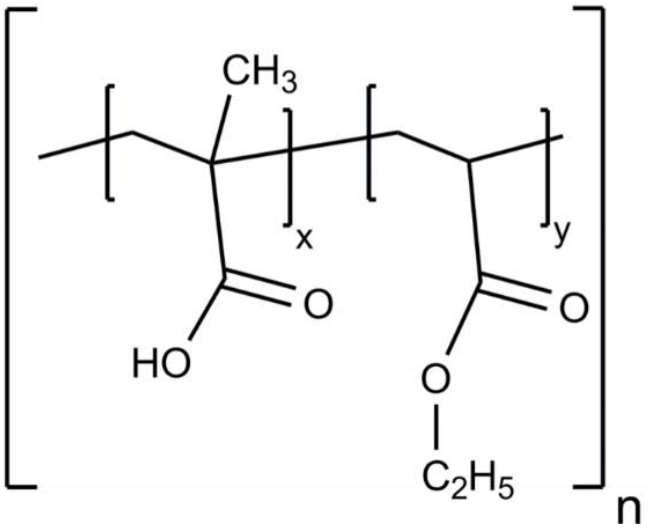


Figure 2.9 Molecular structure of Eudragit® L 100-55 (EUDRAGIT® L 100-55 product specification, 2019)

2.3 Conventional capsule coating processes

2.3.1 Advantages of capsule coating

Capsules are mainly coated to achieve different release properties. Compared to tablets and pellets, capsules have unique advantages during coating process. Due to the existence of capsule shell as a barrier, it separates the enclosed drug and coating materials. Thus, for those drugs which may react with ingredients in the coating materials like talc, plasticizer etc. capsule can provide a good protection to prevent degradation caused by direct contact of drugs and coating materials. While, for tablets or pellets, a sub-coating is required as a barrier if the drugs (like esomeprazole magnesium tri-hydrate) and coating materials will have negative influence on each other.

2.3.2 Organic solvent coating

Figure 2.10 shows the organic solvent coating process. First, most coating materials is dissolved into an organic solvent and the formed solutions will be sprayed onto the solid dosage forms using

a liquid spray gun. At the same time, the organic solvent will be evaporated to let coating polymer molecules contact and form the film (Pearnchob & Bodmeier, 2003; Wesseling & Bodmeier, 1999). After spraying the solution for some time, a uniform coating film will be formed. However, a few polymers cannot be dissolved by organic solvent but disperse in the organic solvent. In this case, this coating process can still be used but with different film formation mechanism.

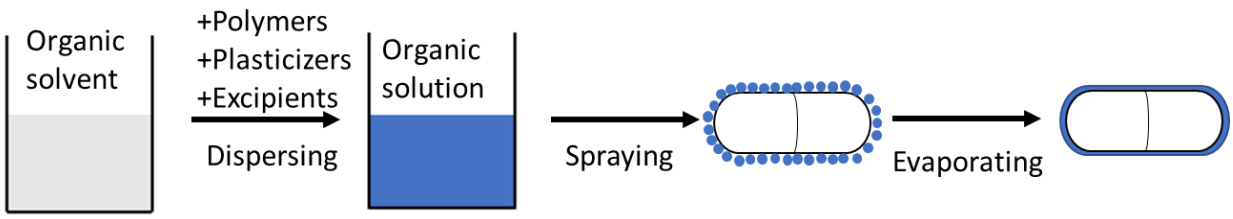


Figure 2.10 Organic solvent coating process

Figure 2.11 is the schematic of organic solvent coating system. It includes a round coating pan, a liquid spraying system, inlet air and outlet air. The round coating pan is porous to let the inlet air be able to go through the loaded substrates in the coating pan and bring the evaporated organic solvent out of the system. The coating pan is rotating when organic solvent is sprayed to let substrates be coated uniformly.

Organic solvent coating process was mainly used to coat gelatin capsules. Pina et al. (1996) coated gelatin capsules by simply immerse capsules into hydroalcoholic solution of formaldehyde and then dried in an oven. Murthy et al. (1986) found that organic solvent coating will lead to poor adhesion of the coating film to the gelatin capsules owing to the smooth surface of the capsules, which is also called orange peel effect. Later, (Murthy, Kubert, & Fawzi, 1988) applied a precoat consisted of HPC to increase the adhesion of enteric coating films.

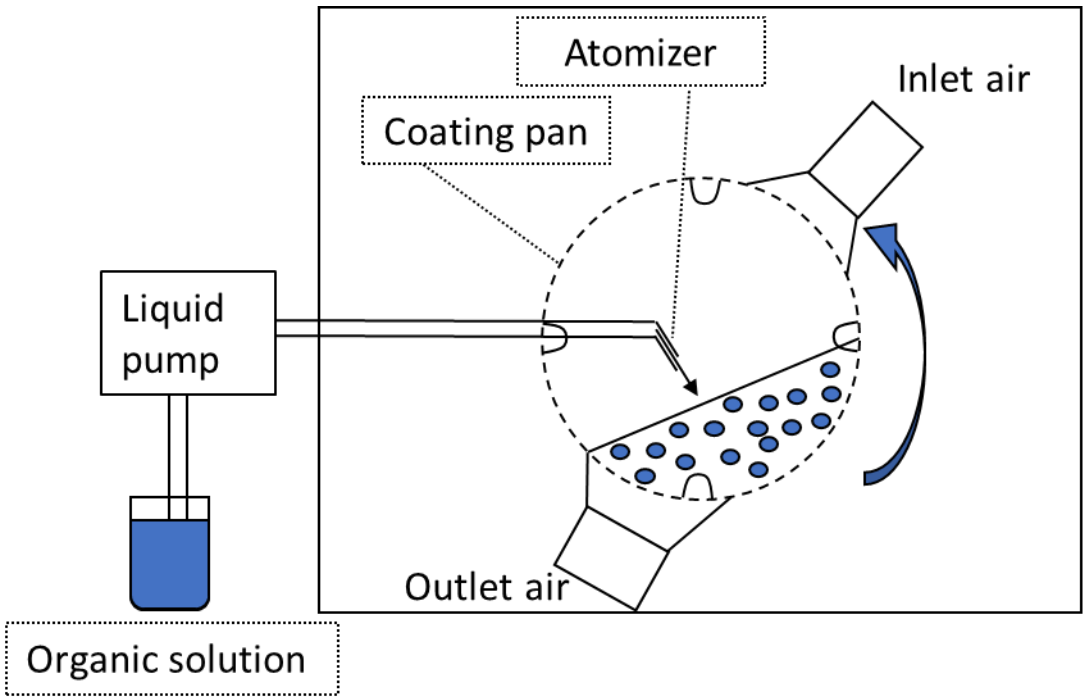


Figure 2.11 Schematic of organic solvent coating system

Except drawbacks of organic solvent coating mentioned above, Film coating based on organic solvent has many other limitations. First, organic solvent coating will cause toxicological, environmental and safety-related issues in the coating process (Aulton et al., 1995). Second, the concentration of coating solution cannot be too high, or the spray nozzle may be blocked due to high viscosity. Consequently, a large amount of organic solvent is required to dilute the solution which prolong the coating time and causes more pollution. Third, after-treatment and recovery of organic solvent is necessary which would significantly increase the overall cost.

2.3.3 Aqueous coating

Owing to the disadvantages of organic solvent coating, aqueous coating was developed to replace organic solvent coating process. However, unlike solvent coating, a lot of polymers are not able to dissolve into water but dispersed in the water. Figure 2.12 is the aqueous coating process with coating dispersion. First, the insoluble coating polymers and other additives are milled into fine particles, then dispersed into water to form a coating dispersion. Then, a liquid atomizer is used to

spray the coating dispersion onto the surface of the substrates to be coated, at the same time, water is evaporated by hot air and the coating particles coalesce together to form the coating film.

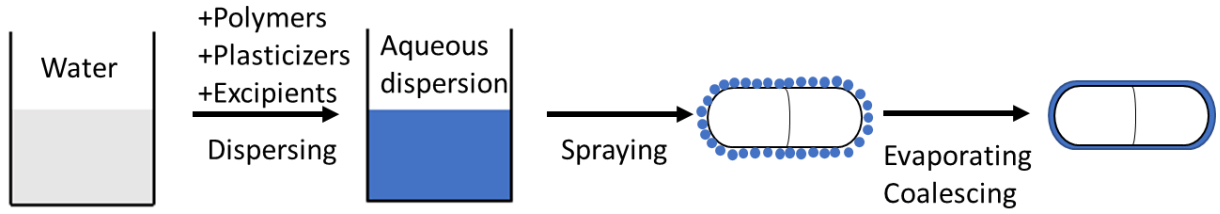


Figure 2.12 Aqueous coating process

Figure 2.13 is the schematic of aqueous coating system. It is same as organic solvent coating system which also includes a round porous coating pan, a liquid spraying system, inlet air and outlet air.

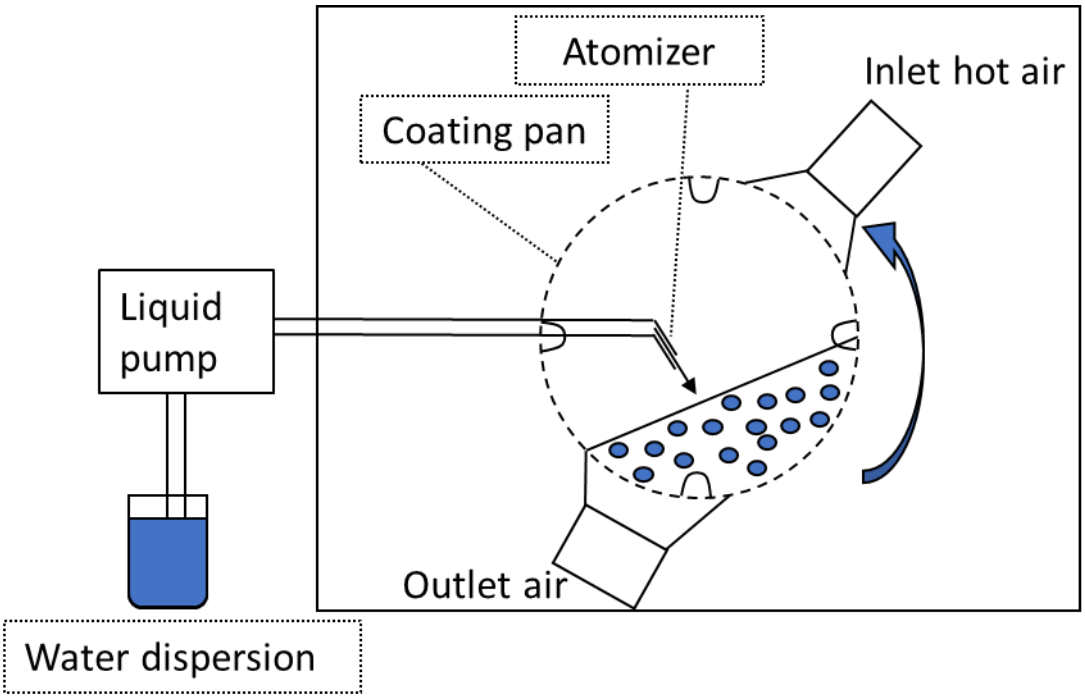


Figure 2.13 Schematic of aqueous coating system

In the aqueous coating process, those wet polymer particles would coalesce after sprayed on the surface of substrate, deform and fuse together to form a coating film. Capillary force between particle and particle, particle and substrate could significantly encourage the coalescence of particles during the water evaporation process. For aqueous coating process, hot air is necessary to carry out the moisture and to provide heat for the deformation and fusion of the coating particles.

For gelatin capsules, Oliveira et al. (2005) used Eudragit®L30 D55 aqueous solution to coat the hard gelatin capsules in a spouted bed and investigated its coating efficiency. Felton et al. (1995) used the same material to coat soft gelatin capsules and examined their properties. Then, Pissinati & Oliveira (2003) also coated soft gelatin capsules with same materials but in a spouted bed to improve the coating efficiency and uniformity of product, and reduced stickiness between gelatin capsules to some extent. However, the main difficulty with aqueous coating process is that the gelatin capsules become soft and sticky due to being partially dissolved after aqueous coating materials were sprayed. In addition, shell embrittlement may also happen in aqueous coating process (Thoma & Bechtold, 1992). Cerea et al. (2008) used a dry coating technology to coat soft gelatin capsules in a rotary fluid bed with enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS) as coating materials. However, a sealing film coated by 10% (wt/wt) solution of copovidone was still required.

HPMC capsules, as a great alternative to gelatin capsules, have also been coated to achieve delayed release. And because of rougher surface of HPMC capsules (Zhang et al., 2008), adhesion of the coating materials may be increased. Cole et al. (2002) use two aqueous solutions, Eudragit®L 30 D-55 and Eudragit® FS 30 D, to achieve enteric release and colon release respectively. This coating process was carried out in a coating pan. Huyghebaert et al. (2004) coated HPMC capsule shells only before drug filling in a fluidizing bed apparatus and developed ready-to-use enteric-coated capsules. Dvořáčková et al. (2010) coated both HPMC and gelatin capsules with isopropyl alcohol solution in Wurster-M 100 coater. The result showed that film peeling occurred for gelatin capsules, but HPMC capsules and gelatin capsules sub-coated with hydroxypropyl cellulose (HPC) did not. Shell humidity loss caused by organic solvent in coating process would cause embrittlement of gelatin capsules but would not influence HPMC capsules owing to relative low moisture content in the capsule shell (Dvořáčková et al., 2011)

Although aqueous coating is still the preferred coating method compared to solvent coating considering its benefits, it still has several disadvantages. First, because the specific heat capacity of water is high, a lot of heat is required for water evaporation. Thus, more energy and longer processing time are required. Second, hot air used to evaporate water is required to be purified entering the and heated up to a certain temperature before enters into coating system. And it also needs to be cleaned again after goes through the coating process and before it leaves the system, which would further increase the overall cost. And most important, aqueous coating technology is not suitable for moisture sensitive drugs since the whole process is carried out in a high humidity environment (Bose & Bogner, 2007; Cahyadi et al., 2015). Therefore, an alternative coating process is required.

2.4 Electrostatic dry powder coating technology

2.4.1 Development of solventless coating process

In the last few decades, many efforts have been devoted to developing pharmaceutical dry coating technologies like compression coating (Rujivipat & Bodmeier, 2012), photocuring coating (Kutal et al., 1991), supercritical fluid coating (Ni et al., 2011; Yue et al., 2004) and hot-melt coating (Achanta et al., 1997; Dreu et al., 2012; Hampel et al., 2013), to overcome the limitations caused by the use of solvent or water. And they all have their advantages and disadvantages.

Compression coating, also named as press coating, is mainly proposed to coat tablets (Kim, 1995). In this process, drugs and excipients are firstly compressed into a core, then the core is embedded in powdered coating materials and be compressed again to form the coated tablets. The main drawback for the compression coating is its uniformity. Because the core cannot always be located at the center of the outer shell, the coated film may be thinner on one side and thicker on the other (Matsuo et al., 1996). In addition, the overall film thickness would be high to ensure the thinner side of the film can protect the tablet core (Ozeki et al., 2004).

Photocuring coating uses polymerization reaction of photo-curable materials to form films (Bose & Bogner, 2007). There are three major components in photocuring coating systems: functionalized liquid prepolymers as reagents of polymerization, a photosensitizer to initiate the reaction and a UV-visible light source to trigger the reaction. This coating process is suitable for

thermosensitive drugs, because it is performed at room temperature. However, it can not be used for photosensitive drugs and has limited types of coating polymers.

Supercritical fluid coating utilizes rapid expansion of supercritical solutions (RESS) (Bose & Bogner, 2007; Tsutsumi et al., 1995) to coat drug cores. In this process, the coating materials are dissolved while drug cores are dispersed in a liquid-like supercritical fluid such as carbon dioxide (Thies, 2003). Then the volume of this fluid is rapidly expanded to let the fluid transfer from a supercritical state in a gas state. The dissolved coating materials will precipitate onto the surface of the undissolved drug cores and form films. This technology avoids use of organic solvent and water and supercritical fluid can be eliminated completely after decompression, but most coating materials have poor solubility in supercritical fluids and drug cores are required to be insoluble in supercritical fluids.

Hot-melt coating includes two main steps: Spraying melted coating materials onto the surface of the substrate, followed by the cooling step for film formation. Normally, this operation is carried out by a rotating pan or fluidized bed with lipids (such as partially hydrogenated cottonseed oil/soybean oil, partially hydrogenated palm oil, beeswax, paraffin wax) as coating agents because of their low melting points (Achanta et al., 2001; Chen et al., 2010; Jannin et al., 2008; Jannin & Cuppok, 2013; Sinchaipanid et al., 2004). The major issue of this technology is requirement of temperature. The temperature needs to be high enough to melt the coating materials and prevent blocking of spray nozzle and tube, while it also needs to be controlled to be low enough to prevent thermosensitive drugs from degradation.

Dry powder coating uses a mixture of powdered coating polymers, pigments and other excipients to coat substrate directly. The mixture is sprayed onto the substrates, followed by curing steps under certain temperature for film formation. There are two key steps in the process: coating powder adhesion and film formation. Better coating powder adhesion on the surface of solid dosage forms can achieve a high coating efficiency and better film formation can lead to high film quality. Heat energy and some forces, like capillary force and electrostatic force, can be used to improve powder adhesion (Luo et al., 2008). And film formation for dry powder coating resulting from viscous flow and particle deformation can be improved by combination of plasticizers and heat (Kablitz & Urbanetz, 2007).

Thermal adhesion powder coating uses heat to promote coating powder adhesion and provide energy for curing and film formation. (Cerea et al., 2004) developed an infrared-assisted powder coating technology and use Eudragit® EPO as the coating material due to its lower glass transition temperature. At the glass transition temperature, the polymer will transit into a reversible viscous state and form a film after levelling, coalescence and cooling. In this coating process, the substrates were first loaded into a rotating disk and fed with coating materials, an infrared lamp was used to provide heat before feeding coating materials to preheat the substrates and during powder feeding to provide energy for powder coalescence. Then the film would be formed after cooling. Although this technology avoids the use of any liquid including plasticizer, it can only be used for drugs that are not thermosensitive and requires coating materials with low glass transition temperature.

Liquid plasticizer-assisted powder coating uses small amount of water or liquid plasticizer to promote coating powder adhesion and film formation (Kablitz et al., 2006; Obara et al., 1999; Pearnchob & Bodmeier, 2003). It is reported that small amount of water can improve the coating film quality, like smoothness and integrity (Obara et al., 1999), which is because it provides capillary force between coating particles. And liquid plasticizer can not only promote powder adhesion, but also reduces glass transition temperature of coating polymers so that drugs can be coated at a lower temperature to prevent degradation. However, this technology is still not suitable for moisture sensitive drugs if water is used. And concentration of liquid plasticizer should be carefully balanced because less plasticizer would have limited promotion to adhesion, but surplus plasticizer would possibly lead to very soft or sticky films. In addition, the coating powder feeding cannot be well controlled resulting in a non-uniform coating film.

2.4.2 Electrostatic dry powder coating

Electrostatic force was introduced in dry powder coating technology to promote coating efficiency and increase film uniformity (Hogan et al., 2000; Hogan et al., 2006; Newman et al., 2007; Reeves et al., 2004). Figure 2.14 is schematic of electrostatic dry powder coating technology. In the coating process, electrostatic spray gun would ionize the air between the gun and the coating substrates by imposing a high voltage. Then when coating particles are sprayed by the gun, they will pick up electron generated by air ionization. These negative charged particles would deposit on substrates more easily and more uniformly leading to more uniform films (Luo et al., 2008).

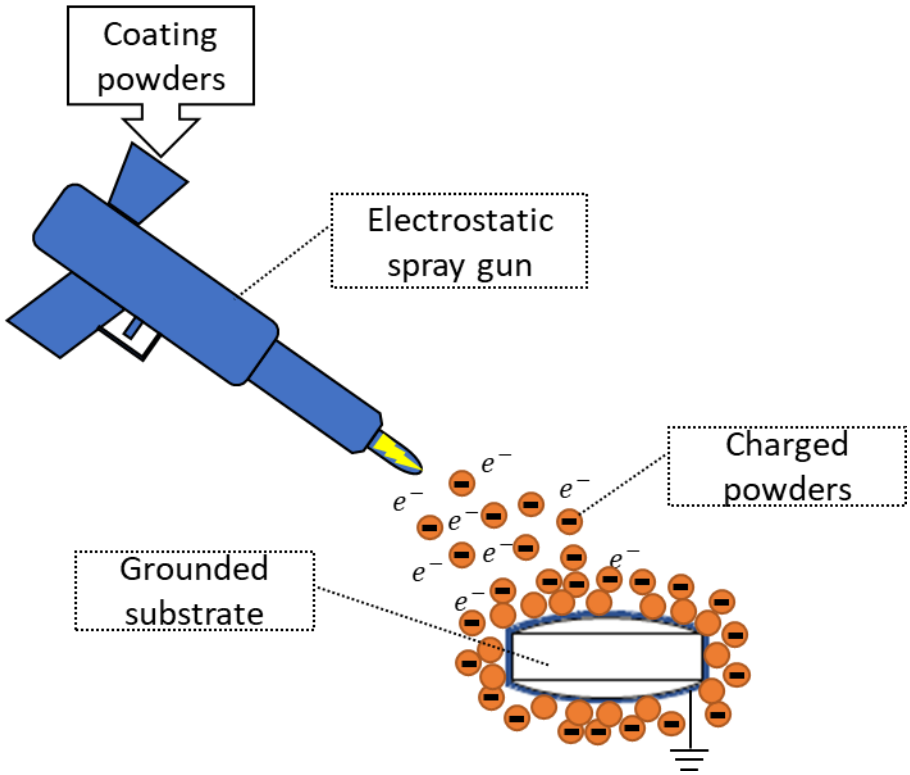


Figure 2.14 Electrostatic powder coating process

Zhu's group developed an electrostatic dry powder coating technology to coat pharmaceutical solid dosage forms without using organic solvent or water (Zhu et al., 2011,2012; Luo et al., 2008). A similar apparatus as conventional organic solvent and aqueous coating apparatus, shown in Figure 2.15, was used to carry out this dry powder coating process. The apparatus mainly consists of a heating system, a grounded rotating coating pan to hold the solid dosage forms, a liquid spraying system which includes a liquid pump and an atomizer to spray the liquid plasticize, and an electrostatic powder spraying gun to spray the coating powders. Since the plasticizer is not the solvent but would be left in the coating film as a coating material, it can be called a "dry" coating process.

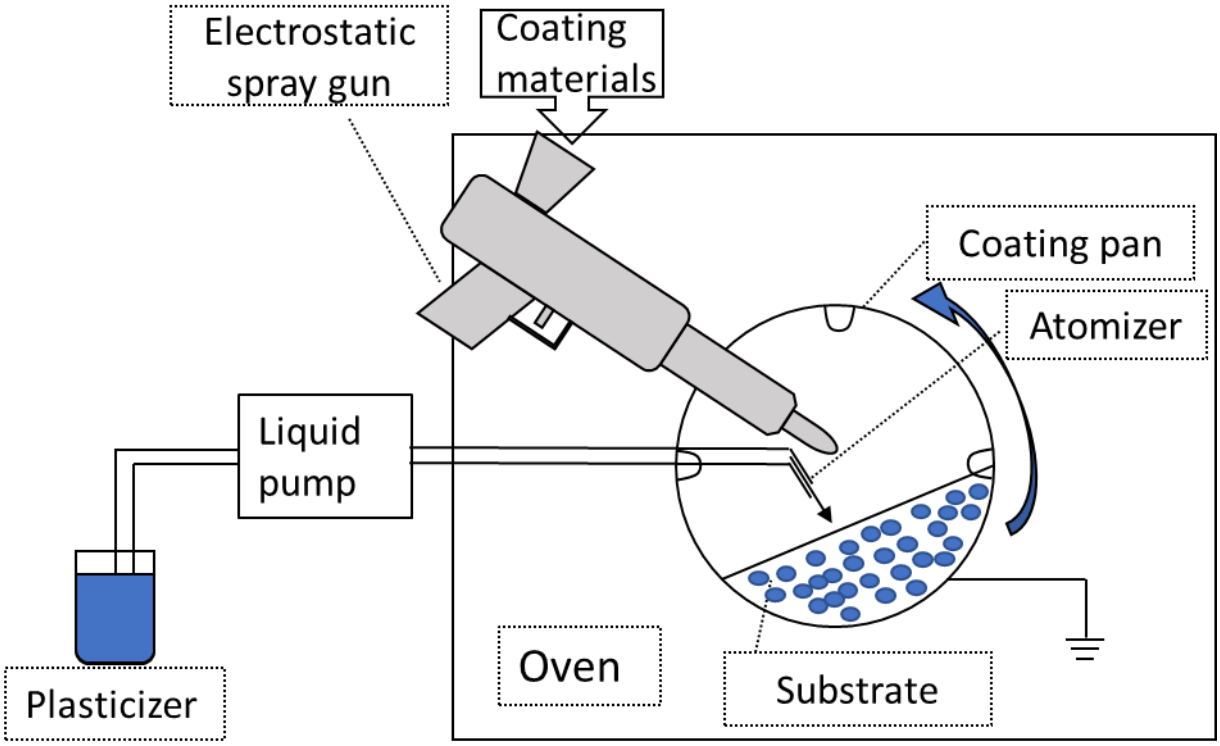


Figure 2.15 Schematic of dry powder coating apparatus

Figure 2.16 is the process of dry powder coating technology. First, substrates are loaded into the coating pan and preheated for a certain period. Second, liquid plasticizer is sprayed first on the substrates and then followed by spraying coating materials. This step can be repeated for several times to increase the film thickness of the final products. Finally, solid dosage forms will be kept in the rotating coating pan to let those deposited coating particles coalesce, curing and form a uniform coating film.

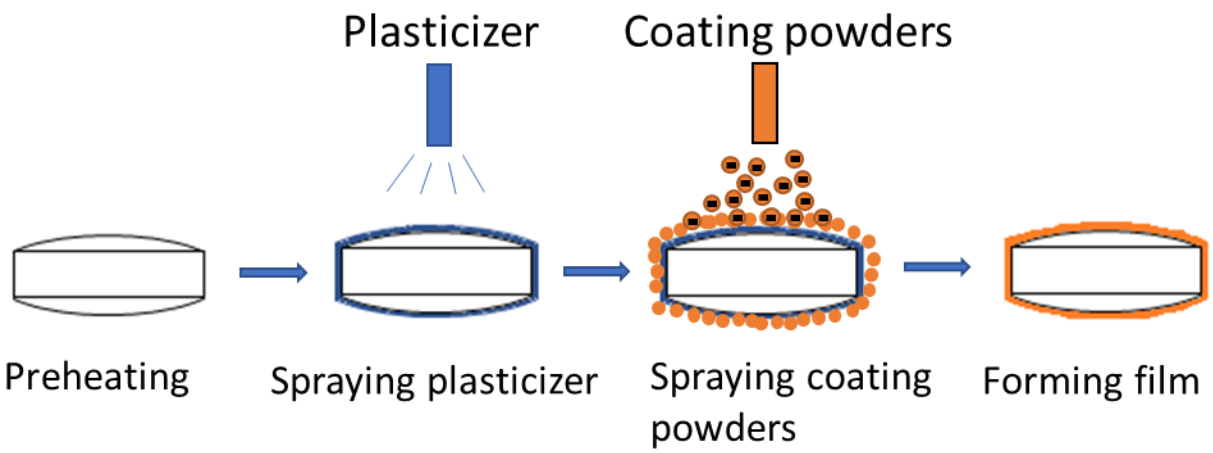


Figure 2.16 The outline of electrostatic dry coating process.

Compared to other pharmaceutical dry coating technologies mentioned above, electrostatic dry powder coating technology is able to coat film with shorter processing time, lower energy and consequently reduces overall operation cost. In addition, due to application of electrostatic force, the adhesion of coating powders is enhanced causing significant promotion of the coating efficiency. This technology has been successfully applied on tablets small pellets to achieve different drug release profiles (Qiao et al., 2010; Qiao et al., 2010; Qiao et al., 2013; Yang et al., 2018; Yang et al., 2015; Yang et al., 2016).

2.4.3 Film formation mechanism

Although organic solvent coating process, aqueous coating process and electrostatic dry powder coating process can all form films, their film formation mechanisms are different. For the solvent coating and aqueous coating processes where coating polymers can be dissolved in the solutions, the process includes the conversion of a viscous liquid into a visco-elastic solid during evaporation of the organic solvent or water (Porter et al., 2017).

However, for the solvent coating or aqueous coating with insoluble coating polymers, the coating dispersion replaces the solution and is sprayed onto the surface of the solid dosage. Its mechanism is fundamentally different from solvent coating or aqueous coating with soluble coating polymers. For coating dispersion, after the evaporation of the solvent or water, particles of coating materials coalesce into a film resulting from the deformation and viscous flow of those deposited coating

powders (Kablitz & Urbanetz, 2007; Keddie et al., 1995). In this process, capillary force has a great function for the coalescence of coating particles and film formation (Klar & Urbanetz, 2009). During the evaporation of organic solvent or water, the porosity of the film is reduced and a capillary network is formed in the film structure, leading to development of capillary force that squeeze the particles together (Porter et al., 2017).

The film formation mechanism of dry powder coating is similar to solvent coating or aqueous coating with insoluble coating polymers (Lecomte et al., 2004; Luo et al., 2008). Figure 2.17 shows the formation of the film in dry powder coating process. First, the powdered polymers are sprayed on the substrate. Then, they will coalesce which includes the deformation and viscous flow of the powders. Finally, the film formed after leveling and cooling. (Kablitz & Urbanetz, 2007; Qiao et al., 2013). In this process, softening, deformation, and curing are the principal steps to form the film (Belder et al., 2001; Pfeffer et al., 2001; Wulf et al., 2000). And these steps can be facilitated by following methods: First, the substrate can be preheated above or close to the glass transition temperature of the coating polymers. Thus, when powders sprayed on the substrate, they can be easily adhered and softened. Second, surface tension could be controlled and adjusted by modifying the coating formulations to increase the film uniformity and forming speed (for example, adding some levelling additives to the formulations to facilitate curing step) (Misev, 1991). Third, owing to thermosensitive properties of most drugs, the operating temperature cannot be too high. Solid or liquid plasticizers are commonly used during coating to reduce the glass transition temperature (Tg) of coating polymers, so that polymers can coalesce under a relatively lower temperature. Liquid plasticizer can also promote adhesion forces between the particles and substrate resulting in higher coating efficiency (Cerea et al., 2004; Kablitz et al., 2006; Kablitz et al., 2008; Lecomte et al., 2004).

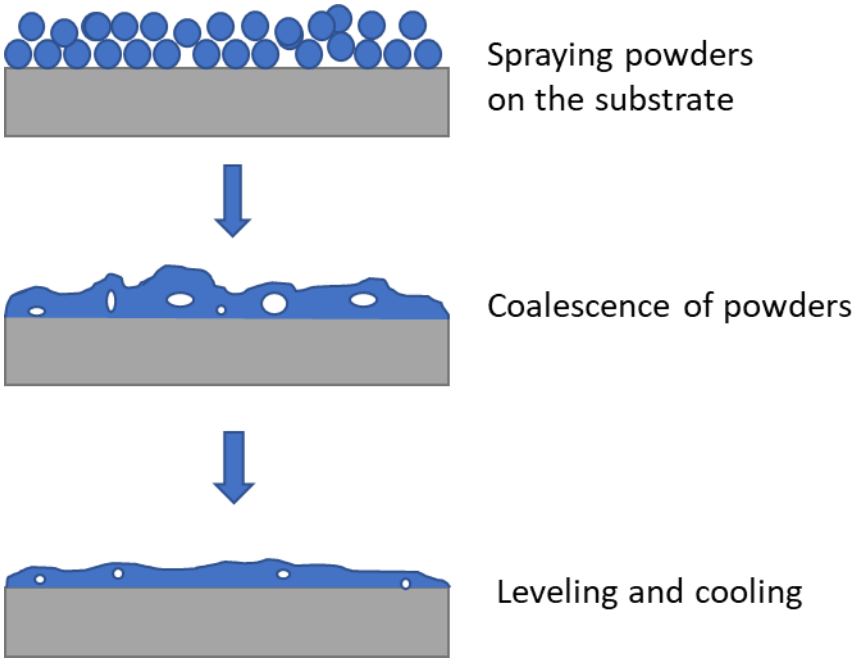


Figure 2.17 Schematic of film formation in dry powder coating systems

2.5 Aspirin

2.5.1 Introduction

Salicylic acid (SA), was first found in bark from the willow tree and has been used to relieve inflammation and fever for at least 2,400 years (Jones, 2005; Ravina, 2011). In 1853, acetylsalicylic acid, also known as aspirin today, was first synthesized by Charles Frédéric Gerhardt by treating sodium salicylate with acetyl chloride (Jeffreys, 2008). The molecule of acetylsalicylic acid was showed in Figure 2.18. However, not much attention was paid on this drug until 1897. Owing to high irritating effect of salicylic acid, Bayer start to investigate acetylsalicylic acid as a replacement to treat fever, pain and inflammation. And by 1899, Bayer sold acetylsalicylic acid around the world and named it Aspirin as a brand name (Mann & Plummer, 1991).

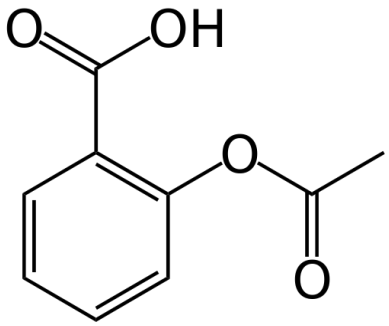


Figure 2.18 Molecule of acetylsalicylic acid

Aspirin is the first non-steroidal anti-inflammatory drug (NSAID) to be discovered. And even after it was founded more than 150 years and sold around the world for more than 100 years, aspirin was still wildly used to treat fever, pain and inflammation.

Cardiovascular disease (CVD), including heart disease and stroke, is one of the major causes of death and disability around the world. It is reported that aspirin can be used to prevent blood clots from forming in the blood vessels owing to its antiplatelet effect. Thus, taking aspirin can help certain people lower their risk of a heart attack or stroke, especially for those people who have already had heart attacks or strokes and people who are at high risk of having one. It is recommended for these certain people to take low dose aspirin for a long term to prevent second heart attack or stroke. Also, taking high dose of aspirin shortly after heart attack will lower the risk of death (Baigent et al., 2009; Erkan et al., 2007; Lansberg et al., 2012; Paikin Jeremy S. & Eikelboom John W., 2012; Patrono et al., 2005).

In addition, some researchers found that aspirin may also be able to lower the risk of colorectal cancer recently (Garcia-Albeniz & Chan, 2011; Patrignani & Patrono, 2016). In 2016, the United States Preventive Services Task Force (USPSTF) recommended the use of low-dose aspirin (75 to 100 mg/day) "for the primary prevention of CVD (cardiovascular disease) and CRC in adults 50 to 59 years of age who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years" (Bibbins-Domingo, 2016).

2.5.2 Enteric release aspirin

However, just like every drug, aspirin has some sides effects. The most common one is gastric irritation. Long-term use of aspirin will increase risk of ulcers gastric bleeding(Baigent et al., 2009; Sørensen et al., 2000). And currently, enteric coating is the widely used to prevent upsets of stomach. It is reported that enteric coated aspirin can reduce gastric mucosal damage and the risk of gastrointestinal bleeding (Hawthorne et al., 1991; Hoftiezer et al., 1980; Lanza et al., 1980; Walker et al., 2007). In addition, aspirin is water sensitive and will be hydrolyzed into salicylic acid (SA) in the presence of water. Figure 2.19 shows the reaction of aspirin hydrolysis. It is claimed that enteric coating can also provide a barrier to protect ASA from hydrolysis during storage (Mujahid et al., 2013).

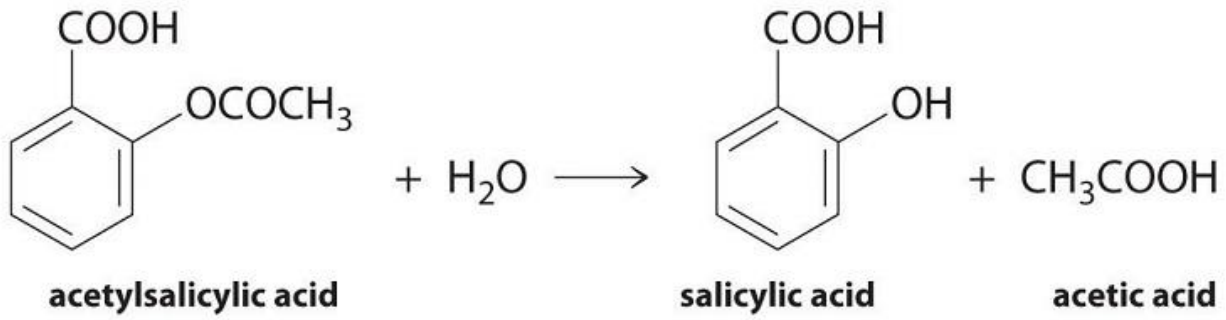


Figure 2.19 Hydrolysis of acetylsalicylic acid

2.5.3 Conventional aspirin coating processes

Conventionally, aspirin was coated either in tablets form or pellets form. Würtz et al. (2014) reported that extended release aspirin would provide anti-thrombotic benefits for a long time. Aspirin particles were coated with release rate limiting polymer and filled into capsules to achieve extend release (Bliden et al., 2015). Tablet was the most common dosage form for aspirin. Normally it is coated by aqueous coating technology in coating pan (Cunningham et al., 2001; John et al., 1981) However, aspirin can be hydrolyzed in presence of water, thus, aqueous coating process may not be suitable for aspirin coating owing to its high moisture environment in the coating process (Mwesigwa et al., 2008).

In addition, aspirin tablets will be hydrolyzed and become salicylic acid during storage. There are three possible theories about what caused the hydrolysis (Wang et al., 2017): First, the water left

at the interface between the film and tablet core during the aqueous coating process causes the hydrolysis (Mwesigwa et al., 2008). Second, the moisture in the environment will penetrate the coating film which causes degradation of drugs (Joshi & Petereit, 2013). Third, aspirin may be react with excipients in the coating film or excipients in the aspirin tablet cores (Petereit & Weisbrod, 1999). It is reported that ASA may migrate form tablet core into coated film and change film properties (Okhamafe & York, 1989; Ruotsalainen et al., 2003). And the additives in the coating materials, such as macrogol and talc may also be the reason why aspirin degrade (Carstensen & Attarchi, 1988; Petereit & Weisbrod, 1999).

In order to avoid aspirin tablets degradation during coating process, a sub-coating layer is applied to separate tablet core and coating film. Opadry® was used as seal coating for highly water-soluble, organic acid to protect it from moisture (Crotts et al., 2001). A hot-melt sub-coating followed by enteric aqueous coating can improve the stability of aspirin tablets (Wang et al., 2017). However, the requirement of sub-coating layer makes the coating process more complicated and increase the cost. Therefore, an alternative coating process is required for aspirin coating process.

Electrostatic dry powder coating process mentioned above is a good alternative technology to coat aspirin because it eliminates organic solvent and water in coating process which would decrease the hydrolysis of aspirin. And by using capsules to deliver aspirin could prevent the potential interaction of aspirin and enteric coating films.

2.6 Summary

Organic solvent and aqueous coating process are still the most commonly used coating technologies to coat pharmaceutical solid dosage forms to modify the release. However, it is not suitable for capsule, who is becoming popular in the last few decades because of the smooth surface, organic solvent and water sensitivity of gelatin capsules and HPMC capsules. Poor adhesion, shell embrittlement and stickiness would appear in organic solvent or aqueous coating process. In addition, organic solvent coating process has toxicity, pollution, safety related issued, while aqueous coating process has energy consumption, processing time issues. And for moisture sensitive drugs, like aspirin, aqueous coating process would cause its degradation. Thus, an alternative coating process is required.

The electrostatic dry powder coating process developed by Zhu's group is considered to a great alternative technology for organic solvent and aqueous coating. This technology eliminates the use of organic solvent and water resulting in a more environmentally friendly, more energy and time saving, more safe and convenient coating process. And the process has no organic solvent or water applied in the coating process which makes it promising to be applied on capsules coating to avoid the difficulties appear in liquid coating process. In addition, apply the dry powder coating technology on moisture sensitive drug, aspirin, could prove the advantages of the coating process for moisture sensitive drugs and provide a better understanding about what is the reason that caused the hydrolysis of enteric coated aspirin during storage.

Bibliography

Achanta, A. S., Adusumilli, P. S., James, K. W., & Rhodes, C. T. (1997). Development of Hot Melt Coating Methods. *Drug Development and Industrial Pharmacy*, *23*(5), 441–449.

Achanta, A. S., Adusumilli, P. S., James, K. W., & Rhodes, C. T. (2001). Hot-Melt Coating: Water Sorption Behavior of Excipient Films. *Drug Development and Industrial Pharmacy*, *27*(3), 241–250.

Aulton, M., Cole, G., & Hogan, J. (1995). *Pharmaceutical coating technology*. Taylor & Francis.

Baigent, C., Blackwell, L., Collins, R., Emberson, J., Godwin, J., Peto, R., Buring, J., et al. (2009). Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)*, *373*(9678), 1849–1860.

Belder, E. G., Rutten, H. J. J., & Perera, D. Y. (2001). Cure characterization of powder coatings. *Progress in Organic Coatings*, *42*(3), 142–149.

Bliden, K. P., Patrick, J., Pennell, A. T., Tantry, U. S., & Gurbel, P. A. (2015). Drug delivery and therapeutic impact of extended-release acetylsalicylic acid. *Future Cardiology*, *12*(1), 45–58.

Bibbins-Domingo, K. (2016). Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force recommendation statement. *Annals of internal medicine*, *164*(12), 836-845.

Bose, S., & Bogner, R. H. (2007). Solventless pharmaceutical coating processes: a review. *Pharmaceutical Development and Technology*, *12*(2), 115–131.

Brown, M. D. (1996). Improvements in or relating to encapsulation. *International Patent Application WO 9 735 537*.

Cahyadi, C., Chan, L. W., & Heng, P. W. S. (2015). A comparative study between conventional pan coater and quasi-continuous small batch coater on the stability of tablets containing acetylsalicylic acid. *European Journal of Pharmaceutics and Biopharmaceutics*, *90*, 30–37.

Carstensen, J. T., & Attarchi, F. (1988). Decomposition of Aspirin in the Solid State in the Presence of Limited Amounts of Moisture II: Kinetics and Salting-in of Aspirin in Aqueous Acetic Acid Solutions. *Journal of Pharmaceutical Sciences*, *77*(4), 314–317.

Cerea, M., Foppoli, A., Maroni, A., Palugan, L., Zema, L., & Sangalli, M. E. (2008). Dry Coating of Soft Gelatin Capsules with HPMCAS. *Drug Development and Industrial Pharmacy*, *34*(11), 1196–1200.

Cerea, M., Zheng, W., Young, C. R., & McGinity, J. W. (2004). A novel powder coating process for attaining taste masking and moisture protective films applied to tablets. *International Journal of Pharmaceutics*, *279*(1), 127–139.

Chiwele, I., Jones, B. E., & Podczeck, F. (2000). The shell dissolution of various empty hard capsules. *Chemical and pharmaceutical bulletin*, *48*(7), 951-956.

Chen, H., Shi, S., Liu, A., & Tang, X. (2010). Combined application of extrusion-spheronization and hot-melt coating technologies for improving moisture-proofing of herbal extracts. *Journal of Pharmaceutical Sciences*, *99*(5), 2444–2454.

Cole, E. T., Cadé, D., & Benameur, H. (2008). Challenges and opportunities in the encapsulation of liquid and semi-solid formulations into capsules for oral administration. *Advanced Drug Delivery Reviews*, Lipid-Based Systems for the Enhanced Delivery of Poorly Water Soluble Drugs, *60*(6), 747–756.

Cole, E. T., Scott, R. A., Connor, A. L., Wilding, I. R., Petereit, H.-U., Schminke, C., Beckert, T., et al. (2002). Enteric coated HPMC capsules designed to achieve intestinal targeting. *International Journal of Pharmaceutics*, *231*(1), 83–95.

Cole, G. (1998). Evaluating development and production costs: Tablets. *Pharm. Technol. Eur*, *5*, 17-26.

Crotts, G., Sheth, A., Twist, J., & Ghebre-Sellassie, I. (2001). Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid. *European Journal of Pharmaceutics and Biopharmaceutics*, *51*(1), 71–76.

Cunningham, C. R., Kinsey, B. R., & Scattergood, L. K. (2001). Formulation of acetylsalicylic acid tablets for aqueous enteric film coating. *Pharm. Technol. Eur*, 4453.

Dreu, R., Luštrik, M., Perpar, M., Žun, I., & Srčič, S. (2012). Fluid-bed coater modifications and study of their influence on the coating process of pellets. *Drug Development and Industrial Pharmacy*, *38*(4), 501–511.

Dvořáčková, K., Rabisková, M., Gajdziok, J., Vetchý, D., Muselík, J., Bernatoniene, J., Bajerová, M., et al. (2010). Coated capsules for drug targeting to proximal and distal part of human intestine. *Acta poloniae pharmaceutica*, *67*(2), 191–199.

Dvořáčková, K., Rabišková, M., Muselík, J., Gajdziok, J., & Bajerová, M. (2011). Coated hard capsules as the pH-dependent drug transport systems to ileo-colonic compartment. *Drug Development and Industrial Pharmacy*, *37*(10), 1131–1140.

EUDRAGIT® L 100-55 product specification. Retrieved April 17, 2019, from https://oncare.evonik.com/media/?file=868_evonik_specification_and_test_methods_eudragit_l_100_55.pdf

EUDRAGIT® RL 100, EUDRAGIT® RL PO, EUDRAGIT® RS 100 and EUDRAGIT® RS PO product specification. Retrieved April 17, 2019, from https://oncare.evonik.com/media/?file=875_evonik_specification_and_test_methods_eudragit_rl_100_rl_po_rs_100_rs_po.pdf

Felton, L. A., Haase, M. M., Shah, N. H., Zhang, G., Infeld, M. H., Malick, A. W., & McGinity, J. W. (1995). Physical and enteric properties of soft gelatin capsules coated with Eudragit® L 30 D-55. *International Journal of Pharmaceutics*, *113*(1), 17–24.

Garcia-Albeniz, X., & Chan, A. T. (2011). Aspirin for the prevention of colorectal cancer. *Best Practice & Research Clinical Gastroenterology*, Chemoprevention in Gastroenterology, *25*(4), 461–472.

Hampel, N., Bück, A., Peglow, M., & Tsotsas, E. (2013). Continuous pellet coating in a Wurster fluidized bed process. *Chemical Engineering Science*, 5th International Granulation Workshop, *86*, 87–98.

Hawthorne, A., Mahida, Y., Cole, A., & Hawkey, C. (1991). Aspirin-induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. *British Journal of Clinical Pharmacology*, *32*(1), 77–83.

Hoag, S. W. (2017). Capsules dosage form: formulation and manufacturing considerations. *Developing Solid Oral Dosage Forms* (pp. 723–747). Elsevier.

Hogan, J. E., Stantiforth, J. N., Reeves, L., & Page, T. (2000). *U.S. Patent No. 6,117,479*. Washington, DC: U.S. Patent and Trademark Office.

Hogan, J. E., Stannforth, J. N., Reeves, L., & Page, T. (2006). *U.S. Patent No. 7,070,656*. Washington, DC: U.S. Patent and Trademark Office.

Hoftiezer, J., Burks, M., Silvoso, G., & Ivey, K. (1980). Comparation of the effects of regular and enteric-coated aspirin on gastroduodenal mucosa of man. *The Lancet*, Originally published as Volume 2, Issue 8195, *316*(8195), 609–612.

Huyghebaert, N., Vermeire, A., & Remon, J. P. (2004). Alternative method for enteric coating of HPMC capsules resulting in ready-to-use enteric-coated capsules. *European Journal of Pharmaceutical Sciences*, *21*(5), 617–623.

Jannin, V., Musakhanian, J., & Marchaud, D. (2008). Approaches for the development of solid and semi-solid lipid-based formulations. *Advanced Drug Delivery Reviews*, Lipid-Based Systems for the Enhanced Delivery of Poorly Water Soluble Drugs, *60*(6), 734–746.

Jannin, Vincent, & Cuppok, Y. (2013). Hot-melt coating with lipid excipients. *International Journal of Pharmaceutics*, Progress in Film Coating, *457*(2), 480–487.

Jeffreys, D. (2008). *Aspirin: The Remarkable Story of a Wonder Drug*. Bloomsbury Publishing USA.

John, P. M., Belanger, R. J., & Paikoff, M. (1981). *U.S. Patent No. 4,302,440*. Washington, DC: U.S. Patent and Trademark Office.

Jones, A. (2005). *Chemistry: An Introduction for Medical and Health Sciences*. John Wiley & Sons.

Joshi, S., & Petereit, H.-U. (2013). Film coatings for taste masking and moisture protection. *International Journal of Pharmaceutics*, Progress in Film Coating, *457*(2), 395–406.

Juliano, R. L. (1980). *Drug delivery systems: characteristics and biomedical applications*. Oxford University Press, USA.

Kablitz, C. D., Harder, K., & Urbanetz, N. A. (2006). Dry coating in a rotary fluid bed. *European Journal of Pharmaceutical Sciences*, *27*(2), 212–219.

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

Kablitz, C. D., & Urbanetz, N. A. (2007). Characterization of the film formation of the dry coating process. *European Journal of Pharmaceutics and Biopharmaceutics*, *67*(2), 449–457.

Keddie, J. L., Meredith, P., Jones, R. A. L., & Donald, A. M. (1995). Kinetics of Film Formation in Acrylic Latices Studied with Multiple-Angle-of-Incidence Ellipsometry and Environmental SEM. *Macromolecules*, *28*(8), 2673–2682.

Kim, C. (1995). Drug Release from Compressed Hydrophilic POLYOX-WSR Tablets. *Journal of Pharmaceutical Sciences*, *84*(3), 303–306.

Klar, F., & Urbanetz, N. A. (2009). The role of capillary force promoters in dry coating procedures – Evaluation of acetylated monoglyceride, isopropyl myristate and palmitate. *European Journal of Pharmaceutics and Biopharmaceutics*, Special Issue: Solid State and Solid Dosage Forms, *71*(1), 124–129.

Ku, M. S., Li, W., Dulin, W., Donahue, F., Cade, D., Benameur, H., & Hutchison, K. (2010). Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical and processability quality attributes of VCaps Plus®, Quali-V® and gelatin capsules. *International journal of pharmaceutics*, *386*(1-2), 30-41.

Kutal, C., Grutsch, P. A., & Yang, D. B. (1991). A novel strategy for photoinitiated anionic polymerization. *Macromolecules*, *24*(26), 6872–6873.

Lanza, F. L., Royer Jr, G. L., & Nelson, R. S. (1980). Endoscopic evaluation of the effects of aspirin, buffered aspirin, and enteric-coated aspirin on gastric and duodenal mucosa. *New England Journal of Medicine*, *303*(3), 136–138.

Lecomte, F., Siepmann, J., Walther, M., MacRae, R. J., & Bodmeier, R. (2004). Polymer Blends Used for the Coating of Multiparticulates: Comparison of Aqueous and Organic Coating Techniques. *Pharmaceutical Research*, *21*(5), 882–890.

Luo, Y., Zhu, J., Ma, Y., & Zhang, H. (2008). Dry coating, a novel coating technology for solid pharmaceutical dosage forms. *International Journal of Pharmaceutics*, *358*(1), 16–22.

Mann, C. C., & Plummer, M. L. (1991). *The aspirin wars: money, medicine, and 100 years of rampant competition*. Alfred a Knopf Inc.

Matsuo, M., Arimori, K., Nakamura, C., & Nakano, M. (1996). Delayed-release tablets using hydroxyethylcellulose as a gel-forming matrix. *International Journal of Pharmaceutics*, *138*(2), 225–235.

Menard, R., Tomka, I., Engel, W. D., & Brocker, E. (1999). Process to manufacture starch-containing shaped bodies, mass containing homogenized starch and device to manufacture soft capsules. *International Patent Application WO 0*, *137*, 817.

Misev, T. A. (1991). *Powder coatings: chemistry and technology*. John Wiley & Sons Inc.

Mujahid, A., Farooq, M. U., Hameed, A., Hussain, T., Shah, A. T., Ahmad, S., & SHEHZAD, K. (2013). Quantitative degradation monitoring in core and enteric coated aspirin tablets. *Int J Curr Pharm Res*, *5*(4), 68–70.

Murthy, K. S., Enders, N. A., Mahjour, M., & Fawzi, M. B. (1986). A comparative evaluation of aqueous enteric polymers in capsule coating. *Pharm. Technol*, *10*(10), 36–46.

Murthy, K. S., Kubert, D. A., & Fawzi, M. B. (1988). In vitro Release Characteristics of Hard Shell Capsule Products Coated with Aqueous- and Organic-Based Enteric Polymers. *Journal of Biomaterials Applications*, *3*(1), 52–79.

Mwesigwa, E., Basit, A. W., & Buckton, G. (2008). Moisture Sorption and Permeability Characteristics of Polymer Films: Implications for Their Use as Barrier Coatings for Solid Dosage Forms Containing Hydrolyzable Drug Substances. *Journal of Pharmaceutical Sciences*, *97*(10), 4433–4445.

Newman, M., Impey, B., Henley, T., Jennings, D., & Hallett, M. (2007). *U.S. Patent Application No. 10/571,909*.

Ni, M., Xu, Q. Q., Xu, G., Wang, E. J., & Yin, J. Z. (2011). Applications of supercritical fluid transport technology in preparation of controlled-release drug delivery systems. *Prog. Chem*, *23*, 1611.

Nokhodchi, A., Raja, S., Patel, P., & Asare-Addo, K. (2012). The role of oral controlled release matrix tablets in drug delivery systems. *BioImpacts: BI*, *2*(4), 175.

Obara, S., Maruyama, N., Nishiyama, Y., & Kokubo, H. (1999). Dry coating: an innovative enteric coating method using a cellulose derivative. *European Journal of Pharmaceutics and Biopharmaceutics*, *47*(1), 51–59.

Okhamafe, A. O., & York, P. (1989). Thermal Characterization of Drug/Polymer and Excipient/Polymer Interactions in Some Film Coating Formulation*. *Journal of Pharmacy and Pharmacology*, *41*(1), 1–6.

Oliveira, H. V. A., Peixoto, M. P. G., & Freitas, L. A. P. (2005). Study on the Efficiency of Hard Gelatin Capsules Coating in a Spouted Bed. *Drying Technology*, *23*(9–11), 2039–2053.

Ozeki, Y., Ando, M., Watanabe, Y., & Danjo, K. (2004). Evaluation of novel one-step dry-coated tablets as a platform for delayed-release tablets. *Journal of Controlled Release*, *95*(1), 51–60.

Patrignani, P., & Patrono, C. (2016). Aspirin and Cancer. *Journal of the American College of Cardiology*, *68*(9), 967–976.

Pearnchob, N., & Bodmeier, R. (2003). Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique. *International Journal of Pharmaceutics*, *268*(1), 1–11.

Perrie, Y., & Rades, T. (2012). *FASTtrack Pharmaceutics: Drug Delivery and Targeting*. Pharmaceutical Press.

Petereit, H.-U., & Weisbrod, W. (1999). Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. *European Journal of Pharmaceutics and Biopharmaceutics*, *47*(1), 15–25.

Pfeffer, R., Dave, R. N., Wei, D., & Ramlakhan, M. (2001). Synthesis of engineered particulates with tailored properties using dry particle coating. *Powder Technology*, Granulation and Coating of Fine Powders, *117*(1), 40–67.

Pina, M. E., Sousa, A. T., & Brojo, A. P. (1996). Enteric coating of hard gelatin capsules. Part 1. Application of hydroalcoholic solutions of formaldehyde in preparation of gastro-resistant capsules. *International Journal of Pharmaceutics*, *133*(1), 139–148.

Pissinati, R., & Oliveira, W. P. (2003). Enteric coating of soft gelatin capsules by spouted bed: effect of operating conditions on coating efficiency and on product quality. *European Journal of Pharmaceutics and Biopharmaceutics*, *55*(3), 313–321.

Porter, S., Sackett, G., & Liu, L. (2017). Chapter 34 - Development, Optimization, and Scale-Up of Process Parameters: Pan Coating. In Y. Qiu, Y. Chen, G. G. Z. Zhang, L. Yu, & R. V. Mantri (Eds.), *Developing Solid Oral Dosage Forms (Second Edition)* (pp. 953–996). Boston: Academic Press.

Qiao, M., Luo, Y., Zhang, L., Ma, Y., Stephenson, T. S., & Zhu, J. (2010). Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process. *International Journal of Pharmaceutics*, *399*(1), 37–43.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Chow, K. (2010). A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *76*(2), 304–310.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Xiao, W. (2013). A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. *European Journal of Pharmaceutics and Biopharmaceutics*, *83*(2), 293–300.

Rabadiya, B., & Rabadiya, P. (2013). Review: Capsule shell material from gelatin to non animal origin material. *International Journal of Pharmaceutical Research and Bio-Science*, *2*(3), 42–71.

Ravina, E. (2011). *The Evolution of Drug Discovery: From Traditional Medicines to Modern Drugs*. John Wiley & Sons.

Reeves, L. A., Feather, D. H., Nelson, D. H., & Whiteman, M. (2004). *U.S. Patent No. 6,806,017*. Washington, DC: U.S. Patent and Trademark Office.

Remington, J. P. (2006). *Remington: the science and practice of pharmacy* (Vol. 1). Lippincott Williams & Wilkins.

Rujivipat, S., & Bodmeier, R. (2012). Moisture plasticization for enteric Eudragit® L30D-55-coated pellets prior to compression into tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *81*(1), 223–229.

Ruotsalainen, M., Heinämäki, J., Guo, H., Laitinen, N., & Yliruusi, J. (2003). A novel technique for imaging film coating defects in the film-core interface and surface of coated tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *56*(3), 381–388.

Sauer, D., Cerea, M., DiNunzio, J., & McGinity, J. (2013). Dry powder coating of pharmaceuticals: A review. *International Journal of Pharmaceutics*, Progress in Film Coating, *457*(2), 488–502.

Savage, G. V., & Rhodes, C. T. (1995). The Sustained Release Coating of Solid Dosage Forms: A Historical Review. *Drug Development and Industrial Pharmacy*, *21*(1), 93–118.

Sinchaipanid, N., Junyaprasert, V., & Mitrevej, A. (2004). Application of hot-melt coating for controlled release of propranolol hydrochloride pellets. *Powder Technology*, Pharmaceutical Particle Formation, *141*(3), 203–209.

Sørensen, H. T., Mellemkjær, L., Blot, W. J., Nielsen, G. L., Steffensen, F. H., McLaughlin, J. K., & Olsen, J. H. (2000). Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *The American journal of gastroenterology*, *95*(9), 2218–2224.

Stegemann, S., & Bornem, C. (2002). Hard gelatin capsules today – and tomorrow.

Thies, C., Dos Santos, I. R., Richard, J., VandeVelde, V., Rolland, H., & Benoit, J. P. (2003). A supercritical fluid-based coating technology 1: Process considerations. *Journal of microencapsulation*, *20*(1), 87-96.

Thoma, K., & Bechtold, K. (1992). *Enteric coated hard gelatin capsules*. Capsugel Library.

Tsutsumi, A., Nakamoto, S., Mineo, T., & Yoshida, K. (1995). A novel fluidized-bed coating of fine particles by rapid expansion of supercritical fluid solutions. *Powder Technology*, *85*(3), 275–278.

Walker, J., Robinson, J., Stewart, J., & Jacob, S. (2007). Does enteric-coated aspirin result in a lower incidence of gastrointestinal complications compared to normal aspirin? *Interactive CardioVascular and Thoracic Surgery*, *6*(4), 519–522.

Wang, X., Wang, P., Huang, C., Lin, X., Gong, H., He, H., & Cai, C. (2017). Hot-melt sub- and outercoating combined with enteric aqueous coating to improve the stability of aspirin tablets. *Asian Journal of Pharmaceutical Sciences*, *12*(3), 266–278.

Wesseling, M., & Bodmeier, R. (1999). Drug release from beads coated with an aqueous colloidal ethylcellulose dispersion, Aquacoat®, or an organic ethylcellulose solution. *European Journal of Pharmaceutics and Biopharmaceutics*, *47*(1), 33–38.

Wulf, M., Uhlmann, P., Michel, S., & Grundke, K. (2000). Surface tension studies of levelling additives in powder coatings. *Progress in Organic Coatings*, *38*(2), 59–66.

Würtz, M., Hvas, A.-M., Jensen, L. O., Kaltoft, A. K., Tilsted, H. H., Kristensen, S. D., & Grove, E. L. (2014). 24-hour antiplatelet effect of aspirin in patients with previous definite stent thrombosis. *International Journal of Cardiology*, *175*(2), 274–279.

Yamashita, S., & Harada, S. (2000). *U.S. Patent No. 6,030,641*. Washington, DC: U.S. Patent and Trademark Office.

Yang, Q., Ma, Y., Shi, K., Yang, G., & Zhu, J. (2018). Electrostatic coated controlled porosity osmotic pump with ultrafine powders. *Powder Technology*, *333*, 71–77.

Yang, Q., Ma, Y., & Zhu, J. (2015). Applying a novel electrostatic dry powder coating technology to pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, *97*, 118–124.

Yang, Q., Ma, Y., & Zhu, J. (2016). Sustained drug release from electrostatic powder coated tablets with ultrafine ethylcellulose powders. *Advanced Powder Technology*, *27*(5), 2145–2152.

Yang, Q., Ma, Y., Zhu, J., Chow, K., & Shi, K. (2017). An update on electrostatic powder coating for pharmaceuticals. *Particuology*, *31*, 1–7.

Yue, B., Yang, J., Wang, Y., Huang, C.-Y., Dave, R., & Pfeffer, R. (2004). Particle encapsulation with polymers via in situ polymerization in supercritical CO2. *Powder Technology*, *146*(1), 32–45.

Zhang, L., Russell, D., Conway, B. R., & Batchelor, H. (2008). Strategies and Therapeutic Opportunities for the Delivery of Drugs to the Esophagus. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *25*(3).

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2011). *U.S. Patent No. 7,862,848*. Washington, DC: U.S. Patent and Trademark Office.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2012). *U.S. Patent No. 8,161,904*. Washington, DC: U.S. Patent and Trademark Office.

Chapter 3

3 Application of dry powder coating technology on sustained release capsules

This chapter discusses the application of electrostatic dry powder coating technology on coating gelatin capsules and HPMC capsules directly to achieve sustained release. Eudragit® RS and Eudragit® RL were used as coating materials. Results showed this technology was successfully applied on gelatin and HPMC capsules to achieve sustained release and behaved good stability during storage. Different ratios of Eudragit® RS/RL and different capsule weight gains were investigated for both gelatin capsules and HPMC capsules to control the drug release rate. Tablets were also coated as comparison. The possible drug release mechanism of sustained release capsules was revealed as well.

3.1 Introduction

In pharmacy, capsule is used primarily to describe a container filled with medicinal substance, a solid dosage form. According to the structure, there are two categories of capsule: hard capsule (two pieces) and soft capsule (one piece). For the hard capsule, there are two materials which have been commercialized to manufacture capsule shell: hydroxypropyl methylcellulose (HPMC) and gelatin.

Compared to other oral solid dosage forms, like tablet or pellet, capsule has its unique advantages: It is tasteless, odorless, easily administered and capable of providing a barrier for light sensitive or moisture sensitive drugs (Rabadiya & Rabadiya, 2013). Also, unlike tablet, compression is avoided for drug enclosed in capsule which makes capsule a better oral dosage form for drugs with low compressibility. In addition, new drugs can be determined without going through complex formulation development which is expensive, time consuming and difficult but inevitable for tablet manufacture (Cole et al., 2002). Given all of these, capsule is a good substitution of tablets.

Capsule has little influence on drug dissolving process, both gelatin capsule and HPMC capsule will dissolve in short but different time after taken. However, some drugs are harmful to stomach or need to be released at certain position of the gastrointestinal tract, some drugs need to be released

with a certain rate to control its concentration in plasma and decrease frequency of taking drugs, modified release process is required. Film coating process is one method to modify release properties of oral solid dosage forms. Tablets, pellets and capsules can achieve different release profiles, like delayed release or extended release, by coating different functional materials.

While, different from tablets or pellets, capsule shell provides a barrier in coating process to separates drugs from coating materials which is essential because some active pharmaceutical ingredients will degrade if contact coating materials directly. While, to avoid direct contact, tablet will need a sub-coating as a separation layer and make the whole process more complex (Crotts et al., 2001).

Most so-called sustained release capsules are made of sustained coated small pellets enclosed in uncoated capsules. The finely powdered drugs are first converted into pellets, usually by attaching it to sugar granules with an adhesive. Then, the pellets are coated with sustained release films that slow the release of the drug, each batch will receive a different thickness. Afterwards, the batches are mixed thoroughly, and suitable doses are filled into capsules to achieve sustained release capsules. There are few researches about coating capsules directly to achieve sustained release.

Conventionally, just like tablets coating, capsule coating is also based on organic or aqueous coating process. However, gelatin capsule, which is still most commonly used (Al-Tabakha, 2010), is quite water sensitive and would stick together when liquid coating process is applied. Also, liquid coating can lead to poor adhesion of the coating film to the smooth gelatin surface (Murthy et al., 1986). And the shell embrittlement may occur owning to capsule moisture loss when organic solution is used. Yamashita & Harada (2000) produced a sustained release hard gelatin capsule by coating a film material comprising a natural polysaccharide/ polyhydric alcohol composition on the capsule surface. This process used liquid coating technology in a conventional coating pan. Pissinati & Oliveira (2003) used a spouted bed to coat soft gelatin capsules by polymer suspension to improve the coating efficiency and uniformity of product, and reduced stickiness between gelatin capsules to some extent. But a large amount of heated air and energy are required.

HPMC, as an alternative material to make capsule, is attracting more and more attention because of its vegetable source and more stable properties (Al-Tabakha, 2010). Cole et al. (2002) coated enteric release HPMC hard capsules in Accela Cota 10 by using aqueous coating process. HPMC

capsules were also coated by (Huyghebaert et al. (2004) in a fluidizing bed apparatus and developed ready-to-use enteric-coated capsules.

Although HPMC and gelatin were both used as capsule material, HPMC and gelatin capsules have different performances in coating process. (Dvořáčková et al., 2010) coated both HPMC and gelatin capsules with solution in Wurster-M 100 coater. The result showed that film peeling occurred for gelatin capsules when higher amount Eudragit® L or Eudragit® S was coated, while HPMC capsules and gelatin capsules sub-coated with hydroxypropyl cellulose (HPC) did not. Besides, gelatin capsules directly coated with Eudragit® L or Eudragit® S did not pass dissolution test because the coated polymer films broke. In the next article (Dvořáčková et al., 2011), they concluded this phenomenon is probably related to capsule shell humidity loss caused by organic solvent in coating process. Thus, to coat gelatin capsule, the application of hydroxypropyl cellulose or hydroxypropyl methyl cellulose as a sub-coat is needed to protect gelatin capsule and increase roughness of capsule surface (Thoma & Bechtold, 1992). But it is time consuming and complex.

Except for difficulties of capsule coating mentioned above, there are some other disadvantages of liquid coating process. Organic coating process suffers from flammability, toxicity and environmental, cost and safety-related issues (Aulton et al., 1995). While aqueous coating process is energy and time consuming (Bose & Bogner, 2007), also, cannot be applied on moisture sensitive active pharmaceutical ingredients (APIs) (Amighi & Moes, 1996; Plaizier-Vercammen & De Neve, 1993).

Considering all these drawbacks of capsule liquid coating, Solvent-free coating processes turned out to be a better option to coat pharmaceutical solid dosage forms (Bose & Bogner, 2007; Luo et al. 2008; Prasad et al., 2016; Sauer et al., 2013). Yang et al. (2018) coated gelatin capsule by two different coating processes: electrostatic dry powder coating and dip coating. In this study, a novel electrostatic dry powder coating process in a pan coater is applied on coating hard gelatin and HPMC capsules. Compared with liquid coating, this process offers many advantages such as shorter process time, elimination of solvent emission and cost reduction. The electrostatic powder coating process has been applied on tablets successfully (Qiao et al., 2010; Qiao et al., 2010; Qiao et al., 2013; Yang et al., 2018; Zhu et al., 2011, 2012). It was found that coating efficiency of electrostatic dry powder coating is higher than liquid coating and dry powder fluidized bed coating

processes (Misev & van der Linde, 1998; Wicks, 2007). And it can achieve a better film uniformity (Qiao et al., 2010). Since there is no water or organic solvent applied in this dry powder coating process, gelatin capsules can also be easily coated regardless its water sensitive nature and smooth surface. In this study, Eudragit® RS and Eudragit® RL were used as functional coating materials for HPMC and gelatin capsules to achieve sustained release purpose.

3.2 Coating equipment and process

The dry powder coating system consists of a coating pan, a liquid spraying gun, and an electrostatic spray gun. In a laboratory scale, diameter of the stainless coating pan is 14 cm and a motor was used to make the coating pan rotate. There are 4 baffles, 90^{o} apart, mounted on the inside wall of coating pan providing tumbling movement to substrate. The liquid spraying gun consists of a spray nozzle and a peristaltic pump. The diagram of this coating equipment is shown in Figure 3.1.

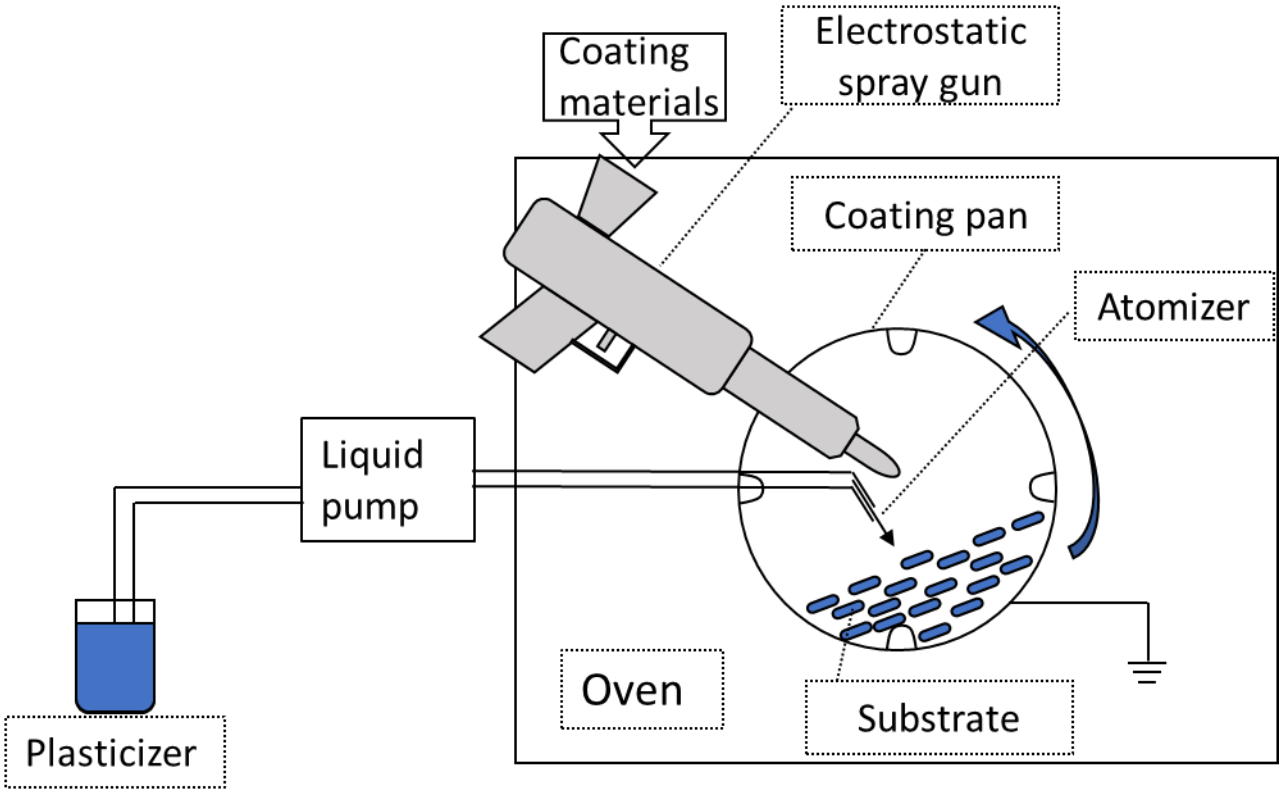


Figure 3.1 Schematic of the electrostatic powder coating system

The coating pan was grounded and put into an oven which can control the temperature of the coating system. There is an opening window at the front of the oven, through which electrostatic spray gun and liquid spray gun can spray powder and plasticizer into coating pan. Also, a vent is located at the top of the opening window and is used to collect particles sprayed by electrostatic spray gun which were not deposited on the substrate.

The coating process has three steps: First, substrate was loaded in the rotating pan and preheated under 50℃ for 10 minutes. The rotating speed of coating pan was set at 15 rpm. Then, spray plasticizer and polymer powders alternatively when the pan was rotating. The rotating speed of coating pan was set at 35 rpm. Flow rate of plasticizer was controlled by a peristaltic pump. Then polymer powders were sprayed by an electrostatic spray gun (Nordson Corporation, USA). This process can be repeat for several times to achieve desired weight gains (defined as weight increased after coating divided initial uncoated substrate). The ratio of the plasticizer and the polymers was 0.28. Finally, the substrate was cured at 50℃ for 2 hours to let the powders coalesce and form films.

3.3 Materials and methods

3.3.1 Materials

Eudragit® RL, Eudragit® RS and Colloidal silicon dioxide (AEROSIL® 200 Pharma) were provided by Evonik Degussa Corporation (Germany). Triethyl citrate (TEC) was purchased from Alfa Aesar (Canada). Talc was purchased from Mallinickrodt Baker, Inc. (Canada). Size 4 HPMC capsules (Vcaps Plus®) and gelatin capsules (Coni-Snap®) were provided by Capsugel Inc. (US). Acetylsalicylic acid was purchased from Sigma-Aldrich (Canada). FD&C Yellow No.6, as pigment, was provided by Food Ingredient Solutions LLC (US). Lactose was obtained from GlaxoSmithKline, Inc. (Canada). Avicel® Microcrystalline cellulose PH-102 was purchased from Food Machinery Corporation (US). Caffeine and magnesium stearate were purchased from Alfa Aesar (US).

3.3.2 Particle size reduction and analysis

Before coating, Eudragit® RS and RL were grounded by blade grind mill and went through ultrasonic sieve (325 mesh) (HK Technologies Ultrasonics, Rugby, United Kingdom) to obtain

small particles. Then a Particle Size Analyzer (TSI Corporation, Model 3603, Shoreview, MN, USA) was used to determine the particle sizes of the coating materials and each test was repeated 3 times. The particle diameter at 50% of total weight fraction was designated as median diameter (D50) (Qiao, 2013). The D50s of Eudragit® RS, Eudragit® RL and talc were 36.8μm, 43.3μm and 41.2μm respectively.

3.3.3 Capsules and tablets preparation

Size 4 capsules were filled by CN 100 capsule filling machine (CapsulCN LTD., China). Weights of each filled aspirin gelatin capsule, aspirin HPMC capsule, caffeine gelatin capsule and caffeine HPMC capsule were $143.7 \pm 7.3\text{mg}$, $142.8 \pm 8.9\text{mg}$, $120.0 \pm 3.9\text{mg}$ and $123.0 \pm 5.7\text{mg}$ (n=10). The formulations of filled ingredients are showed in Table 3.1 and Table 3.2.

Table 3.1 Formulation of aspirin capsules

Ingredient	Weight fraction
Aspirin	74.5%
Microcrystalline cellulose PH102	25%
AEROSIL® 200 Pharma	0.5%

Table 3.2 Formulation of caffeine capsules

Ingredient	Weight fraction
Caffeine	54.5%
Microcrystalline cellulose PH102	45%
AEROSIL® 200 Pharma	0.5%

Aspirin tablets were compressed by rotary tablet press machine (Tianfan Pharmaceutical Machinery Factory, Shanghai, China). Formulation of aspirin tablets and caffeine tablets are listed in Tables 3.3 and 3.4. Other parameters of the tablets are listed in Table 3.5.

Table 3.3 Formulation of aspirin tablets

Ingredients	Weight fraction
Aspirin	63%
Microcrystalline cellulose PH102	21%
Lactose	15%
AEROSIL® 200 Pharma	1%

Table 3.4 Formulation of caffeine tablets

Ingredients	Weight fraction
Caffeine	32%
Microcrystalline cellulose PH102	37%
Lactose	30%
Magnesium stearate	1%

Table 3.5 Properties of aspirin tablets and caffeine tablets

Properties	Aspirin tablets	Caffeine tablets
Weight (mg)	132.3 ± 4.2	138.9 ± 3.9
Diameter (mm)	7.0	7.0
Thickness (mm)	3.0	3.0
Hardness (N)	60	60

3.3.4 Formulation of coating materials

Polymers with different formulation were coated on HPMC, gelatin capsules and tablets to achieve sustained release, shown as Tables 3.6 and 3.7. Eudragit® RS and Eudragit® RL are commonly used to achieve sustained release. Talc was used as anti-stick agent. Yellow No.6 was used as pigment to investigate the uniformity and improve appearance of substrate.

Table 3.6 Formulation of sustained release coating polymer for aspirin

Substrate	Weight Fraction			
	Eudragit® RS	Eudragit® RL	Talc	Yellow No.6
Gelatin capsule	27%	53%	19.5%	0.5%
	16%	64%	19.5%	0.5%
	0%	80%	19.5%	0.5%
HPMC capsule	27%	53%	19.5%	0.5%
	16%	64%	19.5%	0.5%
	0%	80%	19.5%	0.5%
Tablet	27%	53%	19.5%	0.5%

Table 3.7 Formulation of sustained release coating polymer for caffeine

Substrate	Weight Fraction			
	Eudragit® RS	Eudragit® RL	Talc	Yellow No.6
Gelatin capsule	16%	64%	19.5%	0.5%
HPMC capsule	16%	64%	19.5%	0.5%
Tablet	16%	64%	19.5%	0.5%

3.3.5 Scanning electron microscopy (SEM)

Since the electrical conductivity of coating surface is poor, coated capsules were sputter coated with gold for 2 minutes first by using EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK). Then the capsules were put in scanning electron microscope (Hitachi S-2600 N, Ontario, Canada) operated at 5.0kV to observe the coating film appearance.

3.3.6 *In vitro* dissolution test

In vitro dissolution test of capsules was carried out by a dissolution test system (Huanghai Rcz-6c2, Shanghai, China) which complies with the standard of United States Pharmacopeia (USP) (<711> Dissolution, Apparatus 1, Basket). Tablets were tested in the same system according to USP (<711> Dissolution, Apparatus 2, Paddle). Six dosages were tested at the same time. The apparatus was set at 37℃, basket/paddle rotating speed was set at 60rpm in the solution of 900 ml hydrochloric acid (pH=1) for aspirin and in the solution of 900 ml phosphate buffer saline (pH=6.8) for caffeine. 10 ml solution was withdrawn and filtered as sample from each tank by a syringe and replaced with fresh 0.1 mol/L HCl solution with certain time interval. The samples were tested by

8453 UV–Visible Spectrophotometer (Agilent Technologies, Mississauga, Canada) at a wavelength of 276 nm for aspirin and 274 nm for caffeine. The tests lasted for 8 hours.

The standard curve of aspirin in pH=1 hydrochloric acid is shown in Figure 3.2 and standard curve of caffeine in pH=6.8 phosphate buffer saline is shown in Figure 3.3.

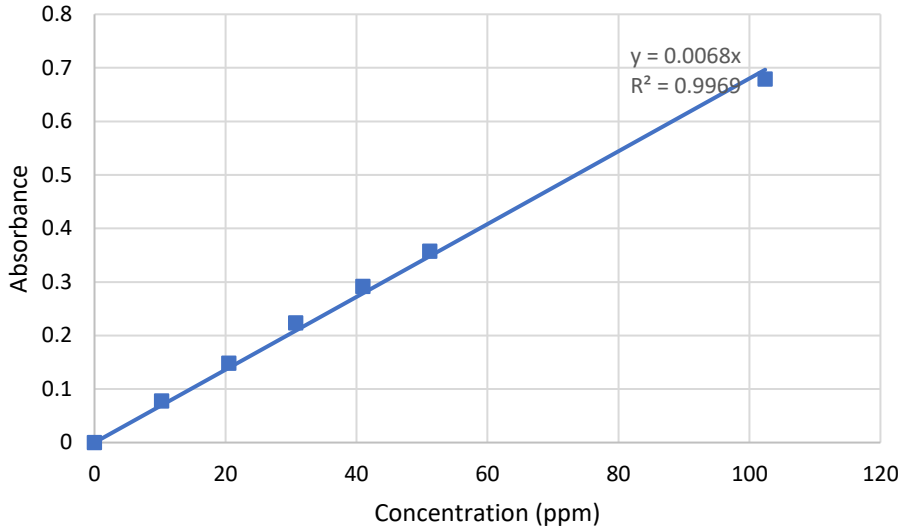


Figure 3.2 Standard curve of aspirin in pH=1 hydrochloric acid at 276nm

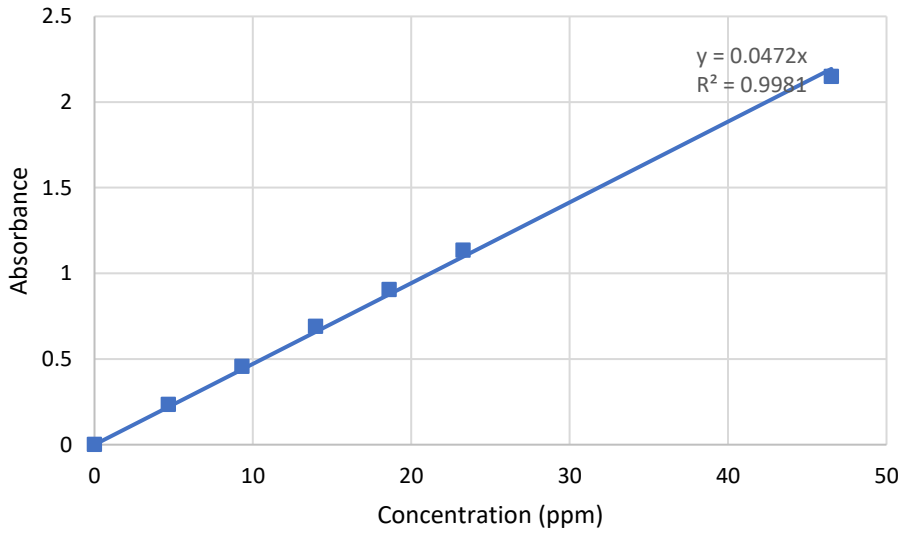


Figure 3.3 Standard curve of caffeine in pH=6.8 phosphate buffer saline at 274nm

3.3.7 Stability test

Both coated gelatin capsules and coated HPMC capsules were prepared for stability test. The capsules were placed in high-density polyethylene (HDPE) vials and stored at 25℃/ 30% RH for 8 months and examined the dissolution profiles according to dissolution test method.

3.4 Results and discussion

Capsules and tablets were coated using Eudragit® RS/RL to achieve sustained release. Aspirin and caffeine were used as sample APIs. By adjusting the weight gains of capsules after coating process and the formulation of the coating polymers, different drug release rates have been achieved (Qiao et al., 2010). Properties of coated capsules and tablets with different weight gains (achieved by spraying different amount of polymers) and formulations of coating materials were shown in Tables 3.8 and 3.9.

During capsule coating process, the problems normally occurred in aqueous coating like poor adhesion of coating materials and sensitivity to water were not observed, because no organic solvent or water was used but only small amount of plasticizer were added. Stickiness, which is also a common problem appears in liquid coating process, can be avoided by controlling the amount of plasticizer sprayed in dry powder coating process. Shell embrittlement may occur in organic solvent coating process was also eliminated. Capsules can be directly coated without pre-coating which is required to increase surface roughness especially for gelatin capsule in aqueous coating process. Form these aspects, the dry powder coating process turns out to be a better method to coat capsules.

Table 3.8 Weight gains of aspirin capsules and tablets

Substrate	Polymer	Coating level	Weight gain (WG) $(\mathbf{mg}/\boldsymbol{cm^2})$
Gelatin capsule	RS: RL=1:2	3.2%	1.91
		6.4%	3.78
		10.8%	6.29
	RS: RL=1:4	2.9%	1.73
		5.3%	3.13
		11.0%	6.40
	RS: RL=0:1	11.0%	6.40
HPMC capsule	RS: RL=1:2	3.9%	2.41
		5.6%	3.47
		10.8%	6.29
	RS: RL=1:4	3.9%	2.41
		6.4%	4.02
		11.5%	6.69
	RS: RL=0:1	10.3%	6.07
Tablet	RS: RL=1:2	2.8%	3.03
		5.7%	6.03
		9.2%	9.54

*Coating level $= \frac{\text{substrate weight after coating}}{\text{substrate weight before coating}} \times 100\%$;

Weight gain $= \frac{\text{weight increased of substrate after coating}}{\text{total surface area of substrate}}$.

Table 3.9 Coating levels of caffeine capsules and tablets

Substrate	Polymer	Coating level	Weight gain (WG) $(\mathbf{mg}/\boldsymbol{cm^2})$
Gelatin capsule	RS: RL=1:4	11.7%	5.95
HPMC capsule	RS: RL=1:4	12.4%	6.11
Tablet	RS: RL=1:4	6.0%	6.39

In- vitro release profile of oral solid dosage forms is important to evaluate the coating film. And it is related to weight gain of dosage forms, formulation of coating materials and properties of dosage forms.

3.4.1 Influence of coating weight gains

The release profiles of gelatin capsules coated with formulation of RS: RL=1:2 is plotted in Figure 3.4 which shows increasing aspirin release rate with decreasing weight gain. This trend is same as the sustained release tablets reported by Qiao et al. (2010). For gelatin capsules, if the weight gain was much lower than 1.91 mg/cm^2, continuous film cannot be formed. Coated gelatin capsules would prone to break and drug release rates were not controllable.

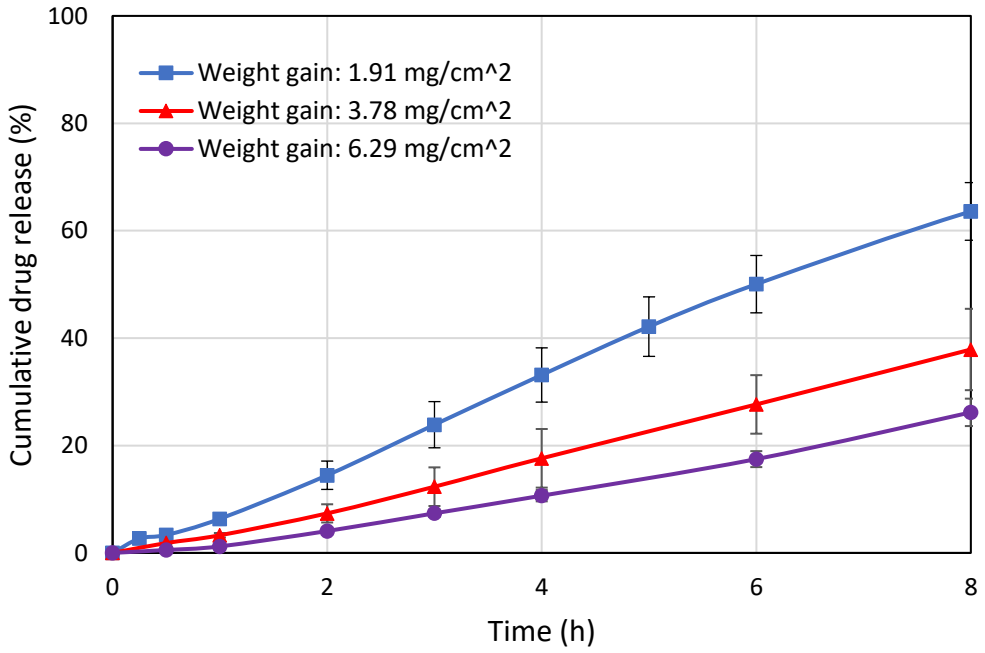


Figure 3.4 Sustained release profile of gelatin capsules (RS: RL=1:2) with different weight gains

Figure 3.5 shows the release profiles of HPMC aspirin capsules with three different weight gains. As gelatin capsules, release rate of HPMC capsules increased as weight gain decreased. This illustrated that both gelatin capsules and HPMC capsules can achieve sustained release after coating.

For comparison, influence of weight gain for aspirin tablets was also tested. As weight gain increased from 3.03mg/cm^2 to 9.50mg/cm^2, 8 hours cumulative drug release was decreased from 80% to 25% which trend is similar as what Qiao et al. (2010) reported.

During the coating process, less coating materials would deposit on the gap of the capsule. SEM figure (Figure 3.6a) clearly shows the gap was not covered for HPMC capsule when weight gain was as low as 2.41mg/cm^2. This problem can be solved by increasing the weight gain. And the gaps were able to be covered when weight gains reach 3.47 mg/cm^2 (Figure 3.6b) and 6.29mg/cm^2 (Figure 3.6c).

In the dissolution test, it is observed that when the weight gain was as low as 2.41mg/cm^2, the capsules were separated into tow parts alone the gap between the cap and the body of capsule. And this caused the uncontrollable and faster release rate of the drug illustrated by larger standard deviation of HPMC capsule release profile showed in Figure 3.5. This is because weaker mechancial strength of the film formed on the gap owing to less coating materials deposited on it in the coating process. When weight gain reached 3.47mg/cm^2, the HPMC capsules stayed integrated and aspirin released through porous films formed by Eudragit® RS/RL slowly. This phenomenon was also reported by Dvořáčková et al. (2011). It was found that capsules were prone to break at the joint of the cap and the body, the weakest area of hard capsules, of ileo-colonic release capsules due to lower weight gain (Dvořáčková et al., 2011).

For either tablet or capsule, there is a minimum weight gain to ensure the tablet or capsule stay integrate and achieve desired sustained release. But the minimum level varies with solid dosage forms and some other parameters.

For the sustained release aspirin dosage forms, when weight gain was about 3mg/cm^2, tablets would break but capsules would not. This means the minimum weight gain of tablets is higher than sustained release capsules. Because tablet was compressed, when it was merged in the solution during dissolution test, it will absorb more water and swelled more. So that a thicker film which can be achieved by increasing weight gain was required to provide enough mechanical strength for tablets.

By comparing sustained release gelatin and HPMC capsules, it was discovered that gelatin capsule has an even lower minimum weight gain than HPMC capsule (HPMC capsules with 2.41mg/cm^2 broke while gelatin capsules with 1.91mg/cm^2 weight gain did not). This can be attributed to two reasons: different size of the gap and different swelling effects between HPMC capsules and gelatin capsules. The sizes of the gaps for size 4 Vcaps Plus® HPMC capsules and Coni-Snap

gelatin capsules are $77.1 \pm 4.66\ \mu m$ and $28.7 \pm 1.41\ \mu m$ (n=3) respectively. Thus, more coating materials are required to cover the gap. In addition, sustained release HPMC capsules would swell more than gelatin capsules in the dissolution test. Figure 3.7 shows different sizes of coated HPMC capsule and gelatin capsules with weight gain of around 3.5 mg/cm^2 after 4 hours of dissolution test compared with undissolved capsule. It is obvious that HPMC capsule became larger than gelatin capsule after 4 hours of dissolution test. Since HPMC capsule provided more swelling force than gelatin capsule to coating film, it would require a thicker film resulted from higher weight gain than gelatin capsule.

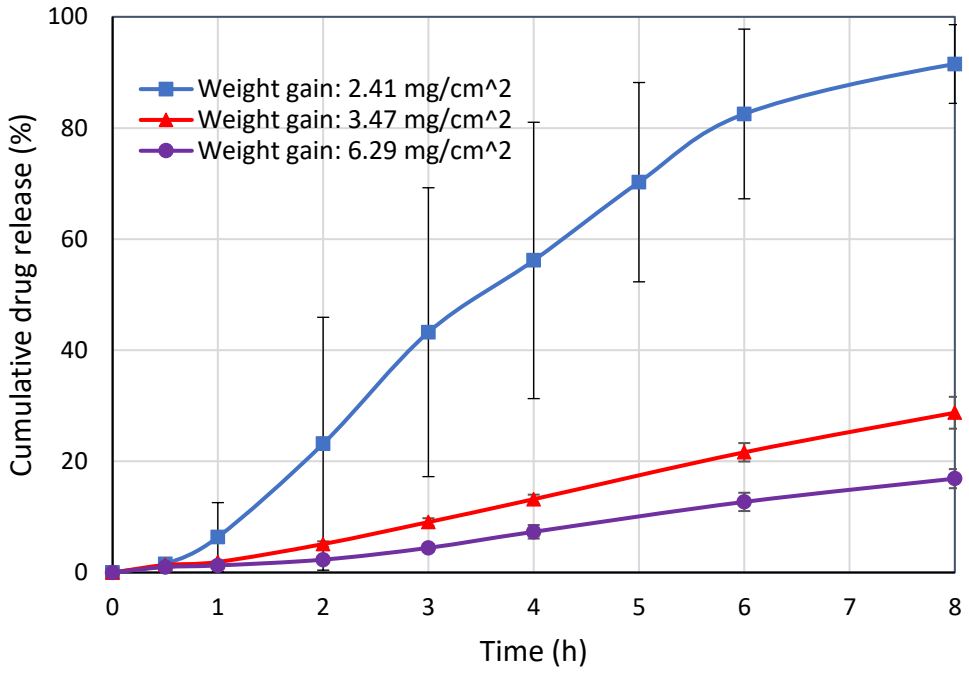


Figure 3.5 Sustained release profile of HPMC capsules (RS: RL=1:2) with different weight gains

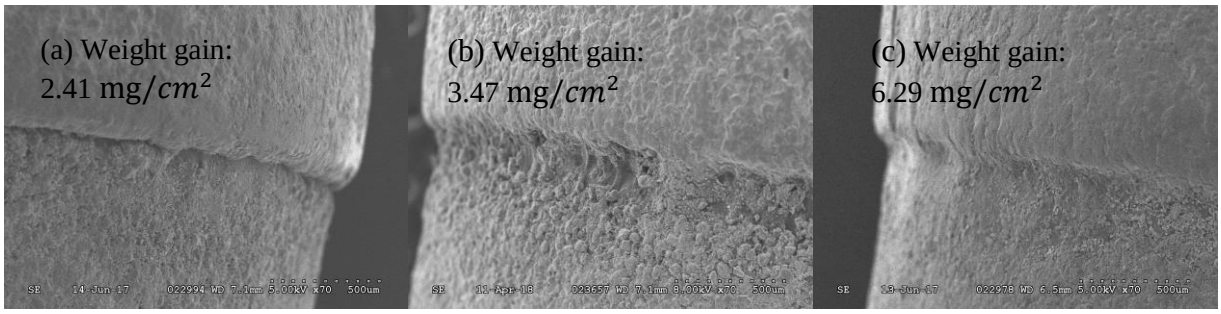


Figure 3.6 SEM of HPMC capsules with different weight gains (RS: RL=1:2)

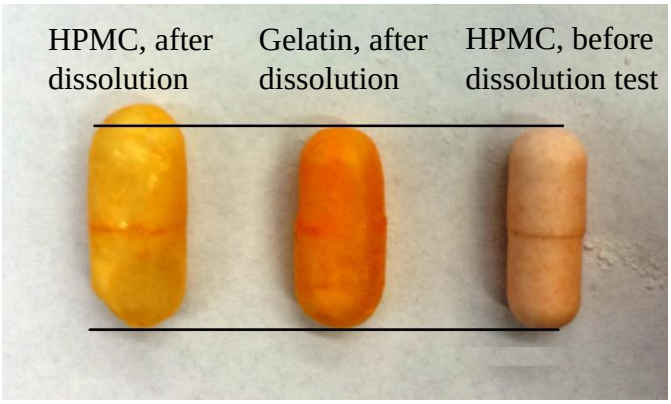


Figure 3.7 Capsule size before and after 4 hours dissolution test

3.4.2 Influence of coating formulations

It has been reported that higher ratio of Eudragit® RS: Eudragit® RL in the coating material for tablets produces less permeable coating film and thus lower drug release rate. Figure 3.8 shows aspirin release profiles of coated gelatin capsules. Different release rates can be achieved by adjusting the formulation of coating materials. When the Eudragit® RS: Eudragit® RL was low (RS:RL=0:1, RS concentration=0%, RL concentration=80%), the release rate was higher. And the release rate was decreased when Eudragit® RS: Eudragit® RL was increased from RS:RL=0:1 to RS:RL=1:4 (RS concentration=16%, RL concentration=64%). By further increase ratio of Eudragit® RS: Eudragit® RL to RS:RL=1:2 (RS concentration=27%, RL concentration=53%), the release rate was further decreased.

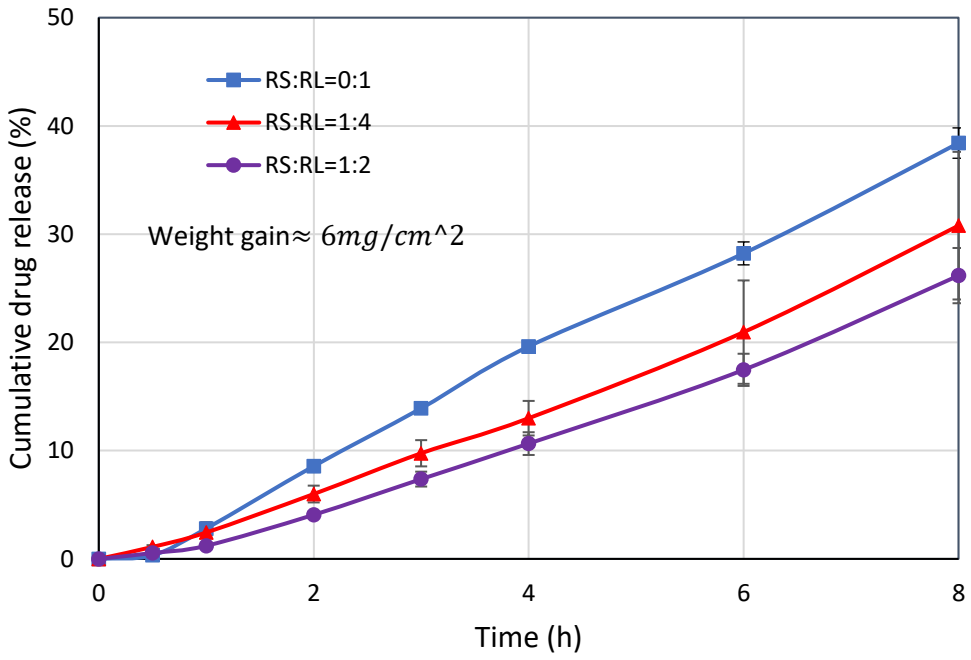


Figure 3.8 Release profiles of gelatin capsules coated with different coating formulations

As gelatin capsules, the release rate of HPMC capsules can also be controlled by applying different combinations of coating materials as Figure 3.9 shows. Aspirin release rate of HPMC capsules was slightly lower compared to gelatin capsules when the weight gain was about 6 mg/cm^2 which can prevent the break of the capsules. This is because HPMC capsules dissolve slower than gelatin capsules (Al-Tabakha, 2010), so that the transport speed of aspirin was slowed down and lead to a lower release rate of aspirin.

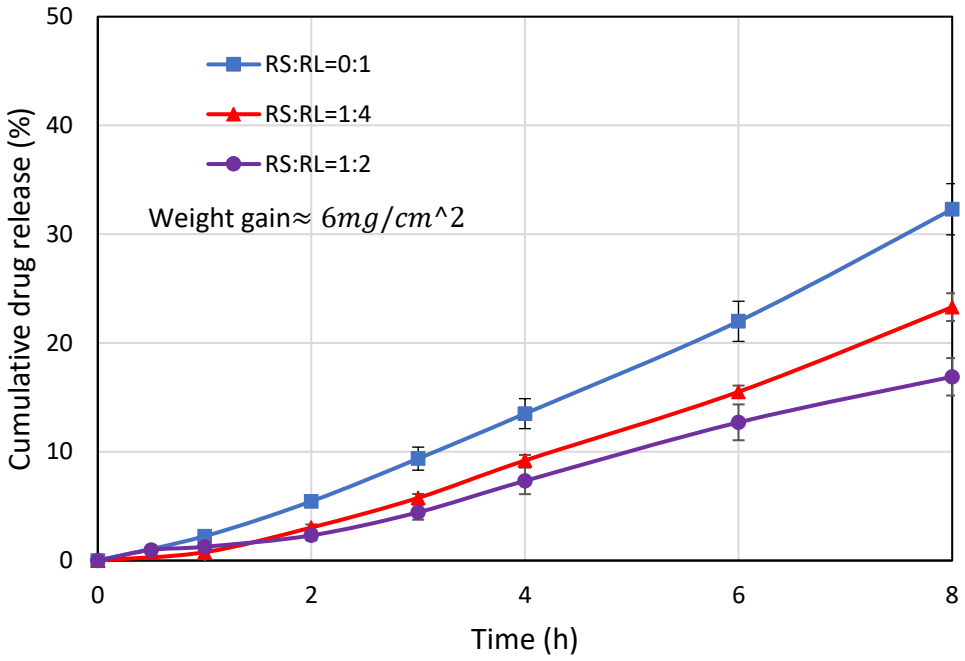


Figure 3.9 Release profiles of HPMC capsules coated with different coating formulations

3.4.3 Influence of capsule materials

Aspirin and caffeine in tablet and capsule forms were both coated with Eudragit® RS: RL=1:2 by the same process and went through in-vitro dissolution test. All of them can achieve sustained release but with different performances. This part compares the different release performances of different drugs in different solid dosage forms.

Figure 3.10 shows the release profiles of sustained release aspirin tablets and capsules. With the similar weight gain, release rates of gelatin capsules and HPMC capsules were both slower than tablets. This is owing to the formation of high viscosity solutions in sustained release capsules. And due to different properties of gelatin and HPMC materials, release rate of HPMC capsules is lower than gelatin capsules.

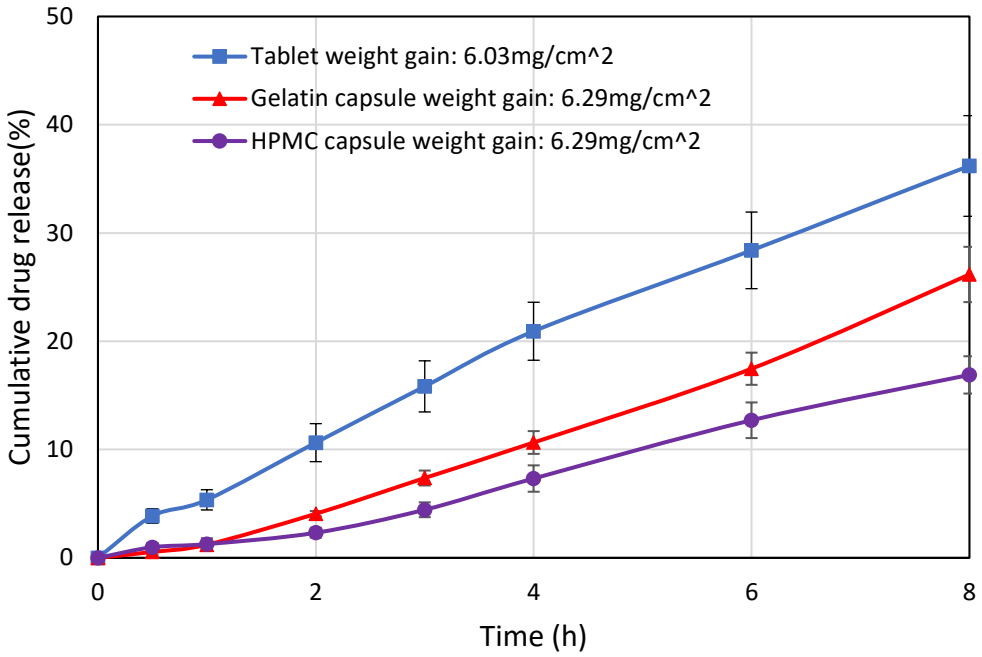


Figure 3.10 Dissolution profile of sustained release aspirin tablets and capsules with similar weight gain (RS: RL=1:2)

For sustained release gelatin and HPMC capsules, the existence of capsule shell has great influences on the release rate. First, it caused a delay for aspirin to be released from capsules compared to tablets. This is because the capsule shells needed to absorb water and partial dissolve first before encapsulated drug dissolved and released afterwards. Second, high viscosity solutions formed from gelatin or HPMC capsule shell influenced the release rate of aspirin. It is reported that gelatin and HPMC can be used to modify drug release by forming swellable matrix tablets (Lin & Metters, 2006; Wise, 2000). So, when the capsule shell dissolved, it mixed with enclosed drug and formed a matrix in the coated film which would change the release mechanism and slow down the release rate of aspirin. And the system became a combination of reservoir matrix system and monolithic matrix system. In addition, for HPMC capsules, by comparing Figures 3.4, Figure 3.5 and Figure 3.10, there was a longer delay than gelatin capsule. This is owing to different dissolving time of gelatin capsules and HPMC capsules and different properties of high viscosity solution formed after dissolved. It is reported that HPMC capsule dissolved slower than gelatin

capsule under 37℃ (Chiwele et al., 2000), which explained why the sustained release HPMC capsule had a longer delay than gelatin capsules.

Compared with capsules, tablets coated with Eudragit® RS/RL had no high viscosity solutions formed which would slow down the release rate formed in sustained release tablets. This explained why the drug release rate of tablets was faster than capsules. During the dissolving process of aspirin tablets, aspirin would dissolve in the dissolution media penetrated the coating film, then aspirin would diffuse through the porous film and release to the dissolution media owing to the different concentrations on the different sides of the coated film.

Korsmeyer–Peppas (Ritger & Peppas, 1987) equation which described drug release from a polymeric system like this case was used to illustrate the mechanism of drug release.

$$\frac{M_t}{M_\infty} = Kt^n$$

where M_t is the amount of drug released at different time t, M_∞ is the total amount of drug, K is the kinetic constant, and n is the diffusion exponent. For a cylindrical dosage form, like tablets and capsules, when $0.45 \leq n$, it indicates Fickian diffusion. If the diffusion exponent $0.45 \leq n \leq 0.89$, it indicates anomalous transport. If $n = 0.89$, it is case II transport. When $n > 0.89$, it is super case II transport.

Tablet 3.10 shows the result of diffusion exponent value for sustained release tablets and capsules whose release profiles showed in Figure 3.10. Below 60% drug release data were fitted in Korsmeyer–Peppas model. For gelatin and HPMC capsules, the drug release follows super case II transport. In super case II transport, the release rate of the drug was accelerated as time goes by. For sustained release gelatin and HPMC capsules, the drug was released slowly at the beginning owing to the dissolution process of capsule shells. Afterwards, the release rate was accelerated because the capsule shell was completely dissolved. Then, when certain amount of drug was released, the release rate was decreased, the system would become diffusion controlled. As for tablets, it was an anomalous drug release because there was no dissolution process of capsule shells for tablets. Thus, the release of drug was both swelling controlled and diffusion controlled.

Table 3.10 Diffusion exponent value for sustained release aspirin tablets and capsules

	n	R^2	Transport
Aspirin tablets	0.8458	0.9929	Anomalous
Aspirin gelatin capsules	1.4292	0.9965	Super case II
Aspirin HPMC capsules	1.3103	0.9874	Super case II

To investigate influence of different drug solubility for this system, a high solubility drug, caffeine was chosen to be tested for comparison. Figure 3.11 is release profiles of sustained release caffeine tablets and capsules. Like aspirin capsules, low release rate was also tested. The values of n in Korsmeyer–Peppas equation for sustained release caffeine tablets and capsules were showed in Table 3.11. Like aspirin, release of caffeine for sustained release capsules in dissolution test was super case II transport. This indicated that the dissolving of gelatin or HPMC has influence on both low solubility and high solubility drugs.

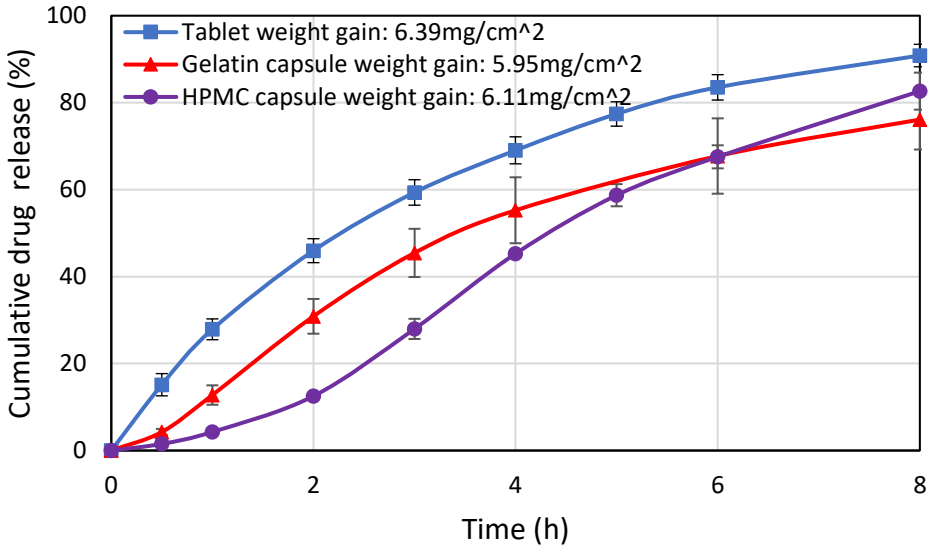


Figure 3.11 Dissolution profile of sustained release caffeine tablets and capsules with similar weight gain (RS: RL=1:4)

Table 3.11 Diffusion exponent value for sustained release caffeine tablets and capsules

	n	R^2	Transport
Caffeine tablets	0.7627	0.9954	Anomalous
Caffeine gelatin capsules	1.2418	0.9851	Super case II
Caffeine HPMC capsules	1.6200	0.9978	Super case II

To further investigate the dissolving process of capsules, capsules were taken out and cut after different dissolving time as showed in Figure 3.12. For HPMC capsule, in the first hour, capsule shell could still be observed but had become soft which means capsule had absorbed some water. And the ingredients inside were still dry which means aspirin had not been dissolved leading to no drug been released. In the second hour, capsule shell absorbed more water and formed high viscosity solution. And the inside of capsule was becoming wetted owing to the diffusion of the water and the high viscosity solution as Figure 3.12 (a). 3 hours later, capsules shell had been fully dissolved and became high viscosity solution. All encapsulated drugs were completely wetted and mixed with high viscosity solution. While for gelatin capsules. As Figure 3.12 (b), in the 1 hour, like HPMC capsule, gelatin capsule shell could still be observed. But the ingredients were partially wetted. In the 1.5 hours, the capsule shell has completely dissolved and formed high viscosity solution. The core of gelatin capsule has been completely wetted and a gel behavior core is formed in the coating film which also illustrated the formation of high viscosity solution.

Figure 3.12 Inside of gelatin and HPMC Capsules after dissolving for different time (RS: RL=1:2; Weight gain ≈ 6 mg/cm^2)

By comparing the differences of in-vitro dissolution tests between tablets and capsules. The dissolving process can be concluded: For the sustained release tablet, it is observed that the tablets would absorb water and swell. Then drug molecular will dissolve into water and diffuse through porous coating film. The release of the drug follows anomalous transport (Dash et al., 2010). While, for a sustained release capsule, it will uptake water and capsule shell is dissolved first which causes a delay. Then, high viscosity solution is formed and mixed with drug and influence the release mechanism. The release of drug follows super case II transport.

3.4.4 Stability tests

Both coated aspirin gelatin capsules (RS: RL=1:4, WG=3.13 mg/cm^2) and coated aspirin HPMC capsules (RS: RL=1:4, WG=4.02 mg/cm^2) were placed in plastic bottles and stored at room temperature (25℃/30%RH) for 8 months. Then they were tested to obtain release profiles and compared with the profiles before stability test, as shown in Figure 3.13 and 3.14. The results show that both dry powder coated gelatin capsules and HPMC capsules have good stability. However, HPMC capsules have better stability owing to their stable properties, especially for moisture sensitive drugs, and they have no risk of capsule cross-linking (Rabadiya & Rabadiya, 2013).

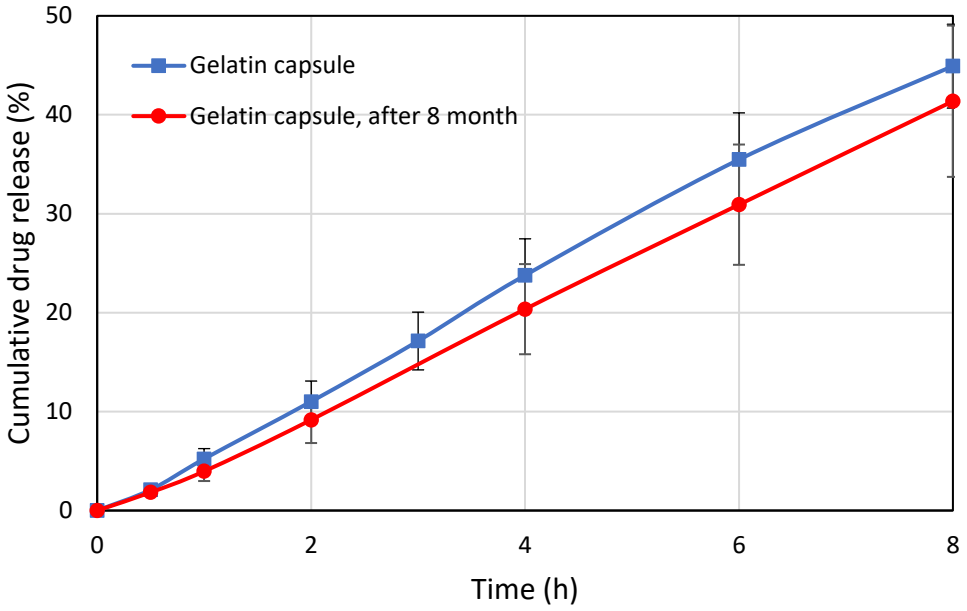


Figure 3.13 Release profiles of coated aspirin gelatin capsules before and after stability test (RS: RL=1:4, WG=3.13 mg/cm^2)

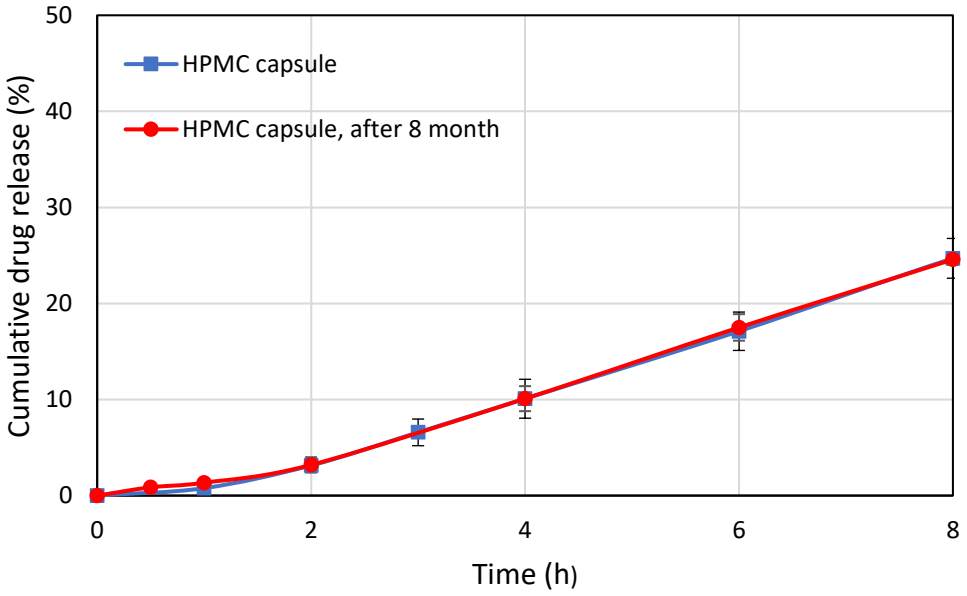


Figure 3.14 Release profiles of coated aspirin HPMC capsules before and after stability test (RS: RL=1:4, WG=4.02 mg/cm^2)

3.5 Conclusion

In this study, a novel electrostatic dry powder coating process was successfully applied on direct coating of hard HPMC and gelatin capsules. In-vitro dissolution test showed sustained releases of aspirin and caffeine were achieved after dry powder coating process. Higher weight gain and higher Eudragit® RS:RL ratio would slow down the release rate. The dry coated sustained release gelatin capsules and HPMC capsules showed good stability stored at 25℃/ 40% RH over 8 months. In addition, by comparing release profiles of sustained release tablet and capsules, the release mechanism of sustained release capsules was revealed. A delay was caused by dissolving of capsule shell for sustained release gelatin as well as HPMC capsules. The high viscosity solution formed by dissolving of gelatin or HPMC capsule shell had great influence on the release of direct coated sustained release capsules. And the release of sustained coated capsules followed super case II transport.

Bibliography

Al-Tabakha, M. M. (2010). HPMC Capsules: Current Status and Future Prospects. *Journal of Pharmacy & Pharmaceutical Sciences*, *13*(3), 428–442.

Amighi, K., & Moes, A. (1996). Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit®RS 30D film-coated sustained-release theophylline pellets. *European journal of pharmaceutics and biopharmaceutics*, *42*(1), 29–35.

Aulton, M., Cole, G., & Hogan, J. (1995). *Pharmaceutical coating technology*. Taylor & Francis.

Bose, S., & Bogner, R. H. (2007). Solventless pharmaceutical coating processes: a review. *Pharmaceutical Development and Technology*, *12*(2), 115–131.

Chiwele, I., Jones, B. E., & Podczeck, F. (2000). The Shell Dissolution of Various Empty Hard Capsules. *Chemical and Pharmaceutical Bulletin*, *48*(7), 951–956.

Cole, E. T., Scott, R. A., Connor, A. L., Wilding, I. R., Petereit, H.-U., Schminke, C., Beckert, T., et al. (2002). Enteric coated HPMC capsules designed to achieve intestinal targeting. *International Journal of Pharmaceutics*, *231*(1), 83–95.

Crotts, G., Sheth, A., Twist, J., & Ghebre-Sellassie, I. (2001). Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid. *European Journal of Pharmaceutics and Biopharmaceutics*, *51*(1), 71–76.

Dash, S., Murthy, P. N., Nath, L., & Chowdhury, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Acta Pol Pharm*, *67*(3), 217–23.

Dvořáčková, K., Rabisková, M., Gajdziok, J., Vetchý, D., Muselík, J., Bernatoniene, J., Bajerová, M., et al. (2010). Coated capsules for drug targeting to proximal and distal part of human intestine. *Acta poloniae pharmaceutica*, *67*(2), 191–199.

Dvořáčková, K., Rabišková, M., Muselík, J., Gajdziok, J., & Bajerová, M. (2011). Coated hard capsules as the pH-dependent drug transport systems to ileo-colonic compartment. *Drug Development and Industrial Pharmacy*, *37*(10), 1131–1140.

Huyghebaert, N., Vermeire, A., & Remon, J. P. (2004). Alternative method for enteric coating of HPMC capsules resulting in ready-to-use enteric-coated capsules. *European Journal of Pharmaceutical Sciences*, *21*(5), 617–623.

Lin, C.-C., & Metters, A. T. (2006). Hydrogels in controlled release formulations: Network design and mathematical modeling. *Advanced Drug Delivery Reviews*, Computational Drug Delivery, *58*(12), 1379–1408.

Luo, Y., Zhu, J., Ma, Y., & Zhang, H. (2008). Dry coating, a novel coating technology for solid pharmaceutical dosage forms. *International Journal of Pharmaceutics*, *358*(1), 16–22.

Misev, T. A., & van der Linde, R. (1998). Powder coatings technology: new developments at the turn of the century. *Progress in Organic Coatings*, *34*(1), 160–168.

Murthy, K. S., Enders, N. A., Mahjour, M., & Fawzi, M. B. (1986). A comparative evaluation of aqueous enteric polymers in capsule coating. *Pharm. Technol*, *10*(10), 36–46.

Pissinati, R., & Oliveira, W. P. (2003). Enteric coating of soft gelatin capsules by spouted bed: effect of operating conditions on coating efficiency and on product quality. *European Journal of Pharmaceutics and Biopharmaceutics*, *55*(3), 313–321.

Plaizier-Vercammen, J. A., & De Neve, R. E. (1993). Evaluation of water and organic coating formulations for the protection of tablets against humidity. *Pharmazie*, *48*(6), 441–446.

Prasad, L. K., McGinity, J. W., & Williams, R. O. (2016). Electrostatic powder coating: Principles and pharmaceutical applications. *International Journal of Pharmaceutics*, *505*(1), 289–302.

Qiao, M., Luo, Y., Zhang, L., Ma, Y., Stephenson, T. S., & Zhu, J. (2010). Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process. *International Journal of Pharmaceutics*, *399*(1), 37–43.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Chow, K. (2010). A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *76*(2), 304–310.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Xiao, W. (2013). A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. *European Journal of Pharmaceutics and Biopharmaceutics*, *83*(2), 293–300.

Rabadiya, B., & Rabadiya, P. (2013). Review: Capsule shell material from gelatin to non animal origin material. *International Journal of Pharmaceutical Research and Bio-Science*, *2*(3), 42–71.

Ritger, P. L., & Peppas, N. A. (1987). A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *Journal of controlled release*, *5*(1), 37-42.

Sauer, D., Cerea, M., DiNunzio, J., & McGinity, J. (2013). Dry powder coating of pharmaceuticals: A review. *International Journal of Pharmaceutics*, Progress in Film Coating, *457*(2), 488–502.

Thoma, K., & Bechtold, K. (1992). *Enteric coated hard gelatin capsules*. Capsugel Library.

Wicks, Z. W. (Ed.). (2007). *Organic coatings: science and technology* (3rd ed.). Hoboken, N.J: Wiley-Interscience.

Wise, D. L. (2000). *Handbook of Pharmaceutical Controlled Release Technology*. CRC Press. Retrieved April 11, 2019, from https://www.taylorfrancis.com/books/9781482289985

Yamashita, S., & Harada, S. (2000). *U.S. Patent No. 6,030,641*. Washington, DC: U.S. Patent and Trademark Office.

Yang, Q., Ma, Y., Shi, K., Yang, G., & Zhu, J. (2018). Electrostatic coated controlled porosity osmotic pump with ultrafine powders. *Powder Technology*, *333*, 71–77.

Yang, Y., Shen, L., Yuan, F., Fu, H., & Shan, W. (2018). Preparation of sustained release capsules by electrostatic dry powder coating, using traditional dip coating as reference. *International Journal of* Pharmaceutics, *543,* 345-351.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2011). *U.S. Patent No. 7,862,848*. Washington, DC: U.S. Patent and Trademark Office.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2012). *U.S. Patent No. 8,161,904*. Washington, DC: U.S. Patent and Trademark Office.

Chapter 4

4 Application of dry powder coating technology on enteric release capsules

This chapter discusses the application of electrostatic dry powder coating technology on gelatin and HPMC capsules to achieve enteric release using Eudragit® L 100-55 as coating material. Higher weight gain of coating prevented capsules from leakage in the acidic solution so that enteric release can be achieved. And compared to gelatin capsules, HPMC capsules showed a slightly delay in the phosphate buffered saline. Results indicated that enteric release capsules with excellent stability were able to be produced successfully. In the coating process, higher weight gain was required to cover the gap at the joint of the capsules to achieve enteric release. To increase the coating weight, a larger amount of plasticizer was used to increase the overall powder adhesion efficiency. The differences of gelatin capsules and HPMC capsules in the coating process and dissolution process were also compared.

4.1 Introduction

Enteric coating is designed to provide a barrier for pharmaceutical drugs that will prevent drugs from dissolving in stomach, but rapidly dissolve in intestine. Owing to its pH sensitivity, enteric coating film can provide several functions. First, it can protect active pharmaceutical ingredients from degradation caused by gastric acid in stomach. Second, it can improve tolerability of medicaments by protecting stomach from being irritated by drugs, so that some side effects of drugs, like stomach bleeding, are minimized. Third, enteric release can be used for certain drugs to achieve target release. For example, if some drugs are designed to treat diseases in intestine, they need to be enteric coated and are not released until reaching intestine (Thoma & Bechtold, 1992).

Different solid dosage forms like tablet, capsule and pellet can be enteric coated. Compared to other solid dosage forms, capsule has some advantages: First, it provides a barrier for moisture and light sensitive active pharmaceutical ingredients (APIs). Second, capsule form is suitable for drugs with low compressibility, slow dissolution or bitter tasting (Al-Tabakha, 2010). Third, capsule shell provides a separate barrier to avoid degradation of active pharmaceutical ingredients resulting from contact with coating materials in the coating process. To reduce the degradation, a sub-coating is often required for tablets or pellets which increases the cost (Crotts et al., 2001).

Normally, hard capsule which is mainly made from gelatin or hydroxypropyl methylcellulose (HPMC) is coated in a coating pan or a fluidized bed by either an organic solvent coating or an aqueous coating process.

For gelatin capsules, Pina et al. (1996) use hydroalcoholic solution of formaldehyde to coat gelatin capsules by simply immerse capsules into solutions and dried in an oven. (Murthy et al., 1986) found that organic solvent coating will lead to poor adhesion of the coating film to the gelatin capsules owing to the smooth surface of the capsules, which is also called orange peel effect. In addition, organic solvent coating will cause toxicological, environmental and safety-related issues (Aulton et al., 1995). Then, aqueous coating technology was used to coat capsules. HPC was applied as a precoat to increase the adhesion of enteric coating films (Murthy et al., 1988). Oliveira et al. (2005) used Eudragit® L30 D55 aqueous solution to coat the hard gelatin capsules in a spouted bed and investigated its coating efficiency. However, the main difficulty with aqueous coating

process is that the gelatin capsules become soft and sticky due to being partially dissolved after aqueous coating materials were sprayed. In addition, shell embrittlement may also happen in aqueous coating process (Thoma & Bechtold, 1992). Cerea et al. (2008) used a dry coating technology to coat soft gelatin capsules in a rotary fluid bed with enteric polymer hydroxypropyl methylcellulose acetate succinate (HPMCAS) as coating materials. However, a sealing film coated by 10% (wt/wt) solution of copovidone was still required.

HPMC capsules, as a great alternative to gelatin capsules, have also been coated to achieve delayed release. And because of rougher surface of HPMC capsules (Cole et al., 2002), adhesion of the coating materials may be increased. Cole et al. (2002) use two aqueous solutions, Eudragit® L 30 D-55 and Eudragit® FS 30 D, to achieve enteric release and colon release respectively. This coating process was carried out in a coating pan. Huyghebaert et al. (2004) coated HPMC capsule shells only before drug filling in a fluidizing bed apparatus and developed ready-to-use enteric-coated capsules. Dvořáčková et al. (2010) coated both HPMC and gelatin capsules with isopropyl alcohol solution in Wurster-M 100 coater. The result showed that film peeling occurred for gelatin capsules, but HPMC capsules and gelatin capsules sub-coated with hydroxypropyl cellulose (HPC) did not. Shell humidity loss caused by organic solvent in coating process would cause embrittlement of gelatin capsules but would not influence HPMC capsules owing to relative low moisture content in the capsule shell (Dvořáčková et al., 2011). Compared to organic solvent coating, aqueous coating requires long operation time because gelatin capsule is water sensitive, so the spraying rate of water solution or dispersion is limited. And more heat is needed to evaporate water owing to its high specific heat capacity. Aqueous coating technology will also cause stickiness of capsules owing to partial dissolving of capsule shell and it is not suitable for moisture sensitive drugs (Bose & Bogner, 2007; Cahyadi et al., 2015).

Solventless pharmaceutical coating processes are growing fast in the last few decades owing to its advantages such as pollution-free, solvent-free, suitable for moisture sensitive drug and so on. (Bose & Bogner, 2007)As one of the solventless coating technologies, the electrostatic powder coating technology developed by Zhu's group eliminates the use of organic solvent and water as well as the cost of evaporation (Zhu et al., 2011, 2012). In addition, introduction of electrostatic force increases the coating efficiency. This technology has been successfully applied on coat tablets and small pellets to achieve different release profiles (Qiao et al., 2010; Qiao et al., 2010;

Qiao et al., 2013; Yang et al., 2018; Yang et al., 2015, 2016). But it has not been applied on capsules to achieve enteric release.

Acetylsalicylic acid (ASA), also known as aspirin, is a wildly used medicament to treat pain, fever, or inflammation. It can decrease the risk of death if taken shortly after heart attack. It is also reported that long-term use of low dosage aspirin can be used to prevent cardiovascular problem (heart attack, stroke, or death) and reduce the risk of cancer (Baigent et al., 2009; Erkan et al., 2007; Lansberg et al., 2012; Paikin Jeremy S. & Eikelboom John W., 2012; Patrignani & Patrono, 2016; Patrono et al., 2005). However, aspirin will cause gastric irritation, especially for long-term usage, resulting in stomach bleeding. So that enteric coating is helpful to reduce the side effect (Hawthorne et al., 1991). Nowadays, most common enteric release aspirin is in tablets form but few researches are about enteric release aspirin capsule. The objective of the present study is to produce enteric coated aspirin capsules by applying electrostatic dry powder coating technology.

4.2 Materials and methods

4.2.1 Materials

Eudragit® L100-55 and Colloidal silicon dioxide (AEROSIL® 200 Pharma) were provided by Evonik Degussa Corporation (Germany). Polyethylene glycol 400 (PEG 400) was purchased from Acros Organics. (Germany). Talc was purchased from Mallinickrodt Baker, Inc. (Canada). FD&C Blue lake No.1 was provided by Food Ingredient Solutions LLC (US). Size 4 HPMC capsules (Vcaps Plus®) and gelatin capsules (Coni-Snap®) were donated by Capsugel Inc. (US). Acetylsalicylic acid was purchased from Huayin Jinjincheng Pharmaceutical Co., Ltd. (China). Lactose was obtained from GlaxoSmithKline, Inc. (Canada). Avicel® Microcrystalline cellulose PH-102 was purchased from Food Machinery Corporation (US). Corn starch 1500 was donated by Colorcon, Inc. (US) and Ac-Di-Sol® SD-711 was provided by FMC Corporation (US).

4.2.2 Particle size reduction and analysis

Because the particle size of purchased Eudragit® L100-55 was too large, it was grounded by a jet mill to obtain smaller particles. And a Particle Size Analyzer (TSI Corporation, Model 3603, Shoreview, MN, USA) was used to determine the particle sizes of the coating materials. Each test

was repeated 3 times. The D50 (the particle diameter at 50% of total weight fraction) of Eudragit® L100-55 and talc were 23.2μm, 41.2μm respectively.

4.2.3 Capsules and tablets preparation

Both gelatin and HPMC size 4 capsules were filled by CN 100 capsule filling machine (CapsulCN LTD., China). Weight of each filled aspirin capsule was 155.3 ± 6.9mg (n=10). The formulation of aspirin capsules is shown in Table 4.1.

Table 4.1 Formulation of aspirin capsules

Ingredient	Weight fraction
Aspirin	69.5%
Microcrystalline cellulose PH102	30%
AEROSIL® 200 Pharma	0.5%

Aspirin tablets were compressed by rotary tablet press machine (Tianfan Pharmaceutical Machinery Factory, Shanghai, China). Formulation and the size of aspirin tablets are listed in Tables 4.2 and Table 4.3.

Table 4.2 Formulation of aspirin tablets

Ingredients	Weight fraction
Aspirin	46%
Microcrystalline cellulose PH102	17%
Lactose	25%
Corn starch 1500	10%
AEROSIL® 200 Pharma	1%
Ac-Di-Sol®SD-711	1%

Table 4.3 Size of aspirin tablets

Properties	Aspirin tablets

Weight (mg)	176.5 ± 6.3
Diameter (mm)	7.0
Thickness (mm)	4.0
Hardness (N)	120

4.2.4 Formulation of coating material

The formulation of enteric release coating material is listed in Table 4.4. Eudragit® L 100-55 is commonly used to achieve enteric release. Talc was used as anti-stick agent. Blue lake No.1 was used as pigment to investigate the uniformity and improve appearance of substrate. The plasticizer and polymers ratio was 0.23.

Table 4.4 Formulation of enteric release coating material

Materials	Weight Fraction
Eudragit® L100-55	40%
Talc	59.5%
Blue lake No.1	0.5%

4.2.5 Contact angle measurement

The contact angles of liquid plasticizer PEG 400 on gelatin capsule and HPMC capsule were determined by optical contact angle measuring and contour analysis system (OCA 30, DataPhysics Instruments, Germany). Before measurement, capsules were cut and made to be flat by sticking it on a plate. Dosing volume were set as $5\ \mu L,\ 1\ \mu L/s$. The test was repeated for 3 times for accuracy.

4.2.6 Powder coating process

The coating equipment are shown in Figure 4.1, it mainly consisted of a heating system, a grounded rotating coating pan, a liquid spraying system which includes a liquid pump and spraying nozzle, and an electrostatic powder spraying gun (Nordson Corporation, USA).

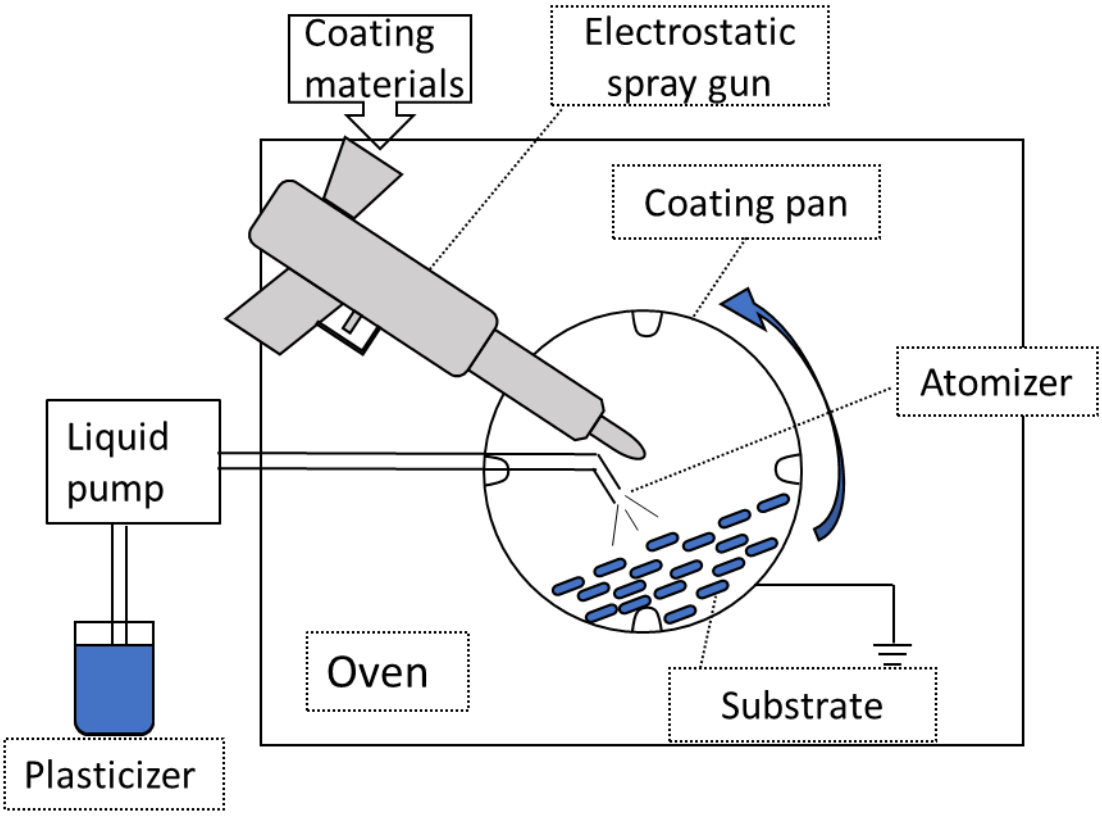


Figure 4.1 Schematic of the electrostatic powder coating system

In the coating process, the temperature of the oven was set at 50℃ first, and when the system equilibrated, the substrate was put into the rotating coating pan in the oven and preheat for 10 minutes. Then, spray the plasticizer (0.4mg/min) first followed by coating powders. To achieve a thicker coating film, plasticizer and coating powders were sprayed alternatively for several times until desired amount of coating materials was deposited on the substrate surface. Finally, the coated substrate was left in the rotating coating pan until the films were formed owing to the coalescence of polymers. In this process, coating powders were sprayed by electrostatic powder spraying gun. After sprayed, powders would be negative charged which will increase the coating efficiency and uniformity (Luo et al., 2008). After deposit on the substrate, the charged electrons would be removed through grounded coating pan and let more particles deposit on the substrate. Plasticizer, also plays an important role, was sprayed by liquid spraying system. It has three functions: First, it can decrease glass transition temperature of polymers, so that the film can be formed under relatively lower temperature. Second, it can increase conductivity of substrate, so

that the charged coating powders (coating materials) can soon be discharged after deposit on the surface of substrate because the substrate contacted with grounded coating pan. Third, liquid plasticizer can increase adhesion force of the substrate. Coating powders would be easier to adhere on the surface of the substrate so that coating efficiency was increased.

4.2.7 Scanning electron microscopy (SEM)

The surface morphology of the dry powder coat capsule was observed by scanning electron microscope (Hitachi S-2600 N, Ontario, Canada) operated at 5.0kV to investigate the coating film and the capsule properties. Before the observation, capsules were sputter coated with gold for 2 minutes first by using EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK) to increase the surface electrical conductivity.

4.2.8 HPLC

High performance liquid chromatography (HPLC) (Waters Corporation, US) was used to examine the concentration of free salicylic acid. Aspirin capsules before and after stored at 40℃/ 75% RH for 2 months were opened and dissolved in a mixture of acetonitrile and formic acid (99:1). The mobile phase was prepared by dissolving 2 g of sodium 1-heptanesulfonate in a mixture of 700 mL of water and 300 mL of acetonitrile, then the solution was adjusted with glacial acetic acid to a pH of 3.4. A Symmertry® C18 analytical column (4.6 mm×150 mm, 5 μm) was used to separate aspirin and salicylic acid and a UV detector (Waters 2487 Dual λ Absorbance Detector) was used to test the concentration of aspirin and salicylic acid at 276 nm wavelength.

4.2.9 *In vitro* dissolution test

In vitro dissolution test of capsules was carried out by a dissolution test system (Huanghai Rcz-6c2, Shanghai, China) which complies with the standard of United States Pharmacopeia (USP) (<711> Dissolution, Apparatus 1, Basket). Tablets were tested in the same system according to USP (<711> Dissolution, Apparatus 2, Paddle). Six dosages were tested at the same time. The apparatus was set at 37℃, basket/paddle rotating speed was set at 100rpm. In the first 2 hours of dissolution test, the solution is 750 ml hydrochloric acid (0.1 mol/L, pH=1), afterwards, 250 ml 0.2 M tribasic sodium phosphate solution was added and form 1000 ml phosphate buffered saline (pH=6.8). Then, the aspirin concentration was tested for another 2 hours. 10 ml solution was

withdrawn and filtered as sample from each tank by a syringe and replaced by fresh solution with certain time interval. The samples were tested by 8453 UV–Visible Spectrophotometer (Agilent Technologies, Mississauga, Canada) at a wavelength of 276 nm and 269 nm in hydrochloric acid solution (pH=1) and phosphate buffer (pH=6.8) respectively. Standard curves of aspirin in hydrochloric acid solution (0.1 mol/L, pH=1) and phosphate buffered saline (pH=6.8) are shown in Figure 4.2 and Figure 4.3.

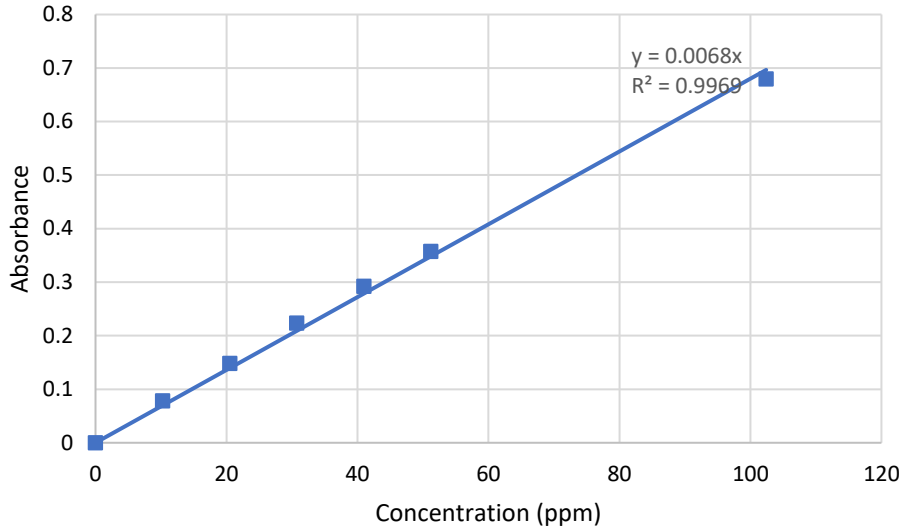


Figure 4.2 Standard curve of aspirin in hydrochloric acid solution (pH=1) at 276 nm

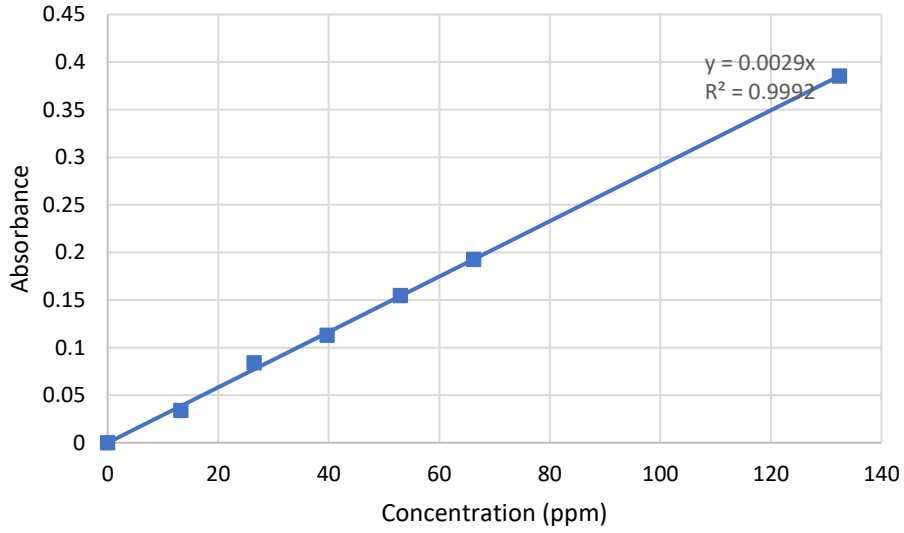


Figure 4.3 Standard curve of aspirin in phosphate buffered saline (pH=6.8) at 269 nm

4.2.10 Stability test

The capsules were placed in high-density polyethylene (HDPE) vials and sealed. Then the vials were stored at 40℃/ 75% RH for 2 months. The dissolution tests of enteric coated capsules before and after storage were carried out to exam their stability.

4.3 Results and discussion

Both aspirin capsules and tablets were coated to achieve enteric release. Coating weight gain for both capsules and tablets will influence whether enteric release can be achieved or not. Different weight gains were obtained as shown in Table 4.5 by controlling different amount of coating materials sprayed on capsules or tablets.

The dry powder coating process was able to successfully eliminate several difficulties associated with aqueous coating process for both gelatin and HPMC capsules. First, the dissolution and swelling of the capsules was avoided by eliminating water from the process. Additionally, through the elimination of water, the stickiness associated with the solubilization of gelatin and HPMC capsules (Cole et al., 2002; Thoma & Bechtold, 1992) was avoided. The capsules coated using the dry powder process also did not experience poor coating adhesion as seen commonly in organic and aqueous coating processes.

Table 4.5 Weight gains of aspirin capsules and tablets

Substrate	Coating level	Weight gain (mg/cm^2)
Gelatin capsule	2.6%	1.7
	7.0%	4.6
	11.0%	6.8
HPMC capsule	2.75%	1.8
	6.0%	3.9
	9.6%	6.3
Tablet	2.0%	2.4
	3.8%	4.6
	5.2%	6.4

*Coating level = $\frac{\text{substrate weight after coating}}{\text{substrate weight before coating}} \times 100\%$;

Weight gain = $\frac{\text{weight increased of substrate after coating}}{\text{total surface area of substrate}}$.

4.3.1 Influence of coating weight gains

For both the hard gelatin capsule and HPMC capsule, the weakest part of the capsule is the gap existing at the joint of the cap and body of the capsule when it is closed. Figure 4.4 shows the gap size of uncoated gelatin capsules and HPMC capsules. It is clear that size 4 Vcaps Plus® HPMC capsule has a larger gap which is $77.06 \pm 4.663\ \mu m$ (n=3) than size 4 Coni-Snap® gelatin capsules which is $28.73 \pm 1.406\ \mu m$ (n=3).

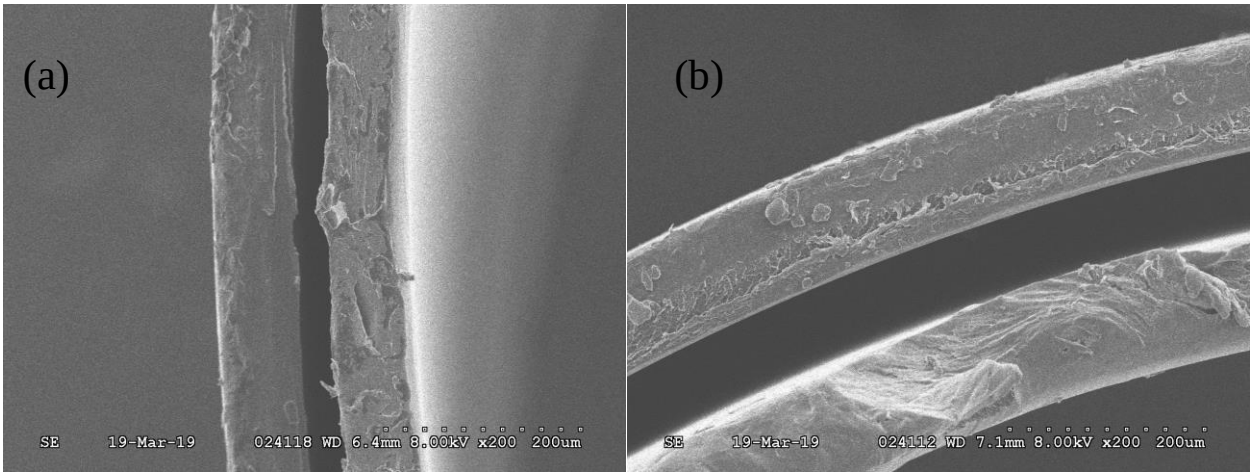


Figure 4.4 Scanning electron micrographs for gaps of capsules (a) gelatin capsule (b) HPMC capsule

The existence of the gaps means that coating films must be thick enough and cover the gaps to prevent leakage and achieve enteric release. Figure 4.5 shows the SEM figures of gelatin and HPMC capsules with different weight gains where higher weight gains result in thicker films. It is found that when coated films are not thick enough, the gap was still obvious as Figure 4.5 (a) and (d). When weight gain increased to around 4 mg/cm^2, most parts of the gaps were covered as Figure 4.5 (b) and (e). By continuously increasing the coating weight gain, the gaps were completely sealed as Figure 4.5 (c) and (f).

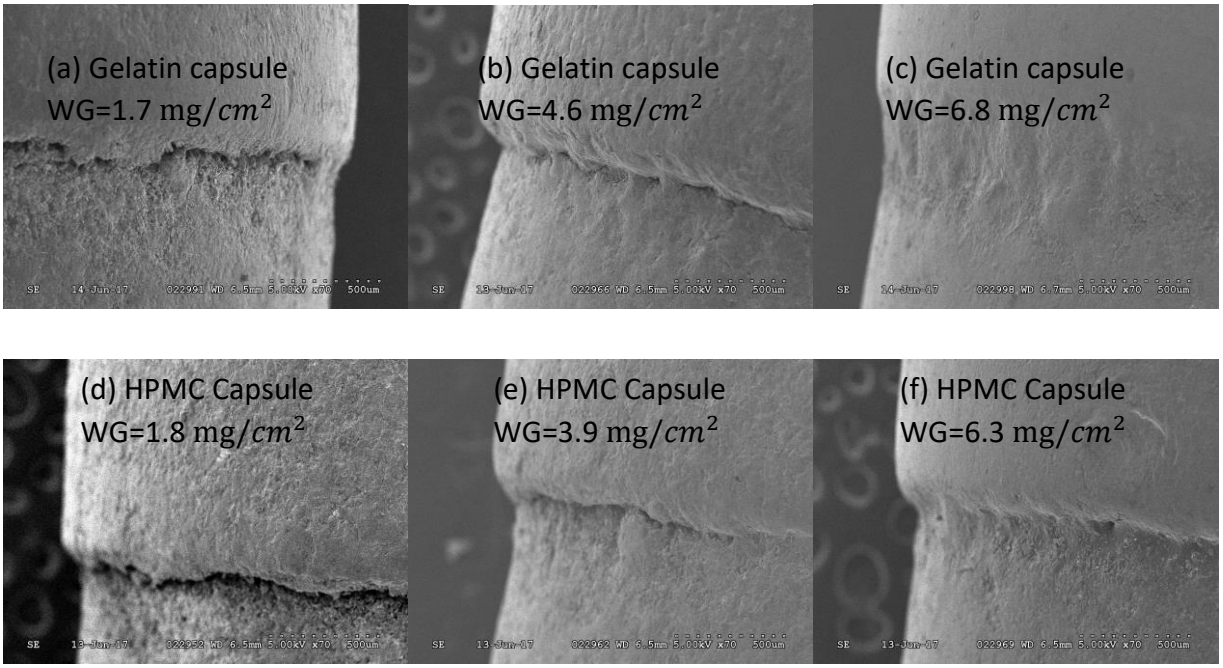


Figure 4.5 SEM pictures of gelatin and HPMC capsules with different weight gains (WG)

For enteric release solid dosage forms such as tablets, pellets, capsules, weight gain has great influence on whether enteric release can be achieved or not. Figure 4.6 and Figure 4.7 are the release profiles of gelatin capsules and HPMC capsules with different weight gains. In U.S. Pharmacopeia, aspirin released during the first 2 hours in HCl solution should be less than 10% for enteric release aspirin capsules ("Aspirin", 2017). However, for both gelatin capsules and HPMC capsules with less than 2 mg/cm^2weight gain, capsules broke along the gaps during first 2 hours in HCl solution resulting in more than 10% aspirin released. This result also matched the result of scanning electron micrographs that the gaps were not covered when weight gain was low. As weight gain increased to about 4 mg/$cm^2$and 6.5 mg/cm^2, the coated capsules stayed intact and less than 1% aspirin was released in the acidic solution (pH 1). After change pH value to 6.8, both coated gelatin capsules and HPMC capsules were dissolved and released more than 80% aspirin in 30 minutes.

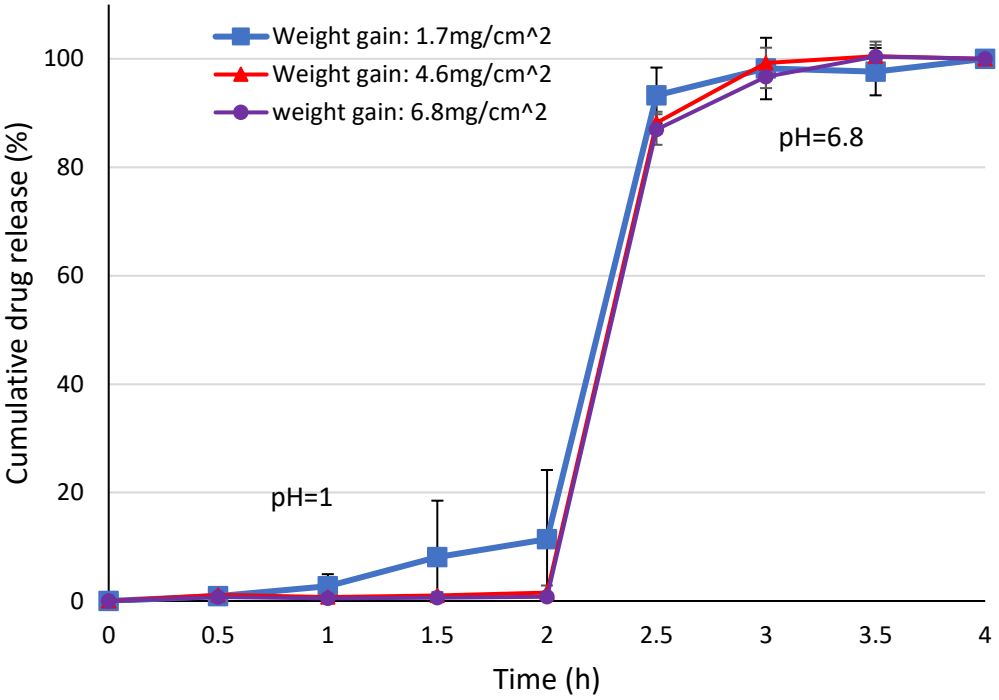


Figure 4.6 Release profiles of gelatin capsules with different weight gains

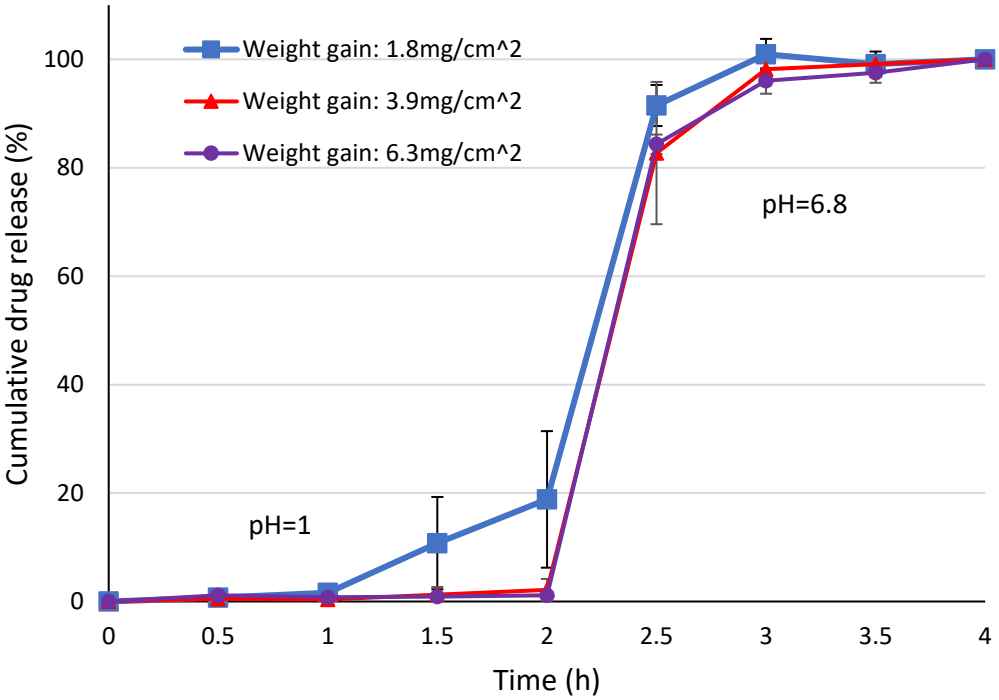


Figure 4.7 Release profiles of HPMC capsules with different weight gains

Enteric release aspirin tablets with different weight gains were also tested. Figure 4.8 illustrates the release profiles of enteric release tablets with different weight gains. For tablets, low weight gain (2.4 mg/cm^2) still cannot provide enough protection and more than 10% aspirin was released in the acidic solution. But as the weight gain increase to 4.6 mg/cm^2 or even higher, enteric release was achieved.

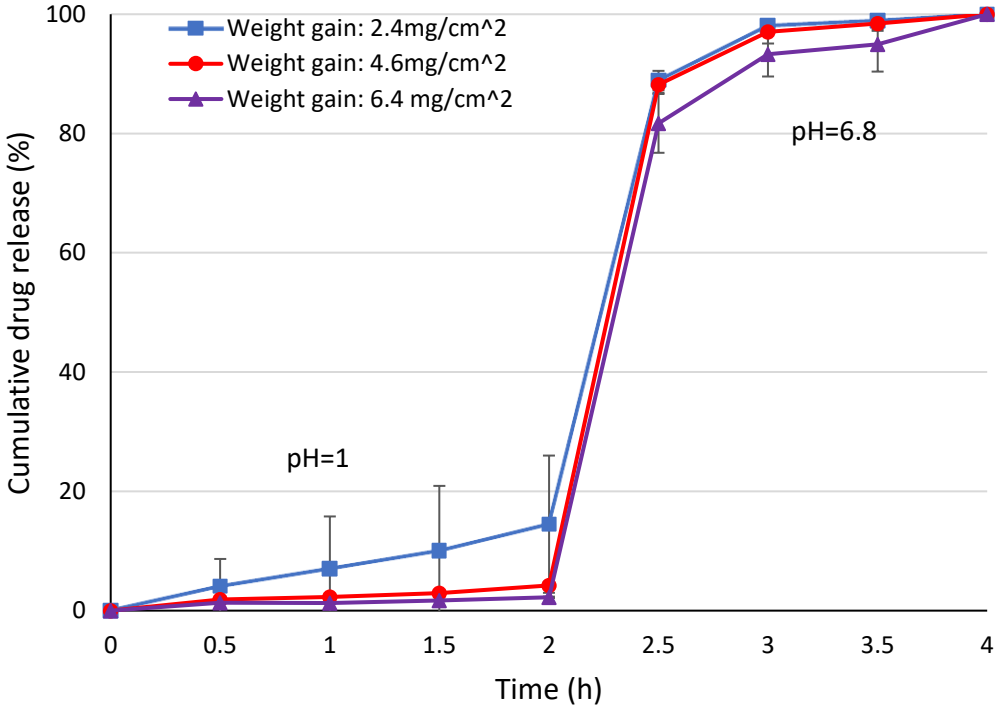


Figure 4.8 Release profiles of tablets with different weight gains

4.3.2 Influence of capsule materials

Gelatin capsules and HPMC capsules both released about 1% aspirin during first 2 hours in the acidic solution as mentioned above, but the performances inside the gelatin capsules and HPMC capsules were different. Figure 4.9 shows the internal changes of gelatin capsules and HPMC capsules after different time points in the acidic solution (pH 1, HCl solution) at 37 ℃. Gelatin capsules were completely wetted after 1.5 hours, while HPMC capsules were still dry after 2 hours.

This is because after capsules were put into the solution, water would penetrate the coating film and start to dissolve capsule shells. When in contact with water, gelatin capsule shells would dissolved fast and the water would be able to reach the contained drugs after shells dissolved. In contrast to the gelatin capsules, HPMC capsules need a longer time to be dissolved under these conditions (Al-Tabakha, 2010). Thus, the water that penetrated the coating film would not be able to reach the contained drugs because it is blocked by HPMC capsule shells.

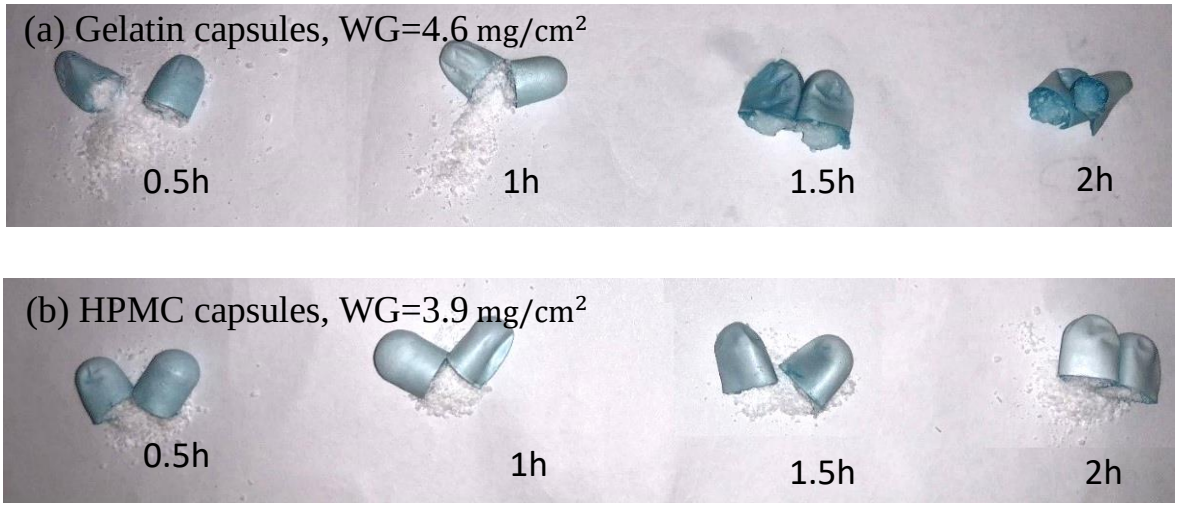


Figure 4.9 Inside of coated aspirin capsules after being merged in acidic solution for different time at 37 ℃

Although enteric release gelatin capsules and HPMC capsules released more than 80% aspirin after changed to buffer solution with pH=6.8. the release rates are different. Figure 4.10 compares the cumulative drug release of aspirin tablets, gelatin capsules and HPMC capsules with weight gain of about 6.5 mg/cm^2 versus time. The figure shows that after 120 minutes in the acidic solution, there was almost no aspirin released by gelatin and HPMC capsules. After 120 minutes, the dissolution medium was changed to buffer solution with pH 6.8. The amount of aspirin released from gelatin capsules was far more than HPMC capsules at 135 minutes, but with level amount of cumulative drug release occurring at 150 minutes. This phenomenon was also a result of the different dissolution rates of gelatin and HPMC materials. Since HPMC capsules dissolve more slowly than gelatin capsules (due to their low chain relaxation rate), there was the delay of HPMC capsules after the solution was changed from pH 1 to pH 6.8.

Enteric release aspirin tablets were also tested to be compared with coated capsules. After 120 minutes in the acidic solution, the amount of aspirin released by the tablets was greater than the amount released by gelatin capsules and HPMC capsules because there was no barrier between tablet cores and coating films to provide extra protection. After the medium was changed to the pH 6.8 buffer solution, the tablets would break and release aspirin quickly without the delay shown for HPMC capsules in the dissolution test using paddle.

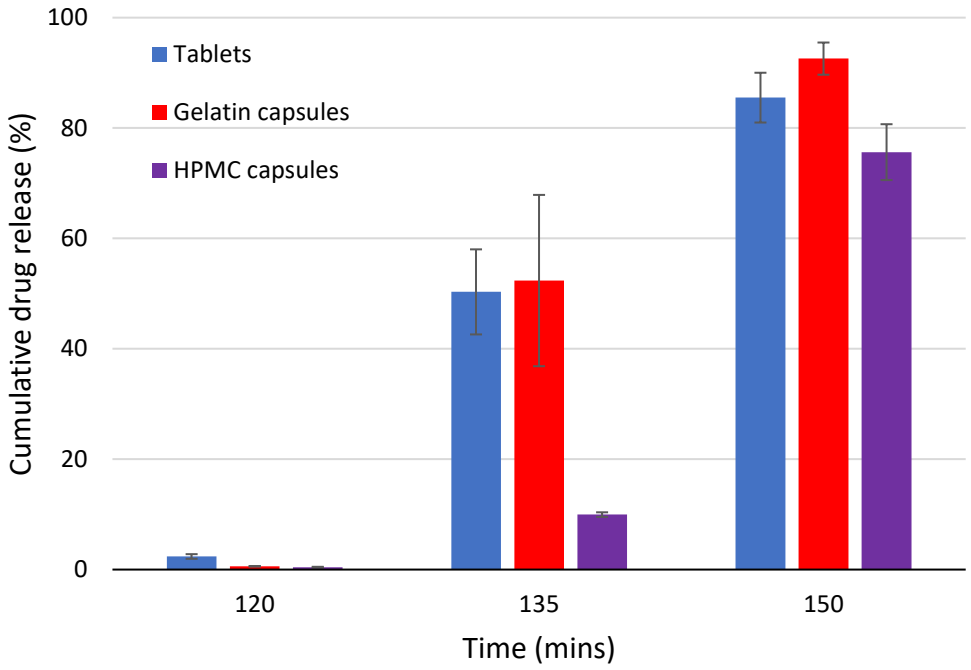


Figure 4.10 Cumulative aspirin release at different time during dissolution test

4.3.3 Moisture loss during coating process

In the coating process, gelatin capsules and HPMC capsules had different performances owing to their different properties. Since gelatin capsules are more hygroscopic than HPMC capsules, moisture contents of the capsule shells are 3-16% for gelatin capsules corresponding to storage at relative humidity 35-65% and 2–7% for the HPMC capsules corresponding to relative humidity 10-60% (Al-Tabakha, 2010). During this dry powder coating process, the operation temperature was controlled at 50℃, and the relative humidity was 0-10%. Under this temperature and relative humidity, gelatin capsules would lose some weight as Figure 4.11 shows. For gelatin capsules,

each capsule lost about 7% of weight due to evaporation of moisture after a 2-hour heating process at 50℃, to which no shell embrittlement was observed. For HPMC capsules, moisture loss was limited due to the relatively low moisture content in the HPMC capsule shells. Shell embrittlement was not observed as well, and the weight of HPMC capsules stayed stable during the 2-hour heat processing.

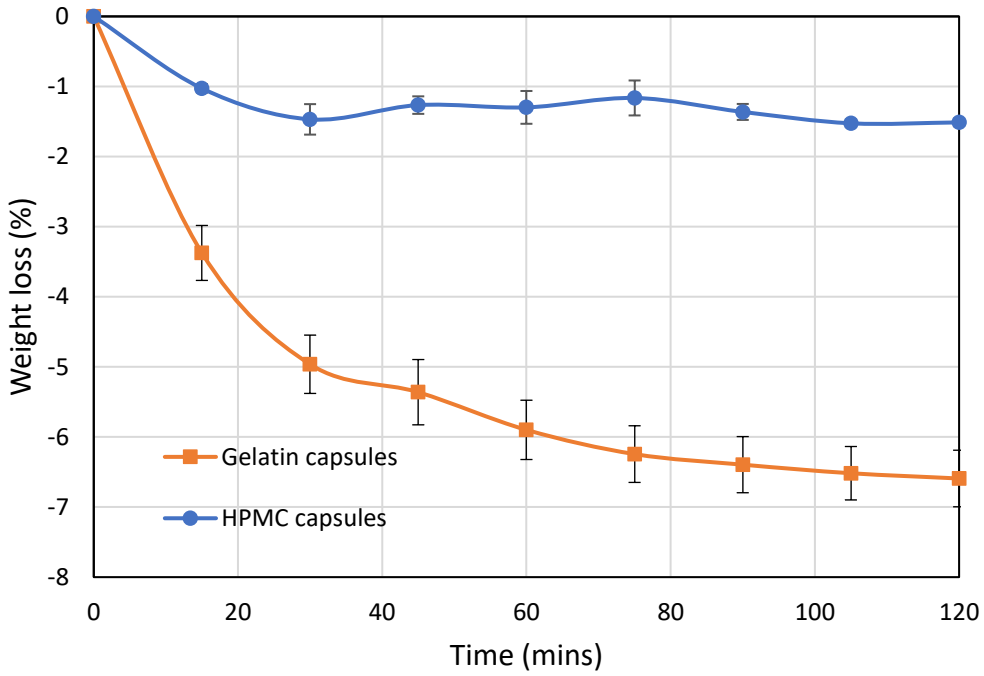


Figure 4.11 Moisture loss of gelatin and HPMC capsules in 50℃ oven for different time

4.3.4 Influence of plasticizer on powder adhesion

In this process, another function of PEG 400 was to increase the adhesion force between substrates and powdered coating materials. The relationship of sprayed plasticizer amount and powder adhesion efficiency was investigated. Excess coating powders were used to provide enough powders to be deposited on capsules which led to relatively low powder adhesion efficiency. As shown in Figure 4.12, the powder adhesion efficiency increased as the amount of sprayed plasticizer increased for both gelatin and HPMC capsules. However, the slopes of Figure 4.12 are decreasing as the plasticizer spray time increases. In the coating process, as plasticizer spraying increases, more plasticizer would be deposited on the surface of capsules and wet the surface.

When the coating powders were sprayed, more powders tend to stick on the surface of capsules where they were wet. Therefore, powder adhesion efficiency increased as more PEG 400 was sprayed and more of the capsule surface was wetted. However, as more PEG 400 is sprayed on capsules surface, the amount of PEG 400 a capsule can occupy becomes saturated resulting a decreased rate of powder adhesion. When the surface is completely saturated, the powder adhesion efficiency will no longer increase even the addition of more PEG 400. However, before the capsule saturation point is reached, the capsules will stick together due to the tackiness of the plasticizer at large volumes. In this experiment, when the amount of PEG 400 was greater than 0.4 g, both the gelatin and HPMC capsules would stick with each other or to the coating pan. So that 0.4 g PEG 400 was established as the optimum plasticizer amount for the coating process to prevent the stickiness of capsules.

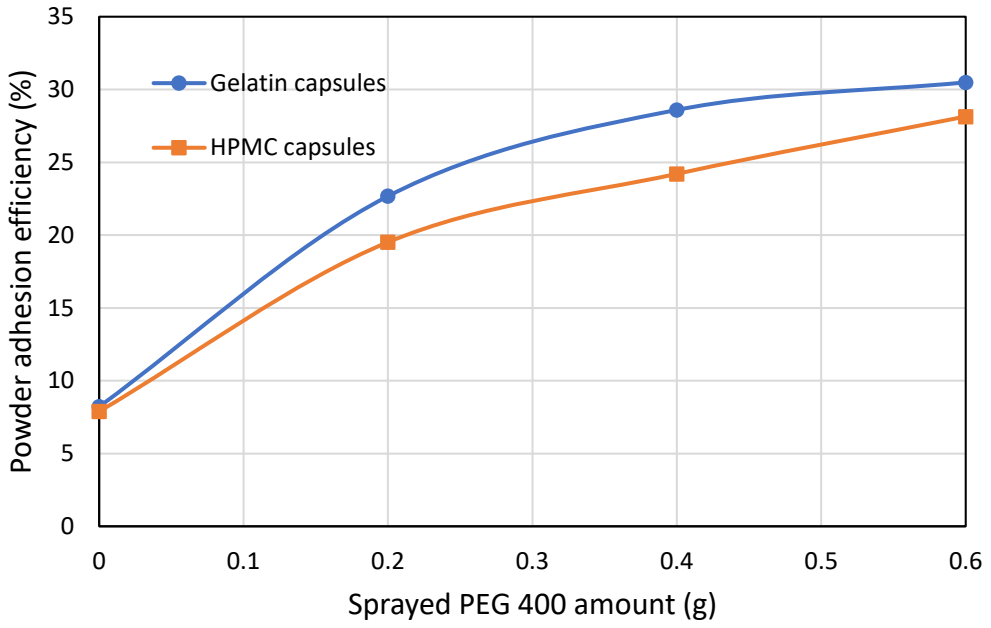


Figure 4.12 The influence of PEG 400 on powder adhesion efficiency (spray rate: 0.4mg/min)

$$*Powder\ adhesion\ efficiency = \frac{Weight\ gain\ of\ capsules}{Weight\ of\ sprayed\ coating\ powders} \times 100\%$$

4.3.5 Contact angle

In Figure 4.12, powder adhesion efficiency of HPMC capsules was always lower than gelatin capsules. This fact was owed to the different surface energies of gelatin capsules and HPMC capsules. The difference in surface energies would lead to different wetting and coating efficiencies of the gelatin and HPMC capsules during coating process. Thus, the contact angle which can be used to reflect wettability was measured.

When PEG 400 was used as liquid phase to measure the contact angle, the contact angle of HPMC capsule was $41.7 \pm 2.71°$, and for gelatin capsules it was $33.2 \pm 1.48°$. Since the contact angle of HPMC capsules was larger than gelatin capsules, some phenomena that occurred in the coating process can be explained.

First, compared to gelatin capsules, HPMC capsules were less sticky when the same amount of plasticizer sprayed on the capsule surface before the coating powders were sprayed. Owing to a larger contact angle, the wettability of HPMC capsule is lower, which represents lower surface energy of HPMC capsule. Thus, the HPMC capsules will have a weaker attractive force to the plasticizer droplets leading to lower interfacial tension between plasticizer and capsules. When two capsules would stick together (due to plasticizer droplets between them), the HPMC capsules would be easier to separate compared to gelatin capsules.

Second, since HPMC capsules have larger contact angle, representing lower wettability, PEG 400 would not spread out the capsule surface as easily, leading to less capsule surface area being covered by plasticizer. It has mentioned that the plasticizer can provide attractive force for the coating powders. Therefore, due to less surface area being covered by the plasticizer, less powders would deposit on HPMC capsules, leading to an overall lower powder adhesion efficiency and coating efficiency when compared to gelatin capsule.

4.3.6 Stability tests

Release profiles after stability test of gelatin capsules (weight gain=6.8 mg/cm^2) and HPMC capsules (weight gain=6.3 mg/cm^2) are shown in Figure 4.13 and Figure 4.14. Both gelatin capsules and HPMC capsules showed great stability during 2-month acceleration test at 40℃/75% RH.

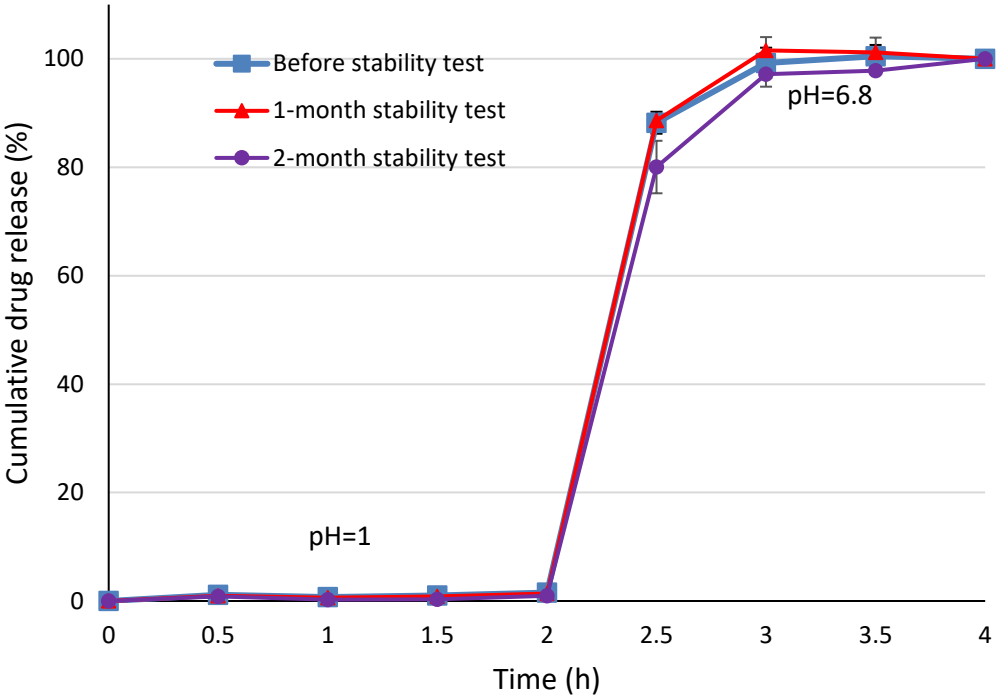


Figure 4.13 Release profile of gelatin capsules after stability test

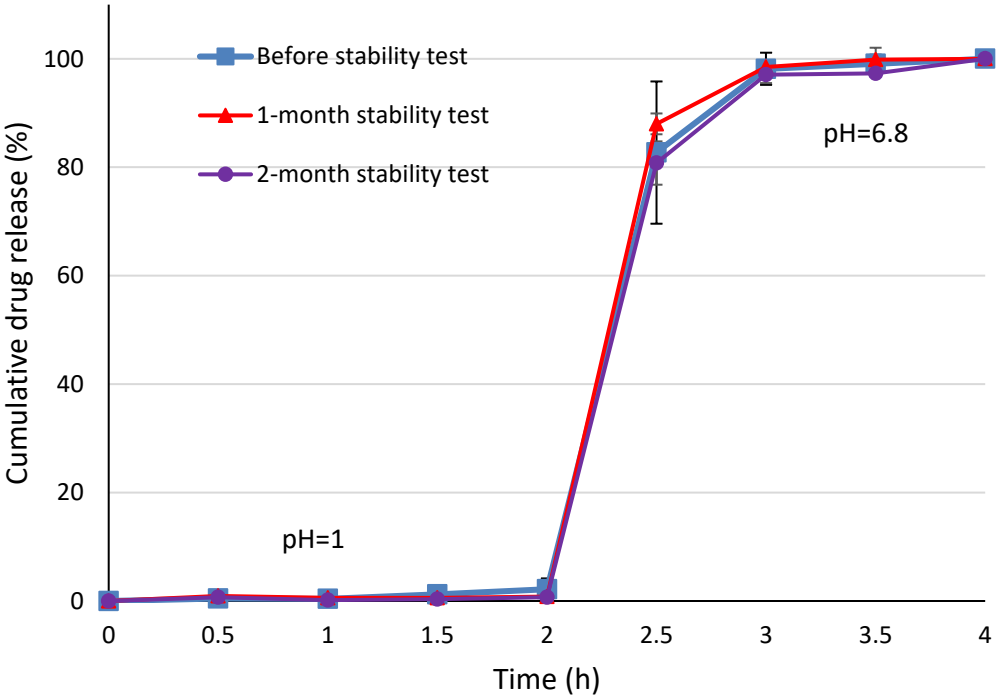


Figure 4.14 Release profile of HPMC capsules after stability test

The concentration of free salicylic acid (SA) before and after the acceleration test was also measured (Figure 4.15). After the acceleration test, the concentration of SA would increase for both gelatin capsules and HPMC capsules. This might be due to the moisture from the environment penetrating the coating film and capsule shells causing the hydrolysis of aspirin. Compared to gelatin capsules, more aspirin was hydrolyzed from HPMC capsules which might be because larger gaps exist at the joints of the HPMC capsules, providing a larger pathway for moisture to reach the enclosed drug. Thus, enteric coated gelatin capsules may be a better option to deliver aspirin.

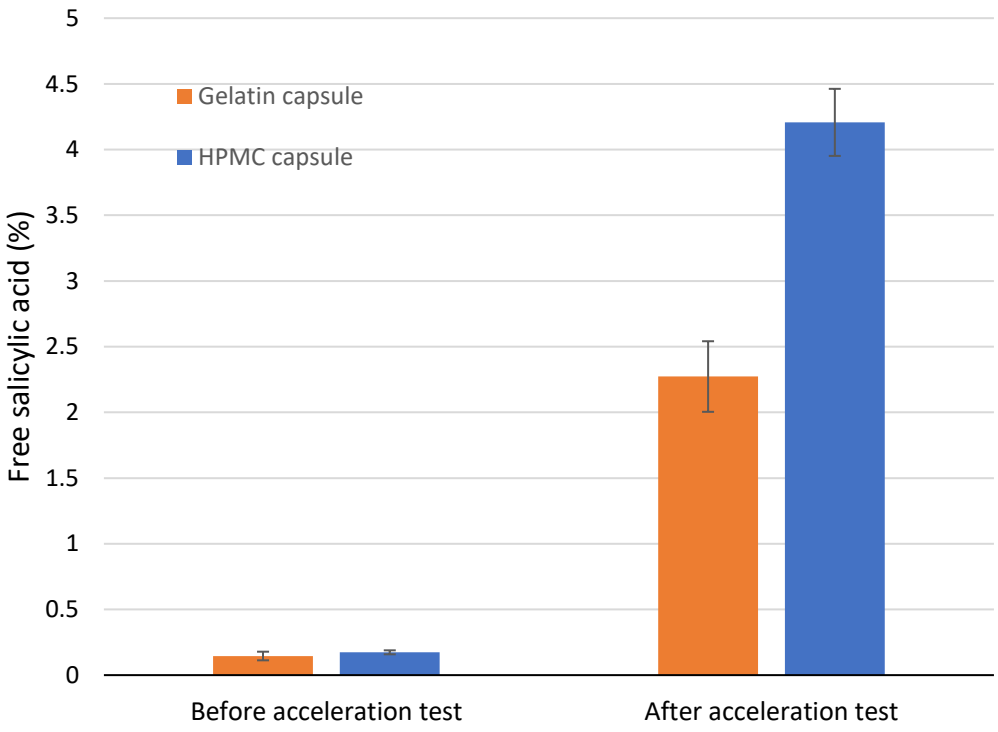


Figure 4.15 Concentration of free salicylic acid before and after 2-month stability test

4.4 Conclusion

In this study, electrostatic dry powder coating process was successfully applied on enteric release hard gelatin capsules and HPMC capsules. The release profiles of the capsules showed both enteric coated gelatin capsules and HPMC capsules had good stability. In the coating process, dry powder coating avoided the difficulties of organic solvent or aqueous capsule coating process like poor adhesion, stickiness and shell embrittlement. By adjusting the amount of plasticizer, powder

adhesion efficiency can be increased. In the dissolution test, higher weight gain was required to cover the gap at the joint of the capsules to prevent the leakage in the acidic solution. Compared with enteric coated gelatin capsules, enteric coated HPMC capsules can prevent water penetration in the acidic solution but also delayed the release in the pH 6.8 phosphate buffered saline.

Bibliography

Al-Tabakha, M. M. (2010). HPMC Capsules: Current Status and Future Prospects. *Journal of Pharmacy & Pharmaceutical Sciences*, *13*(3), 428–442.

"Aspirin" (2017). *The United States Pharmacopeia 2017: USP 40; The National Formulary: NF 35*, United States Pharmacopeia Convention, pp. 2872–2876.

Aulton, M., Cole, G., & Hogan, J. (1995). *Pharmaceutical coating technology*. Taylor & Francis.

Baigent, C., Blackwell, L., Collins, R., Emberson, J., Godwin, J., Peto, R., Buring, J., et al. (2009). Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)*, *373*(9678), 1849–1860.

Bose, S., & Bogner, R. H. (2007). Solventless pharmaceutical coating processes: a review. *Pharmaceutical Development and Technology*, *12*(2), 115–131.

Cahyadi, C., Chan, L. W., & Heng, P. W. S. (2015). A comparative study between conventional pan coater and quasi-continuous small batch coater on the stability of tablets containing acetylsalicylic acid. *European Journal of Pharmaceutics and Biopharmaceutics*, *90*, 30–37.

Cerea, M., Foppoli, A., Maroni, A., Palugan, L., Zema, L., & Sangalli, M. E. (2008). Dry Coating of Soft Gelatin Capsules with HPMCAS. *Drug Development and Industrial Pharmacy*, *34*(11), 1196–1200.

Cole, E. T., Scott, R. A., Connor, A. L., Wilding, I. R., Petereit, H.-U., Schminke, C., Beckert, T., et al. (2002). Enteric coated HPMC capsules designed to achieve intestinal targeting. *International Journal of Pharmaceutics*, *231*(1), 83–95.

Crotts, G., Sheth, A., Twist, J., & Ghebre-Sellassie, I. (2001). Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid. *European Journal of Pharmaceutics and Biopharmaceutics*, *51*(1), 71–76.

Dvorácková, K., Rabisková, M., Gajdziok, J., Vetchý, D., Muselík, J., Bernatoniene, J., Bajerová, M., et al. (2010). Coated capsules for drug targeting to proximal and distal part of human intestine. *Acta poloniae pharmaceutica*, *67*(2), 191–199.

Dvořáčková, K., Rabišková, M., Muselík, J., Gajdziok, J., & Bajerová, M. (2011). Coated hard capsules as the pH-dependent drug transport systems to ileo-colonic compartment. *Drug Development and Industrial Pharmacy*, *37*(10), 1131–1140.

Erkan, D., Harrison, M. J., Levy, R., Peterson, M., Petri, M., Sammaritano, L., Unalp-Arida, A., et al. (2007). Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: A randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody–positive individuals. *Arthritis & Rheumatism*, *56*(7), 2382–2391.

Hawthorne, A., Mahida, Y., Cole, A., & Hawkey, C. (1991). Aspirin-induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. *British Journal of Clinical Pharmacology*, *32*(1), 77–83.

Huyghebaert, N., Vermeire, A., & Remon, J. P. (2004). Alternative method for enteric coating of HPMC capsules resulting in ready-to-use enteric-coated capsules. *European Journal of Pharmaceutical Sciences*, *21*(5), 617–623.

Lansberg, M. G., O'Donnell, M. J., Khatri, P., Lang, E. S., Nguyen-Huynh, M. N., Schwartz, N. E., Sonnenberg, F. A., et al. (2012). Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, *141*(2, Supplement), e601S-e636S.

Murthy, K. S., Enders, N. A., Mahjour, M., & Fawzi, M. B. (1986). A comparative evaluation of aqueous enteric polymers in capsule coating. *Pharm. Technol*, *10*(10), 36–46.

Murthy, K. S., Kubert, D. A., & Fawzi, M. B. (1988). In vitro Release Characteristics of Hard Shell

Capsule Products Coated with Aqueous- and Organic-Based Enteric Polymers. *Journal of Biomaterials Applications*, *3*(1), 52–79.

Oliveira, H. V. A., Peixoto, M. P. G., & Freitas, L. A. P. (2005). Study on the Efficiency of Hard Gelatin Capsules Coating in a Spouted Bed. *Drying Technology*, *23*(9–11), 2039–2053.

Paikin Jeremy S., & Eikelboom John W. (2012). Aspirin. *Circulation*, *125*(10), e439–e442.

Patrignani, P., & Patrono, C. (2016). Aspirin and Cancer. *Journal of the American College of Cardiology*, *68*(9), 967–976.

Patrono, C., García Rodríguez, L. A., Landolfi, R., & Baigent, C. (2005). Low-Dose Aspirin for the Prevention of Atherothrombosis. *New England Journal of Medicine*, *353*(22), 2373–2383.

Pina, M. E., Sousa, A. T., & Brojo, A. P. (1996). Enteric coating of hard gelatin capsules. Part 1. Application of hydroalcoholic solutions of formaldehyde in preparation of gastro-resistant capsules. *International Journal of Pharmaceutics*, *133*(1), 139–148.

Qiao, M., Luo, Y., Zhang, L., Ma, Y., Stephenson, T. S., & Zhu, J. (2010). Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process. *International Journal of Pharmaceutics*, *399*(1), 37–43.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Chow, K. (2010). A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *76*(2), 304–310.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Xiao, W. (2013). A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. *European Journal of Pharmaceutics and Biopharmaceutics*, *83*(2), 293–300.

Thoma, K., & Bechtold, K. (1992). *Enteric coated hard gelatin capsules*. Capsugel Library.

Yang, Q., Ma, Y., Shi, K., Yang, G., & Zhu, J. (2018). Electrostatic coated controlled porosity osmotic pump with ultrafine powders. *Powder Technology*, *333*, 71–77.

Yang, Q., Ma, Y., & Zhu, J. (2015). Applying a novel electrostatic dry powder coating technology

to pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, *97*, 118–124.

Yang, Q., Ma, Y., & Zhu, J. (2016). Sustained drug release from electrostatic powder coated tablets with ultrafine ethylcellulose powders. *Advanced Powder Technology*, *27*(5), 2145–2152.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2011). *U.S. Patent No. 7,862,848*. Washington, DC: U.S. Patent and Trademark Office.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2012). *U.S. Patent No. 8,161,904*. Washington, DC: U.S. Patent and Trademark Office.

Chapter 5

5 Hydrolysis of enteric release aspirin capsules and tablets

This chapter compares the performance of enteric release aspirin tablets and capsules coated by the electrostatic dry powder coating technology. Enteric coated aspirin tablets and capsules vary in their release profiles and stability. For release profile of coated aspirin tablets, a delayed release was observed in phosphate buffered saline solution (pH 6.8). This was attributed to the migration of the drug from the tablet core to the coating film and was subsequently mitigated through the application of a sub-coating. However, for capsules, sub-coating was not required because capsule shells can prevent the drug migration by separating aspirin and coating films. For the stability of aspirin, enteric coating films did not protect aspirin from hydrolysis for both tablets and capsules which might be because the moisture in the environment could still penetrated the films.

5.1 Introduction

Acetylsalicylic acid (ASA), also known as Aspirin, was first synthesized by treat sodium salicylate with acetyl chloride in 1853 (Jeffreys D, 2008). Then, in 1897, Bayer company started to research on it, then it was named it as “Aspirin” and sold around the world by 1899 (Mann CC, Plummer ML, 1991). Now, aspirin is still a most widely used medication to treat pain, fever and inflammation. Also, it has good effectivity in prevention of cardiovascular disease (CVD) and cardiovascular complications. High dose of aspirin will decrease the risk of death if taken shortly after a heart attack, and long-term use of low dose aspirin will reduce the risk of heart attack and strokes by preventing blood clots from forming (Baigent et al., 2009; Erkan et al., 2007; Lansberg et al., 2012; Paikin Jeremy S. & Eikelboom John W., 2012; Patrono et al., 2005). Recently, some researchers found that aspirin may also be able to lower the risk of colorectal cancer (Garcia-Albeniz & Chan, 2011; Patrignani & Patrono, 2016).

However, aspirin has some side effects and the most common one is stomach-ache. It has been shown that the risk of gastrointestinal bleeding will increase after taken aspirin (Baigent et al., 2009; Sørensen et al., 2000). Currently, the most common way to prevent the bleeding is using enteric coating film to cover aspirin which would not let aspirin release until it reached intestine. It has been shown that enteric coated aspirin can reduce gastric mucosal damage and the risk of

gastrointestinal bleeding (Hawthorne et al., 1991; Hoftiezer et al., 1980; Lanza et al., 1980; Walker et al., 2007). In addition, because ASA is water sensitive and will be hydrolyzed into salicylic acid (SA) in the presence of water, it is claimed that enteric coating can also provide a barrier to protect ASA from degradation during storage (Mujahid et al., 2013).

Conventionally, enteric coating was performed by organic coating or aqueous coating process. Compared to organic coating process, aqueous coating is safer and more environmentally friendly and was chosen as current coating technology to coat aspirin tablets. However, aspirin is a moisture sensitive drug and will be hydrolyzed by moisture. Thus, the aspirin may be hydrolyzed in the aqueous coating process. Even after enteric coating, aspirin can still be hydrolyzed.

Regarding the hydrolysis of ASA, it includes three possible theories (Wang et al., 2017): First, the moisture in the environment will penetrate the coating films which would cause the degradation of tablet cores (Joshi & Petereit, 2013). Second, the water left at the interface between the film and tablet core during the aqueous coating process causes the hydrolysis (Mwesigwa et al., 2008). Third, aspirin may be incompatible with excipients in the tablet cores (Petereit & Weisbrod, 1999). And the additives in the coating materials, such as macrogol and talc may also cause degradation of aspirin (Carstensen & Attarchi, 1988; Petereit & Weisbrod, 1999). It is also reported that ASA may migrate form tablet core into coated film and change film properties (Okhamafe & York, 1989; Ruotsalainen et al., 2003).

In order to avoid aspirin degradation and migration during coating process and storage, a sub-coating layer is applied to separate tablet core and enteric coating layer. Opadry® was used as seal coating for highly water-soluble, organic acid to protect it from moisture (Crotts et al., 2001). A hot-melt sub-coating followed by enteric aqueous coating can improve the stability of aspirin tablets (Wang et al., 2017). However, the requirement of sub-coating layer makes the coating process more complicated and increases the cost.

Electrostatic dry powder coating technology applies dry powders on substrates and form films directly without using any organic solution or water (Zhu et al., 2011, 2012). Owing to it is a water free coating technology, it is very suitable for coating of moisture sensitive drugs, like aspirin. This technology has been successfully applied on tablets and small pellets to achieve different drug

release profiles like immediate release, enteric release, sustained release and controlled release (Qiao et al., 2010; Qiao et al., 2010; Qiao et al., 2013; Yang et al., 2015, 2016; Yang et al., 2018).

Capsule, as a solid dosage form with its own advantages, is a better option to deliver some active pharmaceutical ingredients because of the following reasons. First, there is no compression step for capsules while tablets need to be compressed. This makes capsules suitable for drugs with low compressibility and avoids complicated formulation development process for tablets. Second, capsule shell is tasteless and odorless which can cover unpleasant taste and odor of drugs, so that patient's compliance can be increased. Capsule can also provide a barrier for light or moisture sensitive drugs to increase their stability. Third, in the coating process, capsule shell can separate the drugs and coating materials. So that degradation of active pharmaceutical ingredients owing to contact with coating materials can be avoided as well as film properties change owing to drug migration.

5.2 Materials and methods

5.2.1 Materials

Size 4 HPMC capsules (Vcaps Plus®) and gelatin capsules (Coni-Snap®) were kindly donated by Capsugel Inc. (US). Eudragit® L100-55 and Colloidal silicon dioxide (AEROSIL® 200 Pharma) were provided by Evonik Degussa Corporation (Germany). Shellac was purchased from Sigma-Aldrich (Canada). HPC was donated by Ashland Inc. (US). Talc was purchased from Mallinickrodt Baker, Inc. (Canada). Polyethylene glycol 400 (PEG 400) was purchased from Acros Organics. (Germany). FD&C Blue lake No.1 was provided by Food Ingredient Solutions LLC (US). Acetylsalicylic acid was purchased from Huayin Jinjincheng Pharmaceutical Co., Ltd. (China). Avicel® Microcrystalline cellulose PH-102 and Ac-Di-Sol® SD-711 croscarmellose sodium was purchased from Food Machinery Corporation (US). Corn starch 1500 was donated by Colorcon, Inc. (US) Lactose was obtained from GlaxoSmithKline, Inc. (Canada).

5.2.2 Particle size reduction and analysis

Eudragit® L100-55 polymer power was grounded by a jet mill into smaller particles. Particle sizes of the coating materials including talc and milled Eudragit® L100-55 were tested by a Particle Size Analyzer (TSI Corporation, Model 3603, Shoreview, MN, USA). Each test was repeated 3 times

to obtain more reliable number. The D50 (the particle diameter at 50% of total weight fraction) of Eudragit® L100-55 and talc were $23.17 \pm 2.68\mu m$, $41.2 \pm 2.42\mu m$ respectively.

5.2.3 Capsules and tablets preparation

Aspirin tablets with different formulations were compressed by rotary tablet press machine (Tianfan Pharmaceutical Machinery Factory, Shanghai, China). Through comparison, formulations of aspirin tablet were optimized. Placebo tablets were also produced for comparison. The formulations and properties of aspirin tablets and placebo tablets were listed in Tablet 5.1 and 5.2 respectively.

Table 5.1 Formulations and properties of aspirin tablets

	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5
Aspirin	80.25%	46%	46%	46%	46%
Corn Starch 1500	15%	48%	17%	0%	10%
Lactose	0%	0%	0%	17%	25%
Microcrystalline cellulose PH102	3.75%	5%	36%	36%	17%
AEROSIL® 200 Pharma	1%	1%	1%	1%	1%
Ac-Di-Sol® SD-711	0%	0%	0%	0%	1%
Total weight (mg)	100	176	176	176	176
Hardness	35	80	80	120	120
Diameter (mm)	7.0	7.0	7.0	7.0	7.0
Thickness (mm)	1.0	4.0	4.0	4.0	4.0

Table 5.2 Formulation of placebo tablets

Ingredient	Formulation
Corn Starch 1500	19%
Lactose	50%
Microcrystalline cellulose PH102	30%
AEROSIL® 200 Pharma	1%
Total weight (mg)	145
Hardness	80
Diameter (mm)	7.0
Thickness (mm)	4.0

For aspirin capsules, two formulations, as showed in Tablet 5.3, were tested to optimize the formulation. CN 100 capsule filling machine (CapsulCN LTD., China) was used to fill size 4 gelatin capsules and HPMC capsules.

Table 5.3 Formulation of aspirin capsules

Ingredients	Formulation 1	Formulation 2
Aspirin	75%	70%
Microcrystalline cellulose PH102	24.5%	29.5%
AEROSIL® 200 Pharma	0.5%	0.5%
Capsule weight (mg)	145	152

5.2.4 Formulation of coating material

Table 5.4 shows the formulation of enteric coating material used to coat both tablets and capsules. For hydroxypropyl cellulose (HPC) sub-coated aspirin tablets, 99% HPC and 1% AEROSIL® 200 Pharma were mixed together and used as sub-coating material. For shellac sub-coated aspirin tablets, 90% shellac and 10% talc were mixed together and used as sub-coating material. After sub-coating, they were both coated by the enteric coating material.

Table 5.4 Formulation of enteric release coating material

Materials	Weight Fraction
Eudragit® L100-55	40%
Talc	59.5%
Blue lake No.1	0.5%

5.2.5 Powder coating process

All aspirin tables, gelatin and HPMC capsules, placebo tablets were coated by equipment showed in Figure 5.1. For HPC sub-coated aspirin tablets, HPC sub-coating materials were first coated, followed by Eudragit® L100-55 enteric coating materials in the same equipment. PEG 400 was used as plasticizer for both HPC and Eudragit® L100-55.

The coating equipment consisted of a heating system, a grounded rotating coating pan, a liquid spraying system and an electrostatic powder spraying gun (Nordson Corporation, USA) is showed in Figure 5.1.

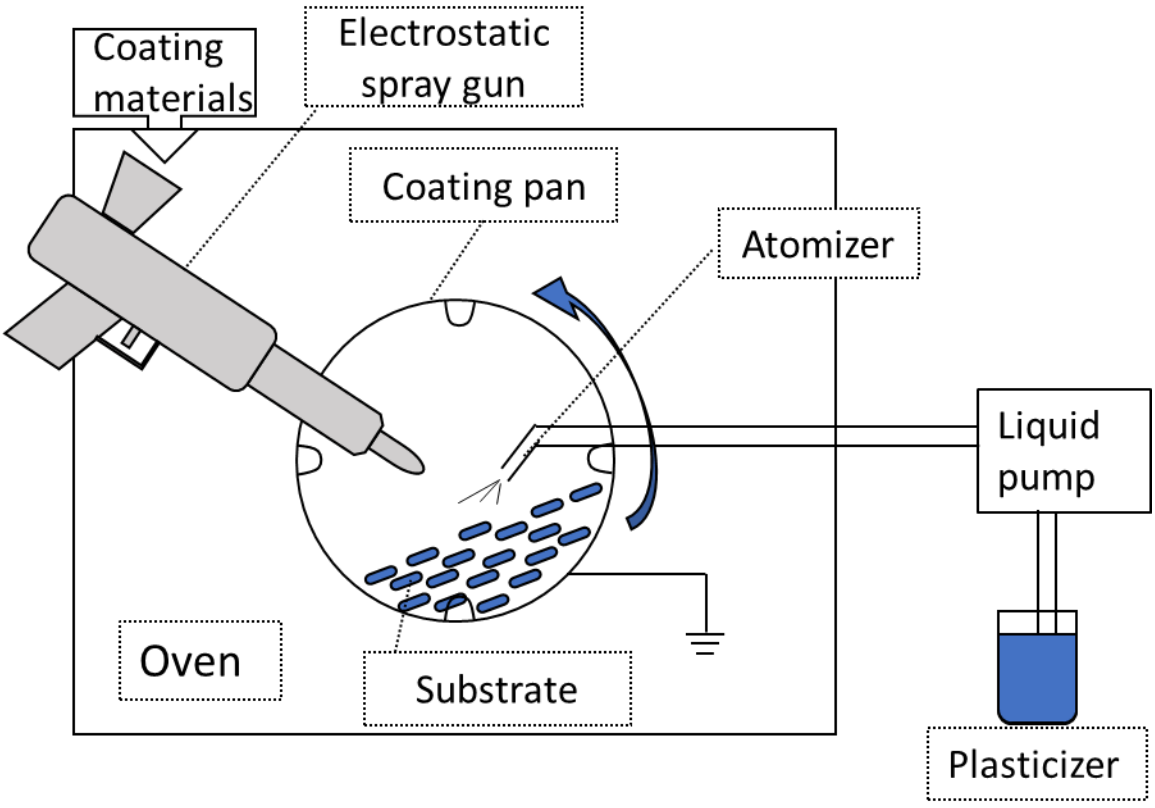


Figure 5.1 Schematic of the electrostatic powder coating system

In the coating process, the oven was heated up first. When it reached the setting temperature which is 50℃, the substrate, tablet or capsule, was put into the rotating coating pan in the oven and preheat for 10 minutes. The rotating speed is 30 rpm Then, PEG 400 as plasticizer was sprayed first followed by spraying coating powders. To achieve desired amount of powder deposition, plasticizer and coating powders were sprayed alternatively for several times. Finally, the coated substrate was kept in the rotating coating pan to let the coating powders coalesce and form the enteric release film. The sub-coating films were coated by this process as well.

In this process, coating powders were sprayed by electrostatic powder spraying gun. After sprayed, powders would be negative charged which will increase the coating efficiency and uniformity (Luo et al., 2008). When powders deposit on the substrate, the charged electrons would be removed through grounded coating pan and let more particles deposit on the substrate.

Plasticizer was sprayed by liquid spraying system including a liquid pump to control the spray rate and a spray nozzle. The plasticizer has three functions: decreasing the glass transition temperature of polymers, increase conductivity of substrate and increase adhesion force to coating powders of the substrate (Luo et al., 2008; Qiao, et al., 2010).

5.2.6 Scanning electron microscopy (SEM)

Since tablets and capsules are not electroconductive, they were first sputter coated with gold for 2 minutes by using EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK) to increase the surface electrical conductivity. Then the surface morphologies of the coated tablets and capsules before and after acceleration test were observed by scanning electron microscope (Hitachi S-2600 N, Ontario, Canada).

5.2.7 HPLC

The concentration of free salicylic acid was determined by high performance liquid chromatography (HPLC) (Waters Corporation, US). Aspirin tablets or aspirin capsules were grounded or opened and dissolved in a mixture of acetonitrile and formic acid (99:1). The mobile phase was prepared by dissolving 2 g of sodium 1-heptanesulfonate in a mixture of 700 mL of water and 300 mL of acetonitrile, then adjusting the solution with glacial acetic acid to a pH of 3.4.

A Symmertry® C18 analytical column (4.6 mm×150 mm, 5 μm) was used to separate aspirin and salicylic acid and a UV detector (Waters 2487 Dual λ Absorbance Detector) was used to test the concentration of aspirin and salicylic acid at 276 nm wavelength.

5.2.8 *In vitro* dissolution test

Coated aspirin tablets and capsules were examined by *in vitro* dissolution test by a dissolution test system (Huanghai Rcz-6c2, Shanghai, China) which complies with the standard of United States Pharmacopeia. Both tablets and capsules were tested in the same system according to USP (<711> Dissolution, Apparatus 1, Basket). Three dosages were tested each time. The apparatus was set with rotating speed of 100rpm and with temperature at 37℃. The tablets or capsules were first merged in 750 ml hydrochloric acid (0.1 mol/L, pH=1) for the first 120 minutes, then 250 ml 0.2 M tribasic sodium phosphate solution was added, and the pH value of the solution changed to 6.8. 10 ml solution was withdrawn and filtered as sample from each tank by a syringe and replaced by fresh solution with certain time interval. Then the samples were tested by 8453 UV–Visible Spectrophotometer (Agilent Technologies, Mississauga, Canada) at a wavelength of 276 nm in hydrochloric acid solution (pH=1) and 269 nm in phosphate buffered saline (pH=6.8).

5.2.9 Stability test

Uncoated and enteric coated aspirin tablets, gelatin capsules, HPMC capsules, placebo tablets and HPC sub-coated enteric release aspirin tablets were placed in high-density polyethylene (HDPE) vials and sealed. Then they were stored at 40℃/ 75% RH for 60 days. At different time during the storage, they were taken out to measure the water adsorption during storage. Then they were put back in the sealed vials and stored at 40℃/ 75% RH again. After 60 days, the surface of tablets and capsules were observed by using SEM and the concentration of salicylic acid in aspirin tablets and capsules were tested by HPLC.

5.3 Results and discussion

5.3.1 Formulation development for aspirin capsules and tablets

The formulation of aspirin tablets was optimized in this project to make it suitable for electrostatic dry powder coating process and be able to achieve desired enteric release characteristics. Five

formulations were tested as Table 5.1 shows. For formulation 1, due to a high concentration of aspirin, the weights of tablets are too small and have insufficient tablet hardness leading to their damage during the coating process. For formulation 2, the uncoated tablets cannot be completely disintegrated in 30 minutes and the inside of the tablet cores are still hard after submerging in the dissolution medium. For formulation 3 and 4, the tablets could be disintegrated rapidly but formed larger pieces resulting in an overall slower release rate. Thus, formulation 5 was chosen to manufacture aspirin tablets because the tablets can be completely disintegrated into small pieces rapidly in the dissolving medium leading to fast release rate. The formulation of aspirin capsules was relatively easier to be optimized since there was no compression step for capsules (formulations shown in Table 5.3). The concentration of aspirin in formulation 1 was too high resulting in the aspirin content of each capsule to exceed 81mg after filling. While capsules filled with formulation 2 have about 81 mg aspirin in each capsule, and they can be dissolved rapidly when submerged in dissolving medium. For this reason, formulation 2 was used to fill the aspirin capsules.

After formulation development, the capsules and tablets were coated and around 8.5 mg/cm^2 weight gain was used to ensure the leakage of enteric release tablets and capsules in acidic solution can be prevented. Results of weight gains for tablets and capsules are showed in Tablet 5.5.

Table 5.5 Weight gains of coated tablets and capsules

	Coating material	Coating level (%)	Weight gain(mg/cm^2)
Dry powder coated tablets	Eudragit® L	7.1	8.74
HPC sub-coated tablets	HPC	3.5	4.31
	Eudragit® L	7.3	8.98
Shellac sub-coated tablets	Shellac	3.5	4.31
	Eudragit® L	7.5	9.23
Gelatin capsules	Eudragit® L	13.1	8.10
HPMC capsules	Eudragit® L	13.3	8.22

*Coating level = $\frac{\text{substrate weight after coating}}{\text{substrate weight before coating}} \times 100\%$;

Weight gain = $\frac{\text{weight increased of substrate after coating}}{\text{total surface area of substrate}}$.

5.3.2 *In vitro* dissolution test

Enteric release aspirin tablets and capsules after storage were tested using *in vitro* dissolution test and the results are shown in Figure 5.2. Basket was used for dissolution test of both capsules and tablets in order to provide same dissolving conditions and investigate the difference of tablets and capsules. For the first 120 minutes in acidic solution, no coated tablets and capsules released more than 10% aspirin which met the requirement of U.S. Pharmacopeia ("Aspirin", 2017). After changing the pH value to 6.8, the tablets and capsules released more than 80 % aspirin at the 180-minute time point. However, they have different release profiles before being completely dissolved.

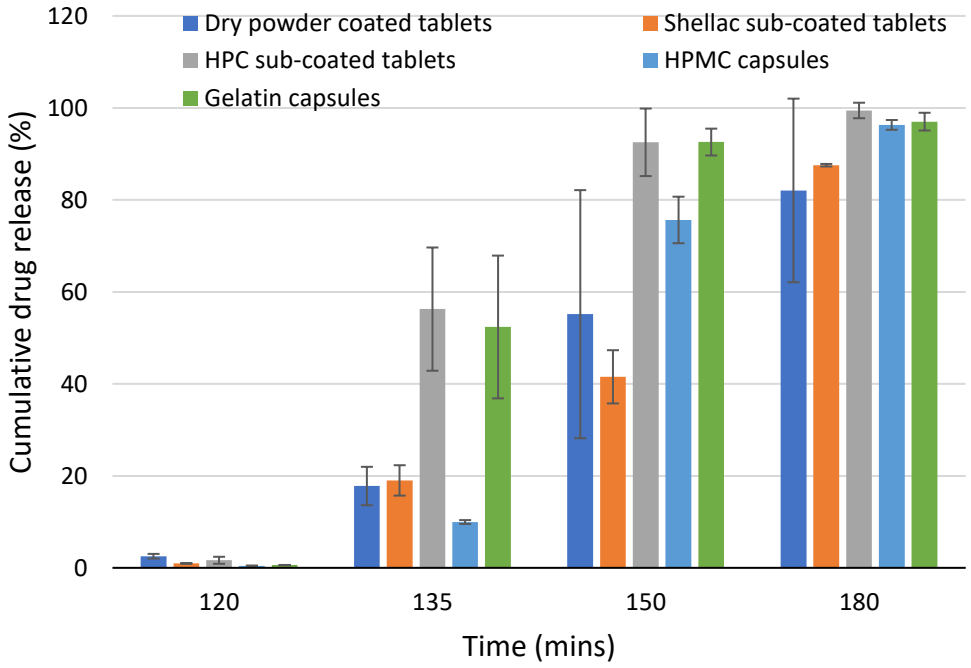


Figure 5.2 Cumulative drug release of enteric coated aspirin tablets and capsules

For dry powder coated tablets without any sub-coating, a delayed release was observed. Only 20% aspirin was released after 135 minutes and about 55% released after 150 minutes. In addition, after the dissolution test, undissolved thin films were found in the basket (as Figure 5.3 shows) which may be the reason for the delayed release. This might result from migration of aspirin from tablet cores to the coating films which changed the properties of the films making them insoluble in the buffer solution. It is reported that salicylic acid could migrate form tablet core into coating films

(Okhamafe & York, 1986; Ruotsalainen et al., 2003), and the migration of the drug can change film properties (Okhamafe & York, 1989). For this reason, hydroxypropyl cellulose (HPC) and shellac were used as sub-coating materials to separate the aspirin tablet cores and coating films.

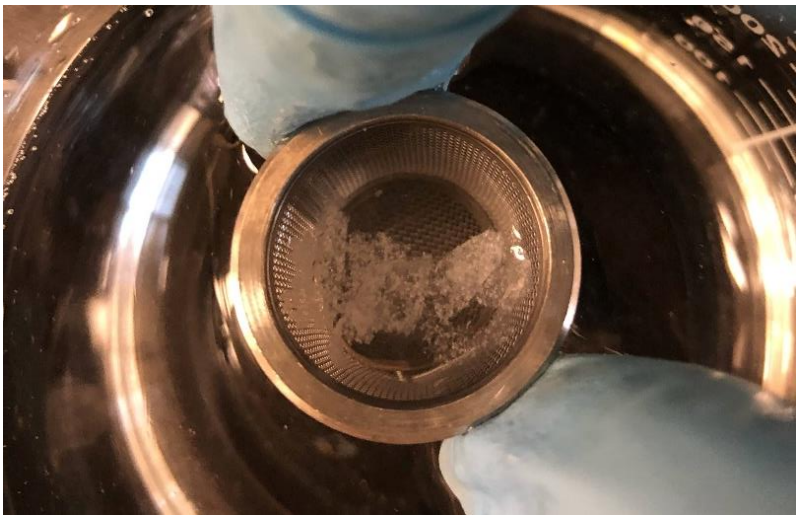


Figure 5.3 The thin film observed after dissolution test of dry powder coated tablets without sub-coating

After the application of the sub-coating, the HPC sub-coated enteric release aspirin tablets were dissolved without the insoluble thin films or the delay previously observed in direct coated aspirin tablets, with more than 80% aspirin being released in 150 minutes (Figure 5.2). The shellac sub-coated enteric release aspirin tablets had no insoluble thin films as well, however, had a delayed release profile owing to the properties of shellac. Shellac will be readily dissolved at pH 7 (Hussan, Santanu, & Bhandari, 2012), which explained why the coated tablets were not dissolved rapidly after merged into pH=6.8 buffered solution.

For enteric coated gelatin capsules, since capsule shells separated aspirin and the coating materials and avoided the migration of the drug from core to coating films, aspirin was released without delay. There was no insoluble film observed in the solution after dissolution test. However, a slight delay was found for enteric coated HPMC capsules which released only 10% aspirin in 135 minutes The delay was observed because HPMC capsules shells dissolved slower than gelatin capsules (Al-Tabakha, 2010), leading to a delayed release for enteric coated HPMC. Once the

capsule shells were dissolved, the drug would be released rapidly where about 80% aspirin was shown to be released from enteric coated HPMC capsules after 150 minutes (Figure 5.2).

5.3.3 Water adsorption

The effect of water adsorption of coated aspirin tablets and capsules was investigated. Figure 5.4 shows the weight change at different time points under 40℃/75% RH for uncoated aspirin tablets as well as aspirin gelatin and HPMC capsules. Results show that for uncoated aspirin tablets, weight increased in the first 30 days and decreased afterwards. During storage, aspirin tablets absorbed water which led to weight increasing at the beginning. Then, aspirin was hydrolyzed and form salicylic acid. Due to the sublimation tendency of salicylic acid during storage at elevated humidity (Gore et al., 1968; Okhamafe & York, 1986), the weight of tablets would lose due to sublimation. After storing the tablets under 40℃/75% RH for some time, the water absorption become saturated, but sublimation of salicylic acid continued which resulted in the weight decreasing for aspirin tablets.

For both gelatin and HPMC capsules, weight increased as time passed indicating that they both absorbed moisture and were not subjected to the sublimation of aspirin due to the presence of the capsule shells. By comparing gelatin capsules and HPMC capsules, it was found that HPMC capsules absorbed more moisture than gelatin capsules. It can be explained by two reasons: First, the water permeability of HPMC capsule is greater than gelatin capsules (Barham et al., 2015) at high relative humidity, which means more moisture can penetrate the HPMC capsule shell and be absorbed by enclosed drug. Second, because the gap of the capsule at the joint of the cap and the body for size 4 Vcaps Plus® HPMC capsules is larger than size 4 Coni-Snap® gelatin capsules ($77.06 \pm 4.663\ \mu m$ vs. $28.73 \pm 1.406\ \mu m$), gap of HPMC capsules provided a wider path for moisture to reach the contained drugs.

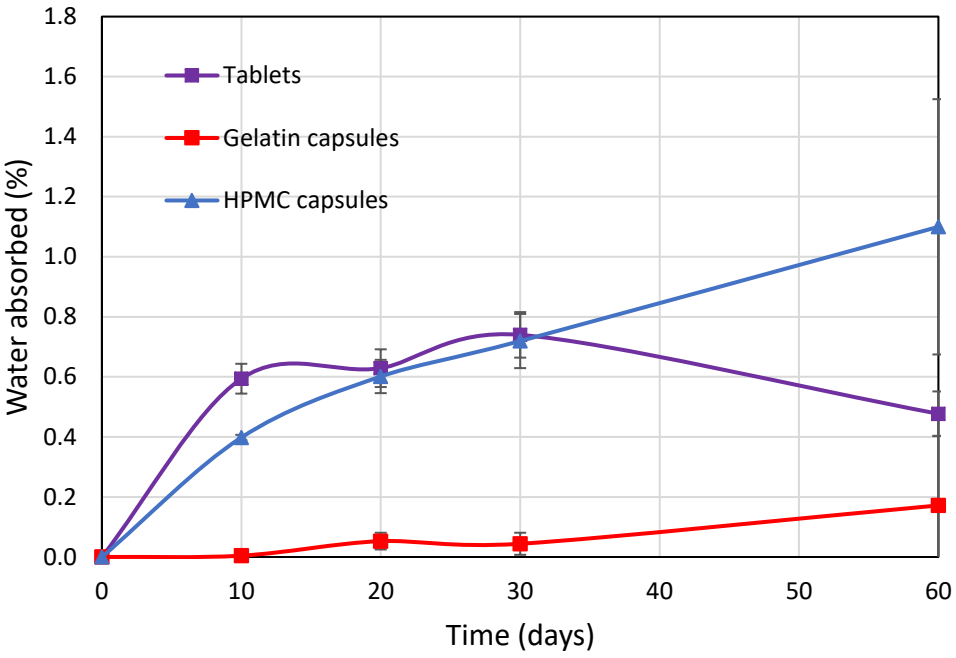


Figure 5.4 Water absorbed of uncoated aspirin tablets and capsules under 40℃/75% RH acceleration test

Figure 5.5 shows the water absorbed of dry powder coated tablets and capsules at different time under a 40℃/75% RH acceleration test.

For dry powder coated tablets with and without HPC sub-coating, weights increased in the first 10 days and decreased afterwards. While for dry powder coated placebo tablets, the weight kept increasing. By comparation, this phenomenon can be explained as follows: First, moisture penetrated into the film and absorbed by tablets core at the beginning, leading to weight increasing. Then, aspirin start to hydrolysis due to the presence of water and generate salicylic acid, the salicylic acid would be sublimated and released from the films leading to weight loss.

For gelatin capsules, owing to moisture loss during the coating process, the water of the capsule shells become unsaturated when they were put into a higher relative humidity environment. So, gelatin capsule shells would tend to absorb moisture from surrounding, and powders filled in the capsules also absorbed moisture both of which made water absorption of coated gelatin capsules

become very high. And owing to the existence of capsule shells, sublimation was prevented avoiding the weight loss.

But for HPMC capsules, since there was almost no moisture loss during the coating process, the water adsorption mainly resulted from powders filled in the capsules, thus, water absorption was not as fast as gelatin capsules but still increased in acceleration test. Also, sublimation was prevented due to HPMC capsule shells.

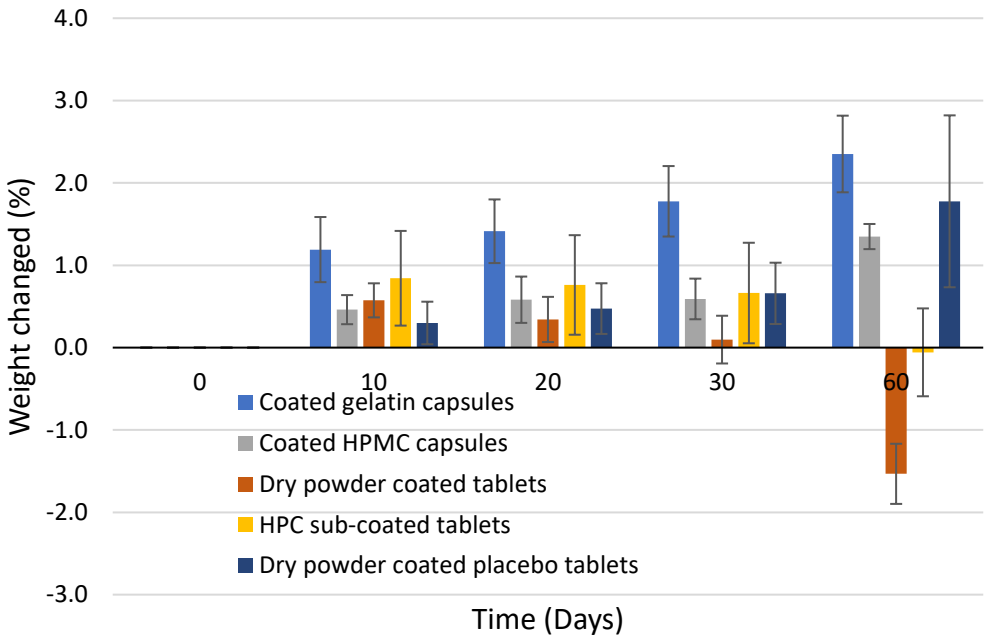


Figure 5.5 Water absorbed of aqueous coated aspirin tablets and dry powder coated aspirin tablets and capsules under 40℃/75% RH acceleration test

5.3.4 Scanning electron microscopy (SEM)

Dry powder coated aspirin tablets and capsules went through acceleration test at 40℃/75% RH for 60 days. Then the film surfaces were observed by scanning electron microscope and compared with the surfaces of the tablets or capsules before acceleration test. SEM figures were showed in Figure 5.6 and Figure 5.7.

For dry powder coated aspirin tablets, some crystals were formed after acceleration test as Figure 5.6 (a2) shows because of the migration of salicylic acid from tablet core to the coating film and it crystallized on the surface of the coating film. But after applying an HPC sub-coating layer, the layer prevented the migration of salicylic acid resulting in few crystals formed on the tablet surface as shown in Figure 5.6 (b2).

For both gelatin capsules and HPMC capsules, although water absorption was high for both gelatin and HPMC capsules, there was no crystal observed on their surfaces as Figure 5.7 (a2) and (b2) show. The migration of the drug was prevented, and no crystal was formed on the film surface due to the existence of capsule shells who separated the aspirin and the coating film.

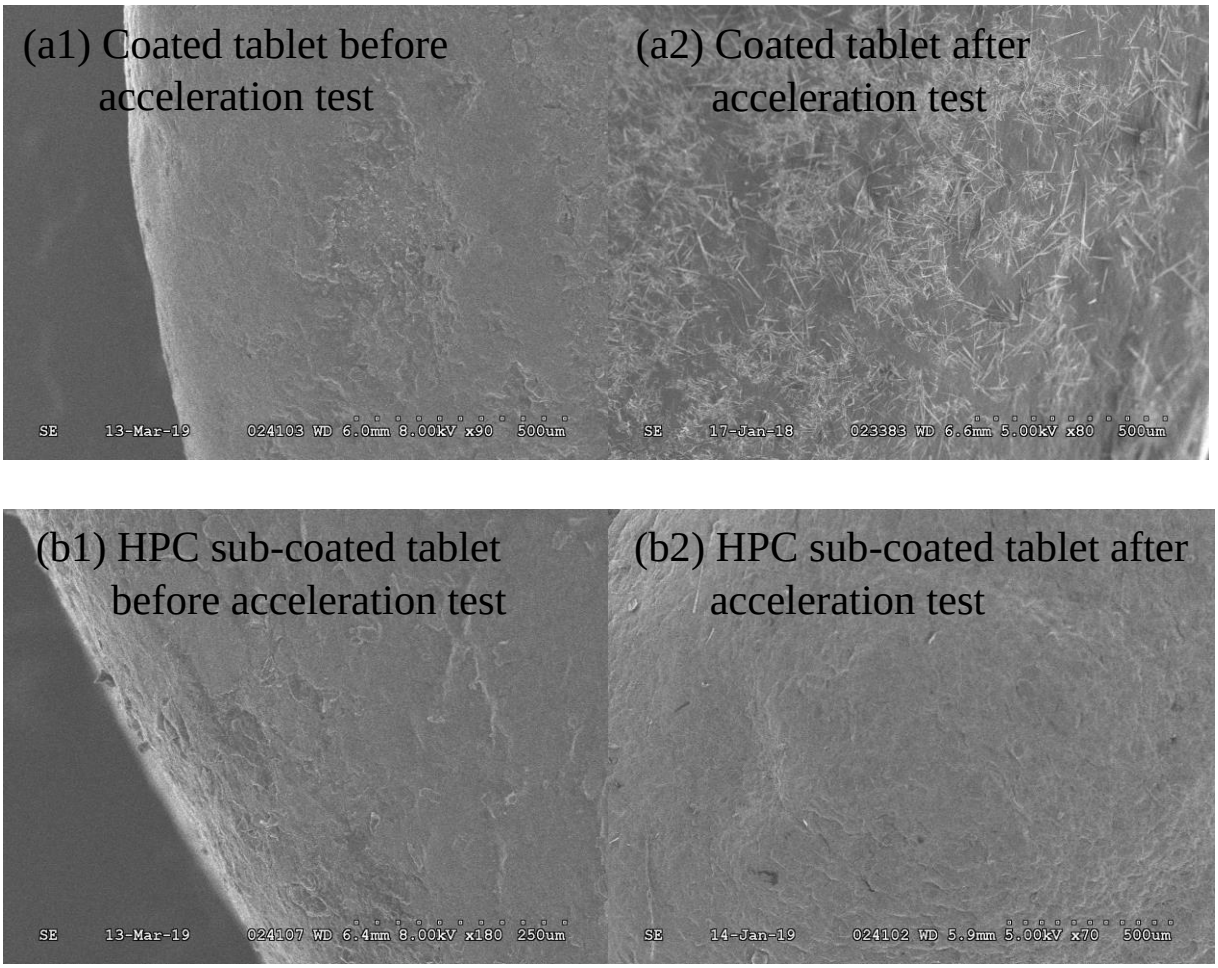


Figure 5.6 SEM of dry powder coated aspirin tablets before and after acceleration test

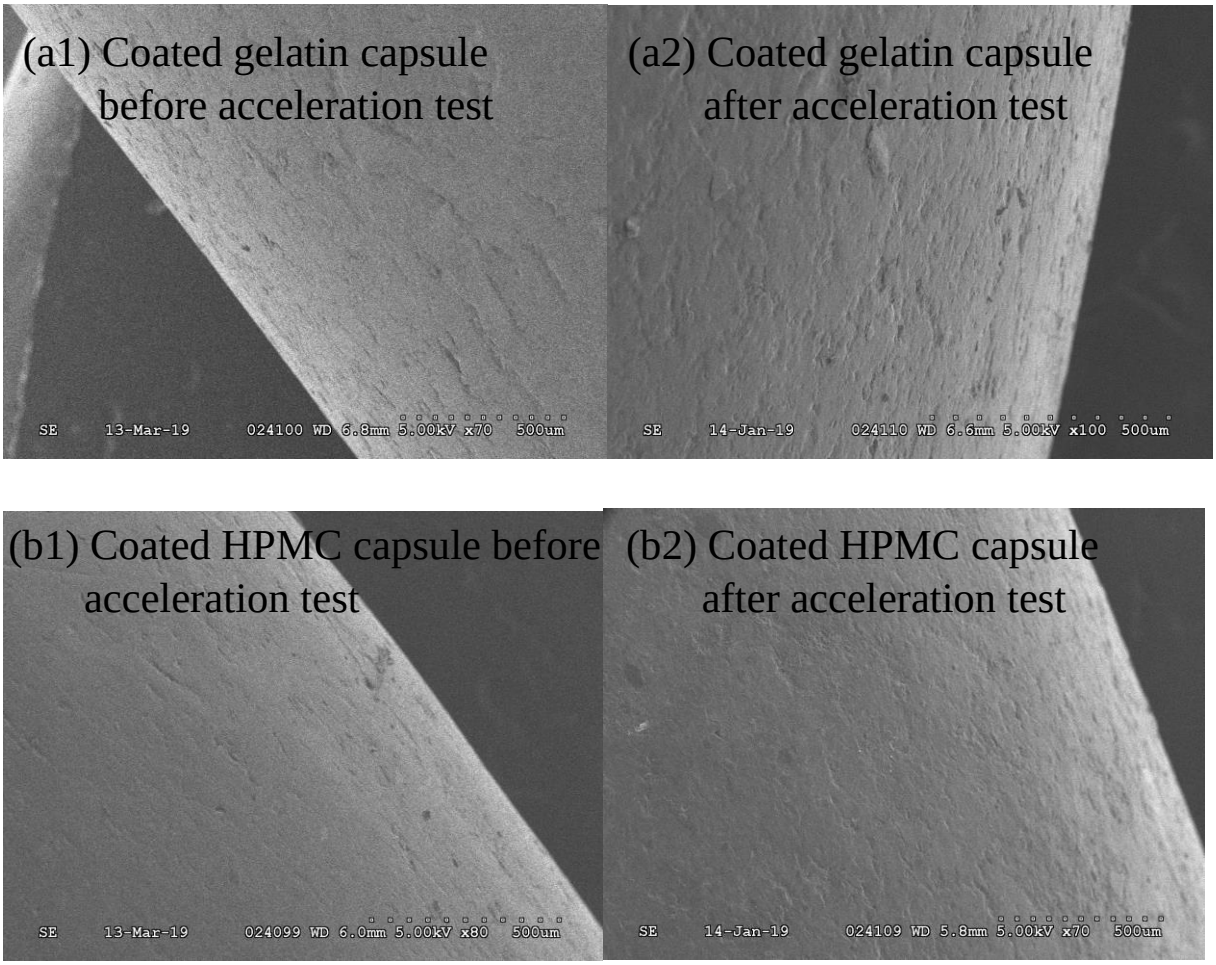


Figure 5.7 SEM of dry powder coated aspirin capsules before and after acceleration test

5.3.5 Free salicylic acid concentration

Concentration of free salicylic acid is important to evaluate the stability of aspirin oral solid dosage forms. Aspirin is a moisture sensitive active pharmaceutical ingredient and will degrade to salicylic acid and acetic acid if contact with water. Since salicylic acid may cause irritation to stomach, the concentration of salicylic acid in solid dosage forms need to be controlled. The free salicylic acid concentration of uncoated and coated aspirin tablets and capsules are tested by using HPLC and the results are showed in Table 5.6.

Table 5.6 Free salicylic acid (SA) of different dosage forms before and after acceleration test

	Concentration of SA before acceleration test (%)	Concentration of SA after acceleration test (%)
Uncoated tablets	0.101±0.004	1.206±0.193
Uncoated gelatin capsules	0.099±0.004	2.693±1.437
Uncoated HPMC capsules	0.100±0.004	3.356±1.112
Dry powder coated tablets	0.164±0.012	3.217±0.666
Dry powder coated gelatin capsules	0.146±0.015	2.273±0.255
Dry powder coated HPMC capsules	0.174±0.033	4.207±0.269
Dry powder coated HPC sub-coated tablets	0.159±0.020	5.745±0.842

After the coating process, concentration of free salicylic acid in aspirin tablets and capsules were all increased slightly owing to aspirin was exposed to a higher temperature for some time. And the concentrations of salicylic acid were similar of coated aspirin tablets and capsules which means the dosage form has no influence for stability of aspirin in the dry powder coating process.

After 60 days acceleration test at 40℃/75% RH, for uncoated capsules, concentrations of free SA for both uncoated aspirin gelatin capsules and HPMC capsules were higher than uncoated aspirin tablets which is owing to two reasons. First, because the drugs in capsules were not compressed, the density of drug was lower than tablets, it will be relatively easier for moisture to transport once absorbed by the drug which caused more degradation. Second, water reached the enclosed drug by penetrating the capsule shells and by going through the gaps at the joint of the capsule cap and body. Since the gaps of the capsules were not sealed, more moisture can reach the drugs enclosed in the capsules through the gaps. Thus, more degradation will happen for uncoated gelatin and HPMC capsules than tablets.

And by comparing uncoated gelatin capsules and HPMC capsules, more salicylic acid was generated after acceleration test for HPMC capsules owing to more moisture was absorbed by HPMC capsules than gelatin capsules as shown in Figure 5.4. This represented that HPMC

capsules did not provide better protection for moisture sensitive drugs than gelatin capsule which was also reported by Barham et al. (2015) and Al-Tabakha (2015).

For enteric coated aspirin tablets, it is found that enteric coated aspirin tablets did not protect aspirin from hydrolysis after 60 days acceleration test at 40℃/75% RH but accelerated the degradation. This phenomenon was also reported by Wang et al. (2017). In addition, although an HPC sub-coating could prevent migration of salicylic acid to the coating film, it did not protect aspirin from hydrolysis in the acceleration test.

It is reported that enteric coated aspirin would still be hydrolyzed is because of the water left at the interface between the film and tablet core during the aqueous coating process (Mwesigwa et al., 2008). In this study, no water was used in the coating process, but the hydrolysis still happened during storage which illustrated that degradation of aspirin may not because of the residual water in the aqueous coating process.

For coated HPMC capsule, enteric coating films also accelerated degradation of aspirin after acceleration test. HPMC capsule separated the coating films and aspirin, however, the aspirin degradation was still accelerated. This phenomenon illustrated that another theory which is that aspirin may be incompatible with excipient in the coating film (Petereit & Weisbrod, 1999) was also not the only reason for aspirin degradation.

For coated gelatin capsule, different from HPMC capsule, it is the only solid dosage forms with the enteric coating films but did not accelerate the degradation of aspirin. However, the water absorbed of enteric coated gelatin capsules during the acceleration test is more than any other dosage forms. The reasons are as follows: Gelatin capsule has a relatively higher water content (13% to 16%) (Chang et al., 1998), while HPMC capsules has lower water content in capsule shells (2% to 6%) (Ku et al., 2010). During the dry powder coating process, since the system is operated under 50℃, under which temperature, gelatin capsules would lose relatively more moisture in the capsule shells while HPMC capsules would not, as previous study indicated. Thus, the water content in the gelatin capsule shells was not saturated and gelatin capsule shells are prone to absorb more water than HPMC capsule shells. Then after stored in a high relative humidity environment during the acceleration test, gelatin capsule would absorb moisture penetrated the coating film and

prevent moisture from reaching enclosed drugs. This explained why water absorption of gelatin capsules is high, but degradation of enclosed aspirin is low.

5.3.6 Discussion

In this study, there was no water used in dry powder coating process, the hydrolysis of aspirin was still accelerated after applying enteric coating films. Thus, it is the residual water between tablet cores and coating films during aqueous coating process that caused hydrolysis of enteric coated aspirin tablets (Mwesigwa et al., 2008) may not be the main reason of aspirin hydrolysis.

It is also reported that the hydrolysis of aspirin was resulting from incompatibility of aspirin and excipients of the coating film (Petereit & Weisbrod, 1999; Wang et al., 2017). In this study, gelatin and HPMC capsules were used as a barrier to separate aspirin and coating films but hydrolysis of aspirin was still accelerated for enteric coated aspirin capsules. This represented that incompatibility of aspirin and excipients of the coating film was not the only reason that caused instability of enteric coated aspirin.

Thus, the hydrolysis for enteric coated aspirin may because of the moisture in the environment that penetrated the coating films of tablets. And the enteric coated films would accelerate the hydrolysis may because the enteric coating films are porous which would uptake more water from surroundings and increase the water concentration around the aspirin solid dosage forms. For aspirin tablets, because water concentration was increased around the tablet cores owing to the water concentrating effect of porous coating films, more water in the coating films would contact tablet cores and cause hydrolysis. For aspirin capsules, it is reported that gelatin and HPMC capsule shells were still water permeable (Barham et al., 2015) and the gap at the joint of the capsule cap and the body also provided a path for moisture to reach enclosed drugs. Therefore, owing to porous enteric coating film absorbed more moisture which increase the moisture concentration around aspirin capsules, the aspirin hydrolysis was accelerated.

5.4 Conclusion

This study compared the different performances of dry powder coated enteric release aspirin tablets (with and without sub-coating), gelatin capsules, and HPMC capsules using a dissolution test and acceleration test. The tests concluded that enteric release capsule could be an alternative

solid dosage form to deliver aspirin. It was found that the drug migration occurred in enteric coated aspirin tablets applied by the dry powder coating process and would change the dissolution property of the films. Application of HPC sub-coating was able to prevent the migration but it made the process more complicated. Different from tablets, gelatin and HPMC capsule shells effectively separated the aspirin and the films, even without a sub-coating, which prevented the migration of the drug, so that the film properties would not be changed and influence the drug release.

Acceleration test showed that neither coated tablets nor coated capsules protected aspirin from hydrolysis. However, by comparing the free salicylic acid concentration before and after the acceleration test, enteric coating film resulted in accelerated hydrolysis of aspirin for both tablets and HPMC capsules which might because the enteric coating film would absorb more water. This led to the moisture concentration around the aspirin tablets and capsules increased resulting in higher levels of aspirin hydrolysis. For gelatin capsules, the enteric coating film did not accelerate the hydrolysis of enclosed aspirin after a 60-day acceleration test at 40℃/75% RH. This is because the moisture that penetrated the film was absorbed by the gelatin capsule shells that were dehydrated during the coating process. Thus, it can be concluded that the moisture of the environment which would penetrate the coating film may be an important reason for the hydrolysis of aspirin and the enteric coating film will concentrate the moisture leading to the acceleration of aspirin hydrolysis.

Bibliography

Al-Tabakha, M. M. (2010). HPMC Capsules: Current Status and Future Prospects. *Journal of Pharmacy & Pharmaceutical Sciences*, *13*(3), 428–442.

"Aspirin" (2017). *The United States Pharmacopeia 2017: USP 40; The National Formulary: NF 35*, United States Pharmacopeia Convention, pp. 2872–2876.

Baigent, C., Blackwell, L., Collins, R., Emberson, J., Godwin, J., Peto, R., Buring, J., et al. (2009). Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)*, *373*(9678), 1849–1860.

Barham, A. S., Tewes, F., & Healy, A. M. (2015). Moisture diffusion and permeability characteristics of hydroxypropylmethylcellulose and hard gelatin capsules. *International Journal of Pharmaceutics*, *478*(2), 796–803.

Carstensen, J. T., & Attarchi, F. (1988). Decomposition of Aspirin in the Solid State in the Presence of Limited Amounts of Moisture II: Kinetics and Salting-in of Aspirin in Aqueous Acetic Acid Solutions. *Journal of Pharmaceutical Sciences*, *77*(4), 314–317.

Chang, R.-K., Raghavan, K. S., & Hussain, M. A. (1998). A study on gelatin capsule brittleness: Moisture tranfer between the capsule shell and its content. *Journal of Pharmaceutical Sciences*, *87*(5), 556–558.

Crotts, G., Sheth, A., Twist, J., & Ghebre-Sellassie, I. (2001). Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid. *European Journal of Pharmaceutics and Biopharmaceutics*, *51*(1), 71–76.

Erkan, D., Harrison, M. J., Levy, R., Peterson, M., Petri, M., Sammaritano, L., Unalp-Arida, A., et al. (2007). Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: A randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody–positive individuals. *Arthritis & Rheumatism*, *56*(7), 2382–2391.

Garcia-Albeniz, X., & Chan, A. T. (2011). Aspirin for the prevention of colorectal cancer. *Best Practice & Research Clinical Gastroenterology*, Chemoprevention in Gastroenterology, *25*(4), 461–472.

Gore, A. Y., Naik, K. B., Kildsig, D. O., Peck, G. E., Smolen, V. F., & Banker, G. S. (1968). Significance of salicylic acid sublimation in stability testing of aspirin-containing solids. *Journal of Pharmaceutical Sciences*, *57*(11), 1850–1854.

Hawthorne, A., Mahida, Y., Cole, A., & Hawkey, C. (1991). Aspirin-induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. *British Journal of Clinical Pharmacology*, *32*(1), 77–83.

Hoftiezer, J., Burks, M., Silvoso, G., & Ivey, K. (1980). Comparation of the effects of regular and enteric-coated aspirin on gastroduodenal mucosa of man. *The Lancet*, Originally published as

Volume 2, Issue 8195, *316*(8195), 609–612.

Hussan, S. D., Santanu, R., & Bhandari, V. (2012). A review on recent advances of enteric coating.

Joshi, S., & Petereit, H.-U. (2013). Film coatings for taste masking and moisture protection. *International Journal of Pharmaceutics*, Progress in Film Coating, *457*(2), 395–406.

Ku, M. S., Li, W., Dulin, W., Donahue, F., Cade, D., Benameur, H., & Hutchison, K. (2010). Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical and processability quality attributes of VCaps Plus®, Quali-V® and gelatin capsules. *International journal of pharmaceutics*, *386*(1-2), 30-41.

Lansberg, M. G., O'Donnell, M. J., Khatri, P., Lang, E. S., Nguyen-Huynh, M. N., Schwartz, N. E., Sonnenberg, F. A., et al. (2012). Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, *141*(2, Supplement), e601S-e636S.

Lanza, F. L., Royer Jr, G. L., & Nelson, R. S. (1980). Endoscopic evaluation of the effects of aspirin, buffered aspirin, and enteric-coated aspirin on gastric and duodenal mucosa. *New England Journal of Medicine*, *303*(3), 136–138.

Luo, Y., Zhu, J., Ma, Y., & Zhang, H. (2008). Dry coating, a novel coating technology for solid pharmaceutical dosage forms. *International Journal of Pharmaceutics*, *358*(1), 16–22.

Mujahid, A., Farooq, M. U., Hameed, A., Hussain, T., Shah, A. T., Ahmad, S., & SHEHZAD, K. (2013). Quantitative degradation monitoring in core and enteric coated aspirin tablets. *Int J Curr Pharm Res*, *5*(4), 68–70.

Mwesigwa, E., Basit, A. W., & Buckton, G. (2008). Moisture Sorption and Permeability Characteristics of Polymer Films: Implications for Their Use as Barrier Coatings for Solid Dosage Forms Containing Hydrolyzable Drug Substances. *Journal of Pharmaceutical Sciences*, *97*(10), 4433–4445.

Okhamafe, A. O., & York, P. (1986). Mechanical properties of some pigmented and unpigmented

aqueous-based film coating formulations applied to aspirin tablets*. *Journal of Pharmacy and Pharmacology*, *38*(6), 414–419.

Okhamafe, A. O., & York, P. (1989). Thermal Characterization of Drug/Polymer and Excipient/Polymer Interactions in Some Film Coating Formulation*. *Journal of Pharmacy and Pharmacology*, *41*(1), 1–6.

Paikin Jeremy S., & Eikelboom John W. (2012). Aspirin. *Circulation*, *125*(10), e439–e442.

Patrignani, P., & Patrono, C. (2016). Aspirin and Cancer. *Journal of the American College of Cardiology*, *68*(9), 967–976.

Patrono, C., García Rodríguez, L. A., Landolfi, R., & Baigent, C. (2005). Low-Dose Aspirin for the Prevention of Atherothrombosis. *New England Journal of Medicine*, *353*(22), 2373–2383.

Petereit, H.-U., & Weisbrod, W. (1999). Formulation and process considerations affecting the stability of solid dosage forms formulated with methacrylate copolymers. *European Journal of Pharmaceutics and Biopharmaceutics*, *47*(1), 15–25.

Qiao, M., Luo, Y., Zhang, L., Ma, Y., Stephenson, T. S., & Zhu, J. (2010). Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process. *International Journal of Pharmaceutics*, *399*(1), 37–43.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Chow, K. (2010). A novel electrostatic dry powder coating process for pharmaceutical dosage forms: Immediate release coatings for tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *76*(2), 304–310.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Xiao, W. (2013). A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. *European Journal of Pharmaceutics and Biopharmaceutics*, *83*(2), 293–300.

Ruotsalainen, M., Heinämäki, J., Guo, H., Laitinen, N., & Yliruusi, J. (2003). A novel technique for imaging film coating defects in the film-core interface and surface of coated tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *56*(3), 381–388.

Sørensen, H. T., Mellemkjær, L., Blot, W. J., Nielsen, G. L., Steffensen, F. H., McLaughlin, J. K., & Olsen, J. H. (2000). Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *The American journal of gastroenterology*, *95*(9), 2218–2224.

Walker, J., Robinson, J., Stewart, J., & Jacob, S. (2007). Does enteric-coated aspirin result in a lower incidence of gastrointestinal complications compared to normal aspirin? *Interactive CardioVascular and Thoracic Surgery*, *6*(4), 519–522.

Wang, X., Wang, P., Huang, C., Lin, X., Gong, H., He, H., & Cai, C. (2017). Hot-melt sub- and outercoating combined with enteric aqueous coating to improve the stability of aspirin tablets. *Asian Journal of Pharmaceutical Sciences*, *12*(3), 266–278.

Yang, Q., Ma, Y., Shi, K., Yang, G., & Zhu, J. (2018). Electrostatic coated controlled porosity osmotic pump with ultrafine powders. *Powder Technology*, *333*, 71–77.

Yang, Q., Ma, Y., & Zhu, J. (2015). Applying a novel electrostatic dry powder coating technology to pellets. *European Journal of Pharmaceutics and Biopharmaceutics*, *97*, 118–124.

Yang, Q., Ma, Y., & Zhu, J. (2016). Sustained drug release from electrostatic powder coated tablets with ultrafine ethylcellulose powders. *Advanced Powder Technology*, *27*(5), 2145–2152.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2011). *U.S. Patent No. 7,862,848*. Washington, DC: U.S. Patent and Trademark Office.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2012). *U.S. Patent No. 8,161,904*. Washington, DC: U.S. Patent and Trademark Office.

Chapter 6

6 Large-scale dry powder coating process

This chapter discusses scale up and optimization of the electrostatic dry powder coating process. Aspirin tablets were used as a substrate because the cooperated company cannot provide the equipment for capsule manufacture. The coating process of tablets can be migrated to a capsules coating process because the same coating apparatus was going to be used. In this chapter, the coating process was scaled up successfully and achieved higher coating efficiency after optimization. Compared to the aqueous coating process, the dry powder coating process had less processing time, less energy consumption and a competitive coating efficiency. Also, the hydrolysis of aspirin tablets after the dry powder coating process was less than the aqueous coating process. However, the films formed by dry powder coating process were more porous than aqueous coating process and did not provide better protection for aspirin during the stability test.

6.1 Introduction

In pharmacy, a coating film is a thin coat that applied on a solid dosage form. It is frequently applied for the following reasons: First, the films can protect drugs from moisture and/or light, enhance the stability of the drugs and give drugs a long shelf time. Second, for drugs with unpleasant odor and/or taste which make them hard to be taken especially for elder people and younger children, coating films can be used to achieve odor and/or taste masking and improve patient compliance. Third, which is also the most important, the films can produce film -controlled drug delivery systems which is becoming more popular in the last few decades. These films can modify the drug release profiles, achieving extended drug release or delayed drug release.

Conventionally, the film coating process is based on either organic solvent or water. Functional polymers and other excipients are dissolved or dispersed in organic solvent or water and sprayed on the surface of substrates. Then the organic solvent or water is evaporated, and the functional polymers will form the film. However, organic solvent coating suffers toxicity, pollution and flammability issues (Aulton et al., 1995), while aqueous coating is energy and time consuming, (Bose, 2007) and cannot be applied on moisture sensitive drugs (Amighi & Moes, 1996; Plaizier-Vercammen & De Neve, 1993).

Acetylsalicylic acid, also known as aspirin is a wildly used medicament to treat fever, pain and inflammation. It can also be used to treat Cardiovascular disease (CVD), like lower the risk of heart attack and stroke. It is recommended for certain people to take low dose aspirin for a long term to prevent second heart attack or stroke (Baigent et al., 2009; Erkan et al., 2007; Lansberg et al., 2012; Paikin Jeremy S. & Eikelboom John W., 2012; Patrono et al., 2005). In addition, aspirin was discovered that it is able to reduce the risk of colorectal cancer recently (Garcia-Albeniz & Chan, 2011; Patrignani & Patrono, 2016).

However, one of the most common side effects of aspirin is gastric irritation which may cause nausea or even stomach bleeding (Baigent et al., 2009; Sørensen et al., 2000). It is reported that enteric coated aspirin can protect the stomach and reduce the side effects (Hawthorne et al., 1991; Hoftiezer et al., 1980; Lanza et al., 1980; Walker et al., 2007). Thus, applying enteric coating film to aspirin is the most wildly used method to decrease its side effects.

Nowadays, aqueous coating process is the most wildly used coating method to produce enteric release aspirin (Patell, 1988). However, since aspirin is moisture sensitive and can be hydrolyzed into salicylic acid if contact water, the high relative humidity environment that tablets exposed during aqueous coating process may accelerate the hydrolysis of aspirin (Mwesigwa et al., 2008). Thus, an alternative coating process is required to coat aspirin tablets.

Zhu's group developed an electrostatic dry powder coating technology which eliminated the use of organic solvent and water (Zhu et al., 2011, 2012). Thus, the degradation of moisture sensitive drugs can be minimized during the coating process. Energy consumption and processing time can also be saved because evaporation process of organic solvent or water is avoided. This technology has been successfully applied on tablets and small pellets to achieve different drug release profiles in lab scale. Qiao et al. (2010) coated tablets to achieve immediate release and investigated the influence of plasticizer, curing temperature, curing time and charging voltage of electrostatic spray gun on coating efficiency and film properties. Then, they optimized the system and applied this technology on sustained release tablets coating (Qiao, Luo, et al., 2010; Yang et al., 2016) and enteric release tablets coating (Qiao et al., 2013). Yang et al. (2015) applied dry powder coating technology on pellets coating to achieve enteric release, the influence of plasticizer, curing temperature, curing time were also investigated. Osmotic pump tablets were also coated and

achieved controlled release (Yang et al., 2018). However, the application of this dry powder coating technology was only in lab scale for now.

Application on the real industry is the target of every new technology after it has been investigated and optimized in the laboratory. The migration of a process from the lab-scale to the pilot plant-scale or commercial scale is called scale up process which is necessary for commercialization of a new technology.

This project is to scale up the electrostatic dry powder coating technology and applied it on aspirin enteric coating process. The aqueous coating process was also investigated as comparison.

6.2 Materials and methods

6.2.1 Materials

Eudragit® L100-55 and Colloidal silicon dioxide (AEROSIL® 200 Pharma) were provided by Evonik Degussa Corporation (Germany). Talc was purchased from Guangxi Longsheng Huamei Talc Development Co., Ltd. (China). Polyethylene glycol 400 (PEG 400) was purchased from Merck Group (Germany). Blue lake No.1 was purchased from Sensient Technologies Corporation (China). Acetylsalicylic acid was purchased from Shandong Xinhua Pharmaceutical Co., Ltd. (China). Microcrystalline cellulose PH-102 was purchased from J. RETTENMAIER & Söhne Corporation (US). Corn starch was purchased from Hubei Gedian Humanwell Pharmaceutical Co., Ltd. (China). Lactose was purchased from Meggle company (Germany). Triethyl citrate (TEC) was purchased from Fengyuan Tushan Pharmacy Ltd. (China).

6.2.2 Preparation of tablets

A V-blender was used to mix the ingredients together. Then the mixture was compressed by rotary tablet press machine (Tianxiang Jiantai Pharmacy Machinery Co., Ltd. Shanghai, China). Table 6.1 shows the formulation and other properties of compressed aspirin tablets.

Table 6.1 Formulation of aspirin tablets

Ingredients	Weight fraction (%)
Aspirin	46%
Corn Starch 1500	10%
Lactose	25%
Microcrystalline cellulose PH102	17%
AEROSIL® 200 Pharma	1%
Ac-Di-Sol® SD-711	1%
Total weight (mg)	176
Hardness	120
Diameter (mm)	7.0
Thickness (mm)	4.0

6.2.3 Formulation of coating materials

Table 6.2 shows the formulation of enteric coating material for the dry powder coating process. Jet mill (YQ100-1, Shanghai Saishan Powder Co., Ltd, Shanghai, China) was used to decrease particle size of Eudragit® L100-55. And Table 6.3 is the formulation of the coating material for aqueous coating process.

Table 6.2 Formulation of powdered coating material

Materials	Weight Fraction
Eudragit® L100-55	40%
Talc	59.5%
Blue lake No.1	0.5%

Table 6.3 Formulation of aqueous dispersion

Materials	Concentration
Eudragit® L100-55	36g
Talc	54g
Triethyl citrate (TEC)	4.5g
NaOH (1mol/L)	12ml
Water	270ml
Blue lake #1	0.5g

6.2.4 Electrostatic dry powder coating process

Electrostatic dry powder coating process was carried out in a pan coater (BGB-5F, Zhejiang Xiaolun Pharmaceutical Machinery Co., Ltd. Zhejiang, China) with slightly adjustment as Figure 6.1 shows. A porous coating pan which is used in aqueous coating process was change to a solid coating pan. And except for a heating system, a grounded rotating coating pan and a liquid spraying system, an additional electrostatic powder spray gun (Nordson Corporation, USA) was required.

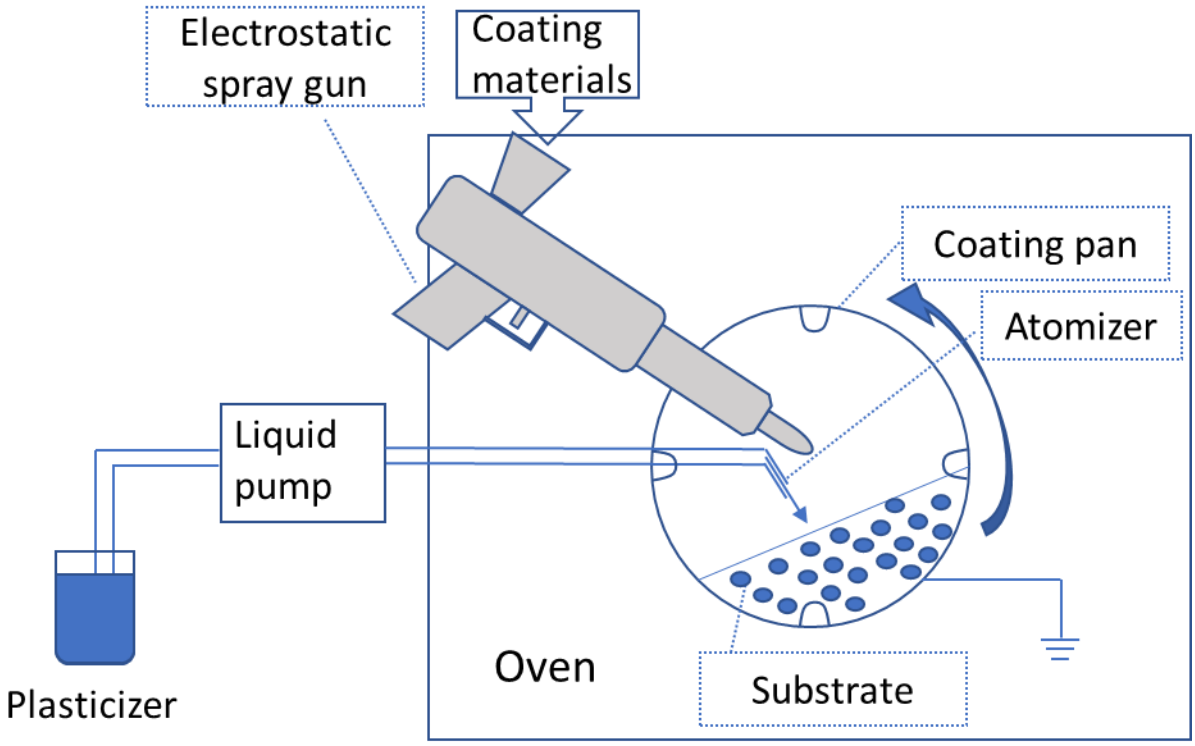


Figure 6.1 Schematic of the electrostatic powder coating system

In the coating process, because there was no other heating system, hot air was used to heat up the system. However, air was not required for the dry powder coating process, only heat is needed. In the future, the heat can be simply provided by an oven. Then, when the system reached the setting temperature, 800g aspirin tablets were loaded in the rotating coating pan and preheated for 10 minutes. Afterwards, PEG 400 as plasticizer was sprayed first followed by spraying coating powders. Plasticizer and coating powders were sprayed alternatively for several times to achieve

desired film thickness after coating. Finally, the coated tablets were tumbled in the rotating coating pan until the powders coalesced and formed films.

6.2.5 Aqueous coating process

Traditional aqueous coating process, which was carried out in the same pan coater but with a porous coating pan as shown in Figure 6.2, was also used to coat aspirin tablets. The whole process included preparation of coating material and coating process. For preparation step, the talc, blue lake NO.1, and triethyl citrate (TEC) were added into 180 ml water and stirred first. Then, 90 ml water was used to disperse Eudragit® L100-55 polymers and add 0.1 mol/L NaOH to the dispersion drop by drop when stirring. After Eudragit® L100-55 polymer dispersion was made, talc dispersion was poured into it and the mixtures were stirred by high-shear mixer for 30 minutes to obtain aqueous coating dispersion. Another 60 minutes stirring were required to ensure the dispersion is well mixed and no sediment were going to form. For coating step, the process parameters were set as follows: inlet air temperature was 45℃, coating dispersion flow rate was 2ml/min and rotating speed of coating pan was 12rpm. 800 g aspirin tablets were first preheated for 10 minutes before dispersion spraying. Then, the aqueous dispersion was sprayed on the tablets bed continuously. After the spraying, aspirin tablets were kept in the rotating coating pan for 1 hour and then stored in an oven with 40℃ for curing and film formation.

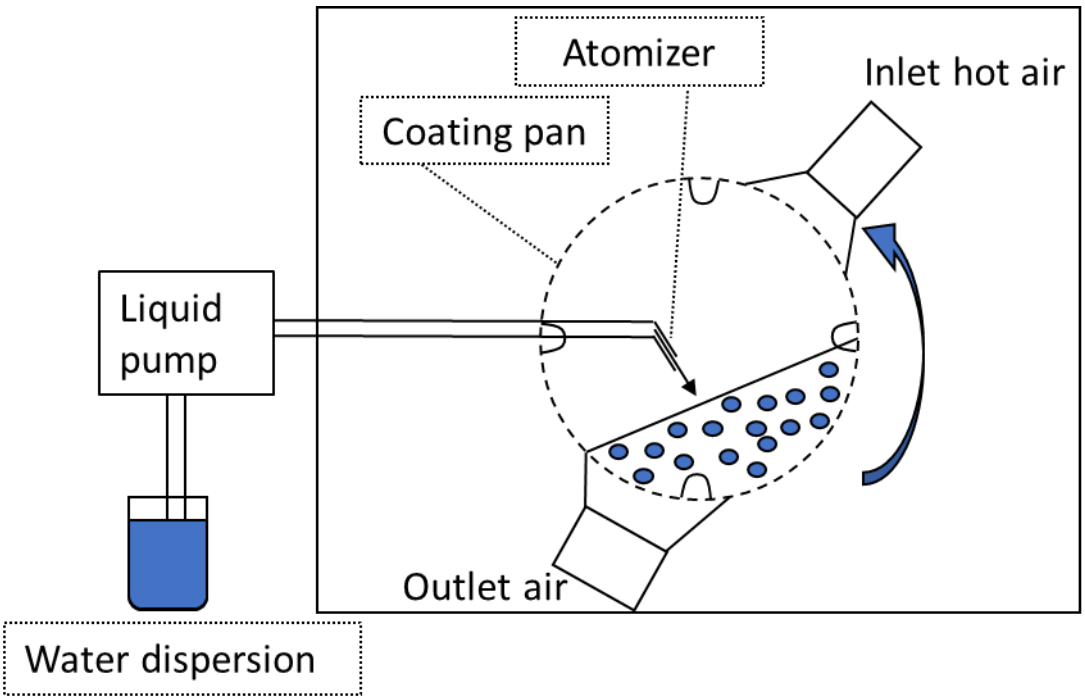


Figure 6.2 Schematic of the aqueous coating system

6.2.6 Scanning electron microscopy (SEM)

Aspirin tablets were first sputter coated with gold for 2 minutes by using EMITECH K550 sputter coater (Emitech Ltd., Ashford, UK) to increase the surface electrical conductivity. Then the surface morphologies of the coated tablets were observed by scanning electron microscope (Hitachi S-2600 N, Ontario, Canada).

6.2.7 HPLC

High performance liquid chromatography (HPLC) (UltiMate™ 3000 Thermo Fisher Scientific, US) was used to investigate the concentration of free salicylic acid before and after coating. Aspirin tablets were grounded and dissolved in a mixture of methanol and formic acid (99:1). The mobile phase was a mixture of acetonitrile, tetrahydrofuran, glacial acetic acid and purified water (20:5:5:70). Amethyst C18-H analytical column (4.6 mm×250 mm, 5 μm) was used to separate aspirin and salicylic acid and the concentration of salicylic acid was test by UV detecter at 276 nm wavelength.

6.2.8 *In vitro* dissolution test

In vitro release profiles of enteric coated aspirin tablets were examined by a dissolution test system (Tianda Tianfa Technology Co., Ltd. ZRS-8GD, Tianjin, China) which complies with the standard of United States Pharmacopeia (<711> Dissolution, Apparatus 2, Paddle). Six dosages were tested at the same time. The apparatus was set with rotating speed of 100rpm and temperature of 37℃. The coated aspirin tablets were first merged in 750 ml hydrochloric acid (0.1 mol/L, pH=1) for two hours, and then 250 ml 0.2 M tribasic sodium phosphate solution was added to change the pH value to 6.8. Syringe is used to take 10 ml solution as sample at different time to test the concentration of aspirin released. UV-1800 Spectrophotometer (Shimadzu Corporation, Japan) was used to test the sample at a wavelength of 276 nm in hydrochloric acid solution (pH=1) and 269 nm in phosphate buffered saline (pH=6.8).

6.2.9 Stability test

Uncoated and enteric coated aspirin tablets were placed in high-density polyethylene (HDPE) vials and sealed. Then they were stored at 40℃/ 75% RH for 60 days. Free salicylic acid concentrations of aqueous coated aspirin tablets and dry powder coated aspirin tablets before and after storage was examined.

6.3 Results and discussion

6.3.1 Scale up of dry powder coating process

The dry powder coating process was scaled up from lab scale to pilot scale. The parameters of lab scale and pilot scale coating process are shown in Table 6.4. Pilot scale coating process was first carried out using the same coating procedures as the lab scale coating process. The coating pan was first heated to a certain temperature, then, 800 g of aspirin tablets were loaded into the coating pan and preheated for 10 mins. Afterwards, plasticizer and coating powders were sprayed alternatively until the desired weight gain was achieved. Finally, the tablets remained in the rotating coating pan until coating films were formed.

Compared to lab scale coating process, pilot scale coating process could provide better tumbling and polish to compress powders adhered on the tablets because more tablets were loaded in the

coating pan. Thus, the bed temperature can be slightly lower than lab scale coating process as shown in Table 6.4. Then, when spraying the plasticizer, the amount of plasticizer sprayed was decreased gradually after each spray to avoid stickiness. For the lab scale coating process, the amount of plasticizer was controlled by spraying duration for each coating application. While for the pilot scale coating process, the amount of plasticizer was controlled by both spraying duration each time and spraying rate because too short spraying duration would cause nonuniform coating films. When spraying the coating powders, the amount of powders sprayed was also decreased gradually. For the lab scale coating process, this was controlled by decrease weight of coating powders sprayed each time, while for the pilot scale process, it is controlled by decreasing powder feeding rate and spraying duration.

After spraying plasticizer and coating powders, the tablets were cured in the coating pan to form the coating film. Due to the better tumbling provided by pilot scale coating process, the curing time of pilot scale coating was much shorter. And compared to lab scale coating process, the coating efficiency of pilot scale coating process was higher.

Table 6.4 Comparison of lab scale and pilot scale coating processes

Parameters		Lab scale	Pilot scale
Capacity (g)		70	800
Diameter of coating pan (cm)		14	38
Rotating speed of coating pan (rpm)	Preheat	15	6
	Coating	35	15
	Curing	15	9
Bed temperature (℃)		48~52	40~43
Preheat time (mins)		10	10
Plasticizer spray rate (g/min)		0.4	From 2.36 to 1.18
Plasticizer used (g)		3.1	19.8
Coating powder spray rate		Form 2g/spray to 1g/spray	From 18g/min to 9g/min
Coating powders used (g)		13.5 (Eudragit® L 40%)	123 (Eudragit® L 40%)
Curing time (mins)		90	20
Total coating time (mins)		190	130
Coating level (%)		7.4	9.3
Coating efficiency (%)		31.2	52.1

*Coating level = $\frac{\text{30 tablets weight after coating}}{\text{30 tablets weight before coating}} \times 100\%$;

*Coating efficiency $= \frac{\text{Total weight gain after coating}}{\text{Theoretical weight gain}} \times 100\%$;
(Theoretical weight gain = Solid content sprayed + Liquid plasticizer sprayed)

Enteric release aspirin tablets coated by lab scale and pilot scale coating processes were examined through an *in vitro* dissolution test (Figure 6.3). By comparison, there was no difference between enteric release aspirin tablets coated by the lab scale coating process and by the pilot scale coating process. Thus, the scale up of the process was successful. However, the coating process can still be optimized to decrease coating time and achieve higher coating efficiency.

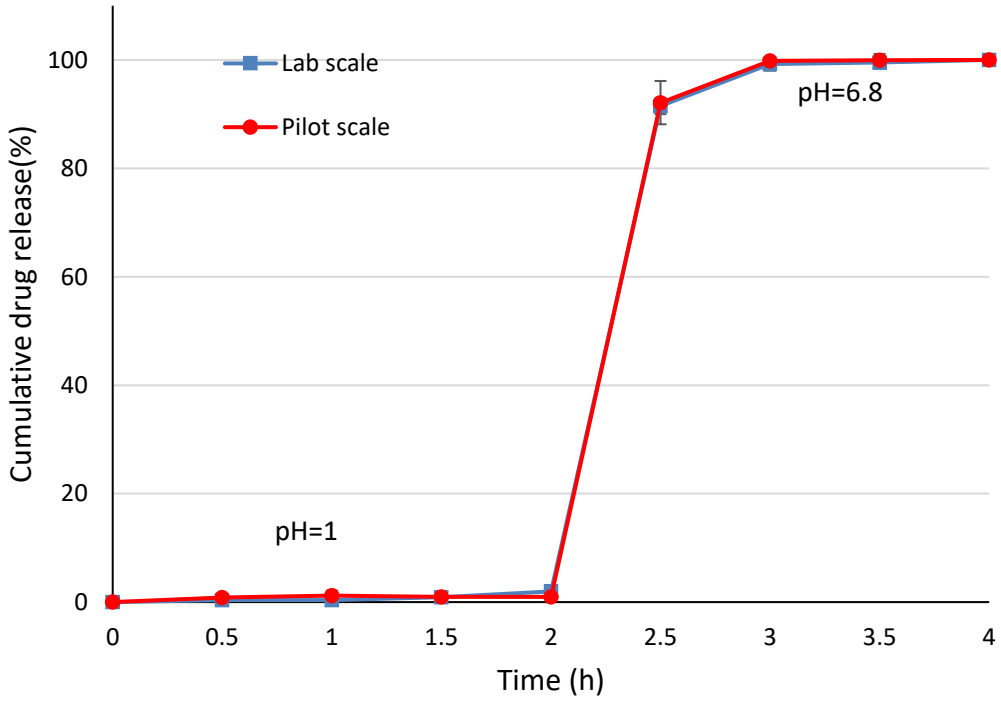


Figure 6.3 Release profiles of aspirin tablets from lab scale and pilot scale coating processes

6.3.2 Optimization of dry powder coating process

Different processes were investigated to optimize the electrostatic dry powder coating process as shown in Figure 6.4.

In process 1, the aspirin tablets were first preheated for 10 minutes, then, plasticizer and coating powder were sprayed alternately. In the beginning, the plasticizer was sprayed first to wet the tablets and provide a better powder adhesion efficiency, followed by spraying coating powder. The amounts of plasticizer and coating powder were high at the beginning to increase the powder adhesion which led to longer curing time to allow the particles coalesce after first spray. Afterwards, the amounts of plasticizer and coating powder were decreased gradually because the formed coating film after last spray would become sticky and be damaged if too much plasticizer was sprayed in the next application. The extent of the stickiness would be exacerbated as the total amount of plasticizer sprayed increased. Thus, the amount of plasticizer sprayed was decreased over time along with the amount of coating powder used.

In process 2, the aspirin tablets were also preheated for 10 minutes, then, the plasticizer was sprayed first to promote the adhesion force for powder which was sprayed following. However, different from process 1, after spraying plasticizer for certain time, the coating powder was sprayed while the spray of plasticizer continued. Plasticizer and powder were sprayed simultaneously for a predetermined time. Then, the plasticizer spray was stopped while the coating powder was continuously sprayed for another short time before the curing step. Similarly to process 1, the amounts of plasticizer and coating powder sprayed were decreased gradually to prevent stickiness of tablets. It is worth mentioning that much less stickiness of tablets was occurred in process 2 compared to process 1.

In addition, by comparing the total powder sprayed and coating level of process 1 and process 2, it is found that process 2 had a higher coating efficiency (72.6% vs. 52.1%). Thus, process 2 was used as the optimized coating process.

Process 1	
Plasticizer spray	Polymer spray
Preheat 10 mins	
2ml/min, 2mins	
	18g/min, 1min 30s
Curing 10 mins	
2ml/min, 1min 20s	
	18g/min, 1min
Curing 5 mins	
2ml/min, 1min	
	18g/min, 1min
Curing 5 mins	
1ml/min, 1min	
	12g/min, 1min
Curing 5 mins	
1ml/min, 1min	
	12g/min, 1min
Curing 5 mins	
1ml/min, 45s	
	9g/min, 50s
Curing 5 mins	
1ml/min, 45s	
	9g/min, 50s
Curing 5 mins	
1ml/min, 45s	
	9g/min, 50s
Curing 5 mins	
1ml/min, 45s	
	9g/min, 50s
Curing 20 mins	
Total plasticizer: 19.8g	Total powders: 123g
Coating level: 9.3%	
Coating efficiency: 52.1%	

Process 2	
Plasticizer spray	Polymer spray
Preheat 10 mins	
1.8ml/min, 1min 30s	
1.8ml/min, 1min 30s	9g/min, 1min 30s
	9g/min, 40s
Curing 10 mins	
1ml/min, 30s	
1ml/min, 2mins 30s	6g/min, 2mins 30s
	6g/min, 40s
Curing 10 mins	
1ml/min, 30s	
1ml/min, 2mins 30s	6g/min, 2mins 30s
	6g/min, 40s
Curing 10 mins	
1ml/min, 30s	
1ml/min, 2mins 30s	6g/min, 2mins 30s
	6g/min, 40s
Curing 10 mins	
1ml/min, 30s	
1ml/min, 2mins 30s	6g/min, 2mins 30s
	6g/min, 40s
Curing 20 mins	
Total plasticizer: 19g	Total powders: 95.5g
Coating level: 10.4%	
Coating efficiency: 72.6%	

Figure 6.4 Electrostatic dry powder coating processes

*Coating level $= \frac{\text{30 tablets weight after coating}}{\text{30 tablets weight before coating}} \times 100\%$;

*Coating efficiency $= \frac{\text{Total weight gain after coating}}{\text{Theoretical weight gain}} \times 100\%$;

(Theoretical weight gain = Solid content sprayed + Liquid plasticizer sprayed)

6.3.3 Comparison to aqueous coating process

Aqueous coating and electrostatic dry powder coating processes were compared as shown in Table 6.5. Compared to the aqueous coating process, although dry powder coating required a higher temperature, the operation time (including time for preparation of coating materials and total coating time) was significantly decreased. Therefore, the electrical energy consumption of the dry powder coating process was also lower than the aqueous coating process (2.37 kW·h vs. 4.35 kW·h). The coating efficiency of the dry powder coating process was slightly lower than the aqueous coating process because the experiments were carried out in an apparatus designed for aqueous coating. It could be improved by optimizing the apparatus like position of powder spray gun and so on. Additionally, an overall decrease in utility cost could be obtained by changing the heating system by utilizing an oven instead of heated air.

Table 6.5 Comparation of dry powder coating process and aqueous coating process

Parameters		Dry powder coating	Aqueous coating process
Rotating speed of coating pan (rpm)	Preheat	6	6
	Coating	15	12
	Curing	9	6
Temperature of inlet air (℃)		55	50
Temperature of outlet air (℃)		38~41	38~40
Bed temperature (℃)		40~43	33~35
Coating materials used (g)		95.5 (Eudragit® L 40%)	377 (solid content: 23.8%, Eudragit® L: 9.5%)
Preparation time (mins)		20	120
Total coating time (mins)		120	250
Coating level (%)		10.4	9.1
Coating efficiency (%)		72.6	75
Electric energy consumption (kW·h)		2.37	4.35

*Coating level = $\frac{\text{30 tablets weight after coating}}{\text{30 tablets weight before coating}} \times 100\%$;

*Coating efficiency = $\frac{\text{Total weight gain after coating}}{\text{Theoretical weight gain}} \times 100\%$;

(Theoretical weight gain = Solid content sprayed + Liquid plasticizer sprayed)

6.3.4 *In vitro* dissolution tests

Both aqueous coated and dry powder coated aspirin tablets were examined through an *in vitro* dissolution test, and the release profiles are shown in Figure 6.5. Results indicated that both aqueous coated aspirin tablets and dry powder coated aspirin tablets did not release any aspirin in the acidic solution for first 2 hours and released more than 80% aspirin in 30 minutes following the change to pH 6.8 buffer solution, which satisfied the requirement of U.S. Pharmacopeia ("Aspirin", 2017).

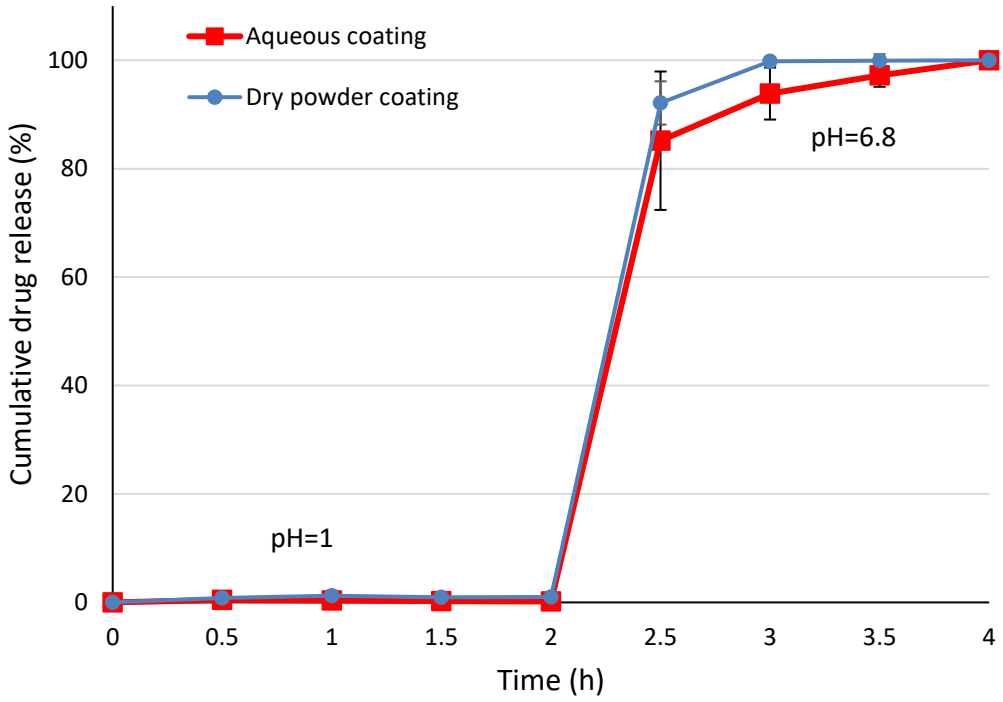


Figure 6.5 Release profile of enteric release coated aspirin tablets

6.3.5 Porosity of dry powder coating film

Figure 6.6 compared the amount of water absorbed at different time points after tablets were submerged in pH 1 HCl solution. Compared to the aqueous coated aspirin tablets, dry powder coated tablets absorbed more water which indicated that the porosity of the dry powder coated films on aspirin tablet was larger than the aqueous coated films. Thus, after placing the tablets in

the solution, water would be able to penetrate the more porous dry powder coated films relatively easier than the aqueous coated tablets. For dry powder coating process, even though the size of particles has been decreased, they are still significantly larger than those present in the aqueous coating process (23.17μm vs. 0.1μm) (Eudragit® Application Guidelines, 2019). Thus, the dry powder coating film may not be as dense as aqueous coating film resulting in larger porosity.

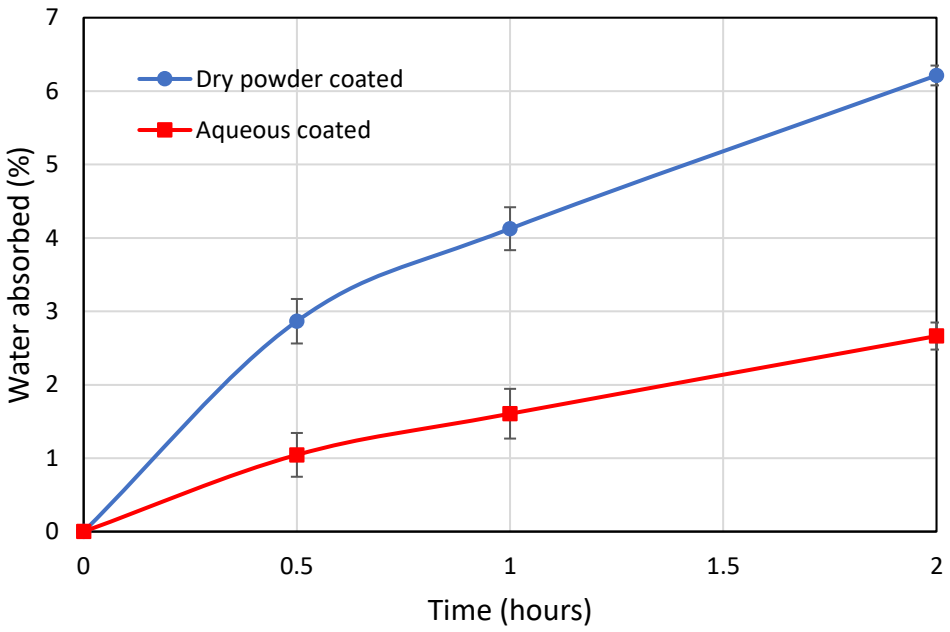


Figure 6.6 Water absorbed of dry powder coated and aqueous coated tablets in pH=1 HCl solution

6.3.6 Scanning electron microscopy (SEM)

SEM figures of aspirin tablets before and after the acceleration test were showed in Figure 6.7. For the aqueous coated tablets, there was no crystals formed on the film surfaces after the acceleration test (Figure 6.7 (a2)). However, previous literature has suggested that there would be some crystals formed on the film surface after 6 months acceleration test at 40℃/ 75% RH (Wang et al., 2017). This phenomenon can be explained as follows: First, the moisture would penetrate the film and reach the tablet cores in the relatively high moisture environment. After water was absorbed by the film, it acted as a plasticizer and increased the mobility of the chain molecules of the coating materials. Due to the increased mobility, the drug would migrate from the tablet core to the film

surface driven by the drug concentration gradient and subsequently crystalize on the surface. The water adsorption and drug migration would damage the film (Rujivipat & Bodmeier, 2012), and the extent of drug migration might be related to the amount of water absorption (Wang et al., 2017).

For the dry powder coated aspirin tablets, some crystals were formed on the surface of aspirin tablets after a 60-day acceleration test (Figure 6.7 (b2)). This might be due to the larger porosity of the films formed during the dry power coating process compared to films formed in aqueous coating process as previous noted. Thus, for the dry powder coated tablets, moisture would penetrate the film more easily and reach the tablet cores at 40℃/ 75% RH. Consequently, more drug would migrate and be crystalized on the surface of dry powder coated film.

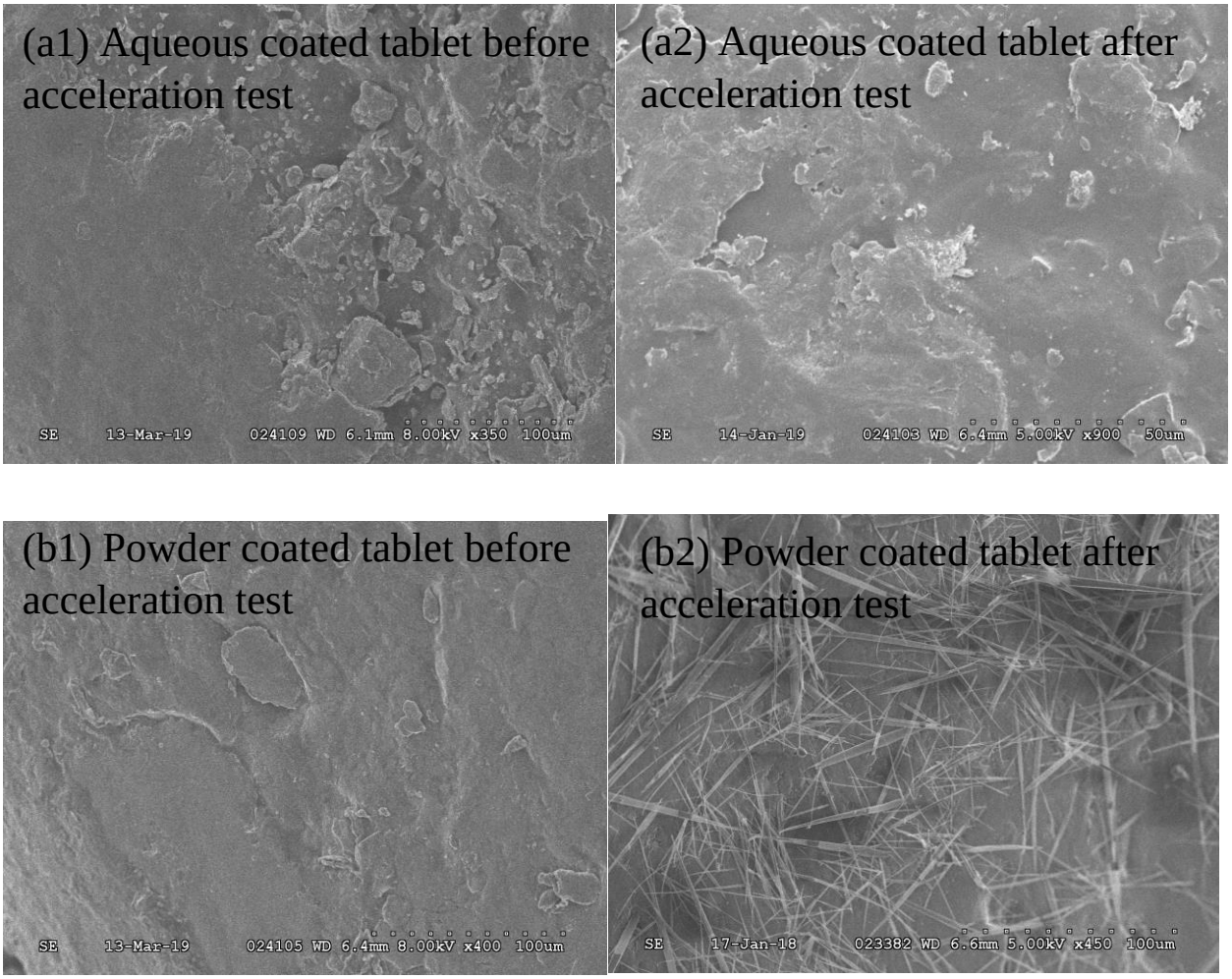


Figure 6.7 Surface of aqueous coated and dry powder coated aspirin tablets before and after acceleration test

6.3.7 Free salicylic acid concentration

Free salicylic acid concentrations of aspirin tablets before and after dry powder coating and aqueous coating process were shown in Figure 6.8. In the aqueous coating process, a water dispersion was sprayed directly on aspirin tablets, then the water was evaporated resulting in an environment with high humidity. The direct contact of water and aspirin tablets as well as the exposure of aspirin tablets under a high humidity and high temperature environment caused the hydrolysis of aspirin. Thus, the salicylic acid concentration increased after the aqueous coating process.

While, for dry powder coating process, aspirin was also hydrolyzed in the coating process due to the application of a high temperature, the salicylic acid concentration of coated aspirin tablets was lower than that of the aqueous coated tablets due to the to elimination of water in coating process. Thus, by comparison, the dry powder coating process would cause less degradation of aspirin tablets than the aqueous coating process.

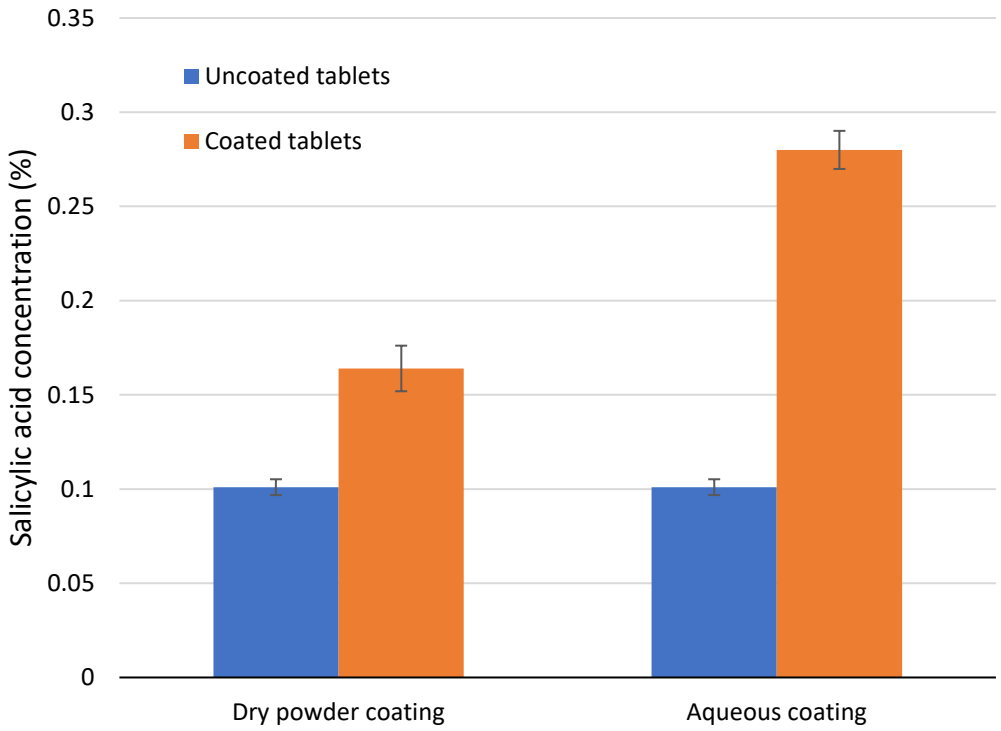


Figure 6.8 Increasing of free salicylic acid concentration during dry powder coating and aqueous coating processes

Figure 6.9 shows the salicylic acid concentration of aspirin tablets before and after a 60-day acceleration test at 40℃/75% RH. It was found that for aspirin tablets, enteric coating films formed by either aqueous or dry powder coating process cannot protect aspirin from hydrolysis after a 60-day acceleration test but accelerate the degradation.

It is reported that the hydrolysis of aspirin tablets during storage was due to the residual water at the interface between the film and tablet core during the aqueous coating process (Mwesigwa et al., 2008). In the dry powder coating process, the water was eliminated, but the hydrolysis of enteric coated aspirin tablets was still accelerated at 40℃/75% RH compared to uncoated aspirin tablets. Thus, the degradation of enteric coated aspirin tablets may because the coating films would uptake more water from surroundings and increase the water concentration near the tablet cores.

Compared to the aqueous coated aspirin tablets, the dry powder coated aspirin tablets had a slightly higher salicylic acid concentration which may be attributed to the larger porosity of dry powder coating films. So, for the stability of aspirin in the storage, the dry powder coating film did not provide better protection than aqueous coating film.

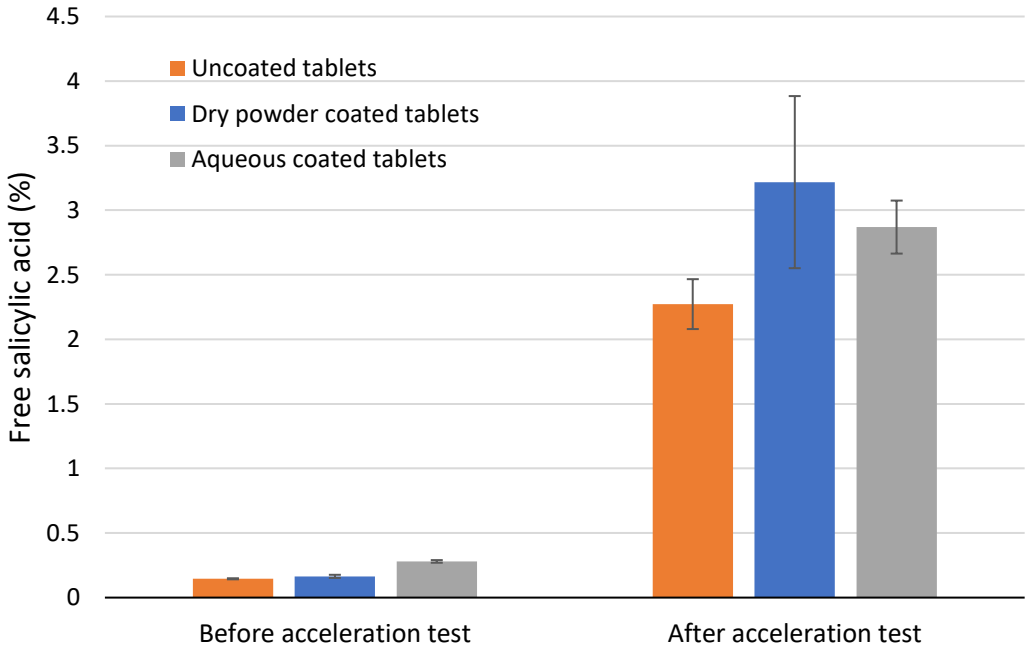


Figure 6.9 Free salicylic acid of aspirin tablets before and after acceleration test

6.4 Conclusion

In this study, electrostatic dry powder coating technology was scaled up to coat aspirin tablets. Different dry powder coating processes were investigated and optimized. The coating process in which plasticizer and coating powder were sprayed simultaneously was chosen as the optimized process because of its high coating efficiency. The optimized dry powder coating process was also compared with the traditional aqueous coating process and the results showed that the dry powder coating process had shorter processing time, lower energy consumption and comparable coating efficiency. In addition, compared to aqueous coating process, the dry powder coating technology reduced the hydrolysis of aspirin tablets during the coating process, due to the elimination of water during the coating process. However, compared to Eudragit® L100-55 films formed by aqueous coating process, films formed by dry powder coating process did not provide better protection for aspirin tablets in stability test.

Bibliography

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

Application Guidelines. Retrieved April 17, 2019, from https://oncare.evonik.com/application_guidelines/1-poly-meth-acrylate-properties/1-5-particle-sizes-of-aqueous-polymer-dispersions/

"Aspirin" (2017). *The United States Pharmacopeia 2017: USP 40; The National Formulary: NF 35*, United States Pharmacopeia Convention, pp. 2872–2876.

Aulton, M., Cole, G., & Hogan, J. (1995). *Pharmaceutical coating technology*. Taylor & Francis.

Baigent, C., Blackwell, L., Collins, R., Emberson, J., Godwin, J., Peto, R., Buring, J., et al. (2009). Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet (London, England)*, *373*(9678), 1849–1860.

Erkan, D., Harrison, M. J., Levy, R., Peterson, M., Petri, M., Sammaritano, L., Unalp-Arida, A., et al. (2007). Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: A randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody–positive individuals. *Arthritis & Rheumatism*, *56*(7), 2382–2391.

Garcia-Albeniz, X., & Chan, A. T. (2011). Aspirin for the prevention of colorectal cancer. *Best Practice & Research Clinical Gastroenterology*, Chemoprevention in Gastroenterology, *25*(4), 461–472.

Hawthorne, A., Mahida, Y., Cole, A., & Hawkey, C. (1991). Aspirin-induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. *British Journal of Clinical Pharmacology*, *32*(1), 77–83.

Hoftiezer, J., Burks, M., Silvoso, G., & Ivey, K. (1980). Comparation of the effects of regular and enteric-coated aspirin on gastroduodenal mucosa of man. *The Lancet*, Originally published as Volume 2, Issue 8195, *316*(8195), 609–612.

Lansberg, M. G., O'Donnell, M. J., Khatri, P., Lang, E. S., Nguyen-Huynh, M. N., Schwartz, N. E., Sonnenberg, F. A., et al. (2012). Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, *141*(2, Supplement), e601S-e636S.

Lanza, F. L., Royer Jr, G. L., & Nelson, R. S. (1980). Endoscopic evaluation of the effects of aspirin, buffered aspirin, and enteric-coated aspirin on gastric and duodenal mucosa. *New England Journal of Medicine*, *303*(3), 136–138.

Mwesigwa, E., Basit, A. W., & Buckton, G. (2008). Moisture Sorption and Permeability Characteristics of Polymer Films: Implications for Their Use as Barrier Coatings for Solid Dosage Forms Containing Hydrolyzable Drug Substances. *Journal of Pharmaceutical Sciences*, *97*(10), 4433–4445.

Paikin Jeremy S., & Eikelboom John W. (2012). Aspirin. *Circulation*, *125*(10), e439–e442.

Patell, M. K. (1988). *U.S. Patent No. 4,775,536*. Washington, DC: U.S. Patent and Trademark Office.

Patrignani, P., & Patrono, C. (2016). Aspirin and Cancer. *Journal of the American College of Cardiology*, *68*(9), 967–976.

Patrono, C., García Rodríguez, L. A., Landolfi, R., & Baigent, C. (2005). Low-Dose Aspirin for the Prevention of Atherothrombosis. *New England Journal of Medicine*, *353*(22), 2373–2383.

Plaizier-Vercammen, J. A., & De Neve, R. E. (1993). Evaluation of water and organic coating formulations for the protection of tablets against humidity. *Pharmazie*, *48*(6), 441–446.

Qiao, M., Luo, Y., Zhang, L., Ma, Y., Stephenson, T. S., & Zhu, J. (2010). Sustained release coating of tablets with Eudragit® RS/RL using a novel electrostatic dry powder coating process. *International Journal of Pharmaceutics*, *399*(1), 37–43.

Qiao, M., Zhang, L., Ma, Y., Zhu, J., & Xiao, W. (2013). A novel electrostatic dry coating process for enteric coating of tablets with Eudragit® L100-55. *European Journal of Pharmaceutics and Biopharmaceutics*, *83*(2), 293–300.

Rujivipat, S., & Bodmeier, R. (2012). Moisture plasticization for enteric Eudragit® L30D-55-coated pellets prior to compression into tablets. *European Journal of Pharmaceutics and Biopharmaceutics*, *81*(1), 223–229.

Sørensen, H. T., Mellemkjær, L., Blot, W. J., Nielsen, G. L., Steffensen, F. H., McLaughlin, J. K., & Olsen, J. H. (2000). Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *The American journal of gastroenterology*, *95*(9), 2218–2224.

Walker, J., Robinson, J., Stewart, J., & Jacob, S. (2007). Does enteric-coated aspirin result in a lower incidence of gastrointestinal complications compared to normal aspirin? *Interactive CardioVascular and Thoracic Surgery*, *6*(4), 519–522.

Wang, X., Wang, P., Huang, C., Lin, X., Gong, H., He, H., & Cai, C. (2017). Hot-melt sub- and outercoating combined with enteric aqueous coating to improve the stability of aspirin tablets. *Asian Journal of Pharmaceutical Sciences*, *12*(3), 266–278.

Yang, Q., Ma, Y., Shi, K., Yang, G., & Zhu, J. (2018). Electrostatic coated controlled porosity osmotic pump with ultrafine powders. *Powder Technology*, *333*, 71–77.

Yang, Q., Ma, Y., & Zhu, J. (2016). Sustained drug release from electrostatic powder coated tablets with ultrafine ethylcellulose powders. *Advanced Powder Technology*, *27*(5), 2145–2152.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2011). *U.S. Patent No. 7,862,848*. Washington, DC: U.S. Patent and Trademark Office.

Zhu, J., Luo, Y., Ma, Y. L., & Zhang, H. (2012). *U.S. Patent No. 8,161,904*. Washington, DC: U.S. Patent and Trademark Office.

Chapter 7

7 Conclusion and recommendation

7.1 Conclusion

A novel electrostatic dry powder coating technology was successfully applied on hard gelatin capsules and hard hydroxypropyl methylcellulose (HPMC) capsules to modify drug release. The dry powder coating process is more environmentally friendly, more efficient and more cost effective compared to organic and aqueous coating processes. In addition, the dry powder coating process eliminates problems associated with shell embrittlement, poor adhesion of coating materials and stickiness that commonly occur during organic solvent and aqueous capsule coating processes.

Sustained release gelatin and HPMC capsules were produced by coating capsules directly using the electrostatic dry powder coating process. Fine Eudragit® RS and Eudragit® RL powders were used as coating materials, and the ratio of Eudragit® RS: RL had influence to the release rate of capsules during the dissolution test. As expected, the thicker coating film, reflected by higher weight gain, would slow down the drug release rate. Coated gelatin capsules and HPMC capsules presented excellent stability over 8 months at 25℃/ 40% RH. The release mechanism of sustained release gelatin capsules and HPMC capsules was investigated and compared with that of tablets. Two active pharmaceutical ingredients (APIs) as samples were examined. It is found that during the dissolution test, the capsule shells were dissolved first before the drug dissolved and the dissolved capsule shells would form high viscosity solutions in the coating films. The dissolution of capsule shells led to different delayed release profiles for both gelatin and HPMC capsules. The high viscosity solution formed by the dissolved capsule shell had a great influence on release rate and release mechanism of APIs. Compared to sustained release tablets whose release mechanism followed anomalous transport, the release mechanism of capsules followed “super case II transport”.

Enteric release gelatin and HPMC capsules were produced by coating capsules directly using the electrostatic dry powder coating process. Fine Eudragit® L 100-55 powders were used as coating materials during the coating process. During the dissolution test, the higher coating film thickness,

reflected by higher weight gain, was shown to provide better protection and prevention of leakage of capsule in the acidic solution. Due to the different dissolution properties of gelatin and HPMC capsules, enteric coated HPMC capsules could prevent water penetration in acidic solutions but also presented a slight delay release in pH 6.8 phosphate buffered saline (PBS). The stability test showed enteric coated gelatin and HPMC capsules had excellent stability following storage at 40℃/ 75% RH for 2 months. In the capsule coating process, plasticizer was used not only to decrease the glass transition temperature of the coating polymers, but also used to increase the powder adhesion efficiency, subsequently higher coating efficiency, of the coating process. By adjusting the amount of plasticizer, higher powder adhesion efficiency can be achieved without causing stickiness. It was also found that a higher wettability, reflected by a lower contact angle between the capsules and plasticizers, can lead to higher the powder adhesion efficiency.

Enteric release aspirin capsule coated by using the electrostatic dry powder coating process, as an alternative solid dosage form for aspirin, were investigated to deliver aspirin and compared with coated tablets. Various formulations to produce aspirin tablets as well as gelatin and HPMC capsules were examined and optimized. After coating, enteric release aspirin tablets and capsules were investigated using a dissolution test. It was found that the dissolution of aspirin tablets in pH 6.8 PBS was delayed due to the migration of the drug from the tablet core to the coating film which altered the film properties. The drug migration of enteric coated aspirin tablets was further confirmed by the observation of crystals on the surface of dry powder coated aspirin tablets after the acceleration test. This migration can be prevented by applying a sub-coating to separate the tablet core from the coating film. For gelatin and HPMC capsules, since the capsule shell separated aspirin from the coating film, the migration of the drug was prevented even without a sub-coating. Thus, enteric coated gelatin capsules showed no delay. However, HPMC capsules had a delayed release in PBS which was owing to dissolving of HPMC capsules is slower. Coated tablets and capsules were stored at 40℃/75% RH for 60 days and tested for their free salicylic acid concentration. It was found that the enteric coating film did not protect aspirin tablets or capsules from hydrolysis, but, accelerated the hydrolysis of aspirin. This might be because the enteric coating film would absorb more water and the moisture concentration around the aspirin tablets or capsules would increased, leading to more water being contact with aspirin. However, it was found that unlike tablets and HPMC capsules, enteric coated gelatin capsules did not accelerate the hydrolysis of encapsulated aspirin. This is because moisture that penetrated the coating films was

absorbed by the gelatin capsule shells. Since the gelatin capsules would be dehydrated during the coating process, moisture was unable to be absorbed by the enclosed aspirin. After comparing the different performances of enteric coated aspirin tablets and capsules, it can be concluded that the moisture that penetrated the coating film from the environment may be an important reason for hydrolysis of aspirin and the enteric coating film would concentrate the moisture around the tablets or capsules leading to an acceleration of aspirin hydrolysis.

Then, the electrostatic dry powder coating process was scaled up in a traditional pan coater to coat aspirin tablets using Eudragit® L100-55 as coating polymer to achieve enteric release. The dry powder coating process was optimized to which plasticizer and coating powder were sprayed simultaneously. This optimization led to a higher coating efficiency, shorter processing time and less stickiness occurred in the coating process. Compared to the aqueous coating process, the electrostatic dry powder coating process had shorter processing time, lower energy consumption and higher coating efficiency. The aspirin tablets coated by the dry powder coating process had less hydrolyzed aspirin due to absence of water and had the similar *in vitro* release profile compared to aqueous coated aspirin tablets. However, after a 60-day acceleration test at 40℃/ 75% RH, crystals were observed on the dry powder coated aspirin tablets but were not observed on aqueous coated tablets. Further, the salicylic acid concentration of the dry powder coated aspirin tablets after the acceleration test was not lower than aqueous coated tablets. These two phenomena occurred because the porosity of films formed by the dry powder coating process was larger than films formed by the aqueous coating process which might enhance the migration and hydrolysis of aspirin.

In conclusion, electrostatic dry powder coating technology was successfully applied on gelatin capsules and HPMC capsules to achieve sustained release and enteric release which avoided the difficulties associated with organic solvent and aqueous coating processes. Capsules also provided a new dosage form to deliver aspirin and showed some benefits compared to the tablet dosage form. In addition, the dry powder coating technology was scaled up successfully and showed some advantages over aqueous coating process but still requires some improvement.

7.2 Recommendation

Although electrostatic dry powder coating technology has many advantages, some problems are still worth considering. The capillary force present in organic and aqueous coating processes are essential to drag coating particles closer in the development of dense films. Electrostatic dry powder coating technology does not utilize capillary forces due to the absence of organic solvents and water from the process, thus, another energy is required to replace this force. This energy should be forced on the surface of substrate so that the drug would not be degraded, and this energy should be able to be removed after coating so that the coating film would not be unstable due to containing too much energy. Light energy might be good option if the issue of uniformity can be solved. Another thing can be done is to apply two films on substrate and improve overall film properties. Also, the porosity of coating film could be measured by Barrett-Joyner-Halenda (BJH) analysis. For capsule coating, because of their lower density compared to tablets, the amount of plasticizer needs to be controlled in a range to avoid stickiness. Introducing air to promote the disturbance of the capsule bed may further increase the range.

Curriculum Vitae

Name: Zhehao Jing

Post-secondary Education and Degrees:
Tianjin University
Tianjin, China
2011-2015 B.E.

The University of Western Ontario
London, Ontario, Canada
2015-2019 Ph.D.

Honours and Awards:
Mitacs Accelerate PhD Fellowship
2015-2018

Related Work Experience
Research Assistant and Teaching Assistant
University of Western Ontario
2015-2019

Publications:

Zhu, J., Jing, Z., Yang, Q., Ma, Y., Chow, K., and Shi, K., (2019) Chapter 16 Dry Powder Coating of Pharmaceutical Solid Dosages, Green Chemistry for Surface Coatings, Inks and Adhesives: Sustainable Applications. The Royal Society of Chemistry. (Accepted)

Jing Z., Ma Y., Zhu J., Application of dry powder coating technology on sustained release capsules. International Journal of Pharmaceutics, ready to submit.

Jing Z., Ma Y., Zhu J., Application of dry powder coating technology on enteric release capsules. International Journal of Pharmaceutics, ready to submit.

Jing Z., Ma Y., Zhu J., Enteric release aspirin capsules and tablets, a comparison. International Journal of Pharmaceutics, ready to submit.

Jing Z., Ma Y., Zhu J., Large-scale dry powder coating process. International Journal of Pharmaceutics, ready to submit.