# TACK REDUCTION BY SURFACTANTS AND DEVELOPMENT OF ACRYLATE POLYMER FILMS FOR PHARMACEUTICAL COATINGS

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**A THESIS SUBMITTED IN PARTIAL FULFILLMENT**
**OF THE REQUIREMENTS FOR**
**THE DEGREE OF DOCTOR OF PHILOSOPHY**
**(POLYMER SCIENCE AND TECHNOLOGY)**
**FACULTY OF GRADUATE STUDIES**
**MAHIDOL UNIVERSITY**
**2005**

**ISBN 974-04-6148-4**

Thesis
Entitled

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was submitted to the Faculty of Graduate Studies, Mahidol University
for the degree of Doctor of Philosophy (Polymer Science and Technology)
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# ACKNOWLEDGEMENTS

The success of this dissertation can be attributed to the extensive support and assistance from my major advisor, Assistant Professor Dr. Krisda Suchiva. I deeply thank him for his valuable advice and guidance in this research.

I wish to thank my co-advisors, Associate Professor Dr. Pranee Phinyocheep and Associate Professor Dr. Satit Puttipipatkhachorn, for their meaningful advice, criticism, encouragement and providing me the research facilities.

I would like to thank Assistant Professor Dr. Jatuphorn Wootthikanokkhan, King Mongkut's University of Technology Thonburi, for his valuable criticism on my dissertation as the external examiner.

I would like to extend my sincere thanks to Professor Dr. Roland Bodmeier, Freie University Berlin, Germany, for his valuable guidance and kind support while I was doing my research in Germany.

I am grateful to all the lecturers and staffs of Faculty of Science for their valuable teaching and thanks also go to all my classmates for their help and friendship during my study.

I would like to acknowledge the Ministry of Education for scholarship and research grant during my study as well as support for doing research at the College of Pharmacy, Freie University Berlin, Germany.

My appreciation is given to all my colleagues in Faculty of Pharmacy, Srinakharinwirot University, for their endless help, encouragement and friendship. Special thanks are given to Assistant Professor Dr. Ornlaksana Paeratakul for her help and kind support.

Finally, I would like to express my gratitude to my parents and family for their entirely care and love. The usefulness of this dissertation, I dedicate to my father, my mother and all the teachers who have taught me since my childhood.

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TACK REDUCTION BY SURFACTANTS AND DEVELOPMENT OF ACRYLATE POLYMER FILMS FOR PHARMACEUTICAL COATINGS

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## ABSTRACT

This study is divided into two main sections. The objective of the first section was to investigate the ability of certain nonionic surfactants in a group of sorbitan ester in reducing the tackiness of films obtained from aqueous acrylic polymer dispersions (Eudragit®). The results from the peel tests demonstrated that glyceryl monostearate (GMS), Span 60 and Span 40 could reduce the tackiness of both Eudragit NE30D and Eudragit RS30D films. The components and mechanical properties of the films were investigated and the results indicated that these surfactants reduced the film tackiness by decreasing the polymer contents at the film surfaces, resulting in a notable reduction in the contact area of the polymers between the surfaces. The use of only 5% w/w of either GMS, Span 60 or Span 40 in the coating formulations is enough to prevent pellet agglomeration without adverse effects on film flexibility. The pellets coated with Eudragit RS30D/RL30D (9:1 w/w) did not exhibit any difference in the drug release profiles when either 100% w/w talc or 5% w/w GMS was used, whereas the formulations containing Span 60 or Span 40 gave a slightly faster release rate.

The objective of the second section was to find new copolymers, which can form enteric films in the aqueous coating process without the use of an external plasticizer. A variety of copolymer latices comprising of methacrylic acid (MA) and ethyl acrylate (EA) were synthesized by emulsion polymerization. The synthesized latices were characterized and the films from the latices were determined for their thermal properties, mechanical properties and dissolution. The results indicated that the minimum film-forming temperature (MFT) was lowered as the ratio of MA to EA decreased. The MA-EA (2:3) copolymer could form a film at the coating temperature and the film started to dissolve at pH 6.0. With the polymer coating level of 6 mg/cm$^2$, the coated tablets were very resistant to gastric fluid and the drug release in pH 6.8 buffer conformed to the requirement of the pharmacopeia. The results indicated that the MA-EA (2:3) copolymer could be used in the coating process for the design of oral delayed-release dosage forms without plasticizer required.

KEYWORDS: TACKINESS/ ACRYLIC COPOLYMER/ FILM COATING/NONIONIC SURFACTANT/ EMULSION POLYMERIZATION

200 P. ISBN 974-04-6148-4

การลดการแตะติดด้วยสารลดแรงตึงผิวและการพัฒนาฟิล์มอะคริเลทพอลิเมอร์เพื่อการเคลือบทางเภสัชกรรม
(TACK REDUCTION BY SURFACTANTS AND DEVELOPMENT OF ACRYLATE POLYMER FILMS FOR PHARMACEUTICAL COATINGS)

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## บทคัดย่อ

การศึกษานี้ได้แบ่งงานเป็นสองส่วนหลัก วัตถุประสงค์ของงานส่วนแรกคือเพื่อศึกษาถึงความสามารถของสารลดแรงตึงผิวชนิดไม่มีประจุในกลุ่ม sorbitan ester ในการลดการแตะติดของฟิล์มที่ได้จากสารกระจายตัวของพอลิเมอร์อะคริลิกในน้ำ (Eudragit®) ผลจากการทดสอบการลอกฟิล์มแสดงให้เห็นว่า glyceryl monostearate (GMS), Span 60 และ Span 40 สามารถลดการแตะติดของทั้งฟิล์ม Eudragit NE 30D และฟิล์ม Eudragit RS 30D ได้ มีการศึกษาองค์ประกอบและสมบัติเชิงกลของฟิล์มและผลที่ได้ชี้ให้เห็นว่าสารลดแรงตึงผิวเหล่านี้ลดการแตะติดของฟิล์มได้โดยการไปลดปริมาณของพอลิเมอร์ที่ผิวฟิล์มส่งผลให้พื้นที่สัมผัสของพอลิเมอร์ระหว่างผิวลดลงอย่างมาก การใส่ GMS, Span 60 หรือ Span 40 เพียง 5% โดยน้ำหนักในสูตรน้ำยาเคลือบก็เพียงพอที่จะป้องกันการเกาะกลุ่มกันของเพลเลตโดยไม่ส่งผลเสียต่อความสามารถในการบิดงอของฟิล์ม การใช้ talc 100% หรือ GMS 5% ในสูตรตำรับไม่มีผลให้เค้าโครงการปลดปล่อยยาของเพลเลตที่เคลือบด้วย Eudragit RS30D/RL30D (9:1 โดยน้ำหนัก) แตกต่างกัน ขณะที่อัตราการปลดปล่อยยาของสูตรที่ใส่ Span 60 หรือ Span 40 จะเร็วกว่าเล็กน้อย

วัตถุประสงค์ของงานส่วนที่สองคือเพื่อค้นหาโคพอลิเมอร์ตัวใหม่ที่สามารถก่อฟิล์มเอนเทอริกได้ในกระบวนการเคลือบระบบน้ำโดยไม่ต้องอาศัยพลาสติไซเซอร์ภายนอกช่วย เลเทกซ์โคพอลิเมอร์ชนิดต่างๆที่ประกอบด้วย methacrylic acid (MA) และ ethyl acrylate (EA) ได้รับการสังเคราะห์ขึ้นโดยวิธี emulsion polymerization มีการตรวจสอบลักษณะเฉพาะของเลเทกซ์ที่สังเคราะห์ขึ้นรวมทั้งทดสอบสมบัติเชิงความร้อน สมบัติเชิงกล และการละลายของฟิล์มที่ได้จากเลเทกซ์ ผลการทดสอบชี้ให้เห็นว่าค่า minimum film-forming temperature (MFT) ต่ำลงเมื่ออัตราส่วนของ MA ต่อ EA ลดลง โคพอลิเมอร์ MA-EA (2:3) สามารถก่อฟิล์มได้ที่อุณหภูมิการเคลือบและฟิล์มที่ได้เริ่มต้นละลายที่พีเอช 6.0 ที่ระดับการเคลือบ 6 มก./ซม.$^2$ เม็ดยาที่เคลือบสามารถทนต่อน้ำย่อยในกระเพาะได้อย่างดีและการปลดปล่อยยาในบัฟเฟอร์ที่พีเอช 6.8 ก็เป็นไปตามข้อกำหนดของเภสัชตำรับ ผลที่ได้จากการทดลองชี้ให้เห็นว่าโคพอลิเมอร์ MA-EA (2:3) สามารถนำมาใช้ในกระบวนการเคลือบเพื่อสร้างรูปแบบยาชนิด delayed-release ได้โดยไม่จำเป็นต้องใส่พลาสติไซเซอร์

200 หน้า ISBN 974-04-6148-4

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ATBC | acetyltributyl citrate |
| ATR-IR | Attenuated total internal reflectance-Infrared |
| CMC | critical micelle concentration |
| $^{o}$C | degree Celsius |
| DMA | dynamic mechanical analyzer |
| EA | ethyl acrylate |
| et al. | et alii, and others |
| FTIR | Fourier-transform infrared |
| g | gram |
| GMS | glyceryl monostearate |
| h | hour |
| HCl | hydrochloric acid |
| HEM | hydroxyethyl methacrylate |
| i.e. | id est, that is |
| kg | kilogram |
| L | liter |
| MA | methacrylic acid |
| MFT | minimum film-forming temperature |
| MMA | methyl methacrylate |
| mg | milligram |
| min | minutes |
| ml | milliliter |
| mm | millimeter |
| MPa | megapascal |
| µg | microgram |
| µm | micrometer |
| N | Newton |
| N | normal |

# LIST OF ABBREVIATIONS (cont.)

| | |
|---|---|
| nm | nanometer |
| R.H. | relative humidity |
| rpm | revolutions per minute |
| $r^2$ | coefficient of determination |
| S.D. | standard deviation |
| sec | second |
| TEC | triethyl citrate |
| $T_g$ | glass transition temperature |
| USP | The United States Pharmacopeia |
| UV | ultraviolet |
| w/w | weight by weight |

# CHAPTER 1
# INTRODUCTION

The application of a polymer film coat is a common practice in the preparation of sustained and controlled release dosage forms (1). Recently, aqueous polymeric dispersions have gained popularity and are replacing solvent-based coating systems due to their lower toxicity level and environmental friendly standpoint (2,3). The formation of a continuous film from the aqueous polymeric dispersion arises from the coalescence of the individual latex particles, which is dependent on the minimum film-forming temperature (MFT) of the polymer. If the polymer dispersion is cast or sprayed below its MFT, a friable discontinuous film or powder compact may form and the requirement for the controlled release will not be achieved. To ensure the formation of homogeneous polymer layers on the substrates during the coating, the product bed temperature is recommended to be 10-20 $^{o}$C above the MFT (4). Practically, the bed temperature should be kept between 30-35 $^{o}$C, therefore the MFT of the latex at lower than 20 $^{o}$C is preferable for the coating.

In the coating of dosage forms by aqueous polymeric dispersions, sticking of the coated substrates always occurs simultaneously during the coating or the curing process. This is due to the tackiness of the films. This tackiness creates a tremendous handling problem as the coated substrates stick to each other as well as to the wall of the coating chamber, and sometimes irreversible agglomeration of several beads or the complete batch can occur, especially at higher product temperatures or higher plasticizer content in the coating formulation (5). A fine balance has to be found between sufficiently high temperatures and non- agglomeration (6). Usually glidants or anti-tacking agents are added to coating dispersions in order to reduce sticking of coated substrates. A polymer formulation with a low tackiness shows less tendency for film coating defects, it results in an easier handling of the coating process and also reduces the process time. Different substances have been recommended for this purpose. Mostly, talc is used, but some adverse effects have been reported such as the differences in quality (7,8), high amount (20-200% based on dry polymer) used

leading to sedimentation in tanks, tubes and clogging of the spray system which cause processing inconvenience, incompatibilities with certain drugs etc. Other substances like magnesium stearate or kaolin have also been used, but are no more advantageous than talc. Colloidal silica is another choice for reducing the tackiness of films. It was found that the amount of 30-60% of colloidal silica (based on dry polymer) was effective and no sticking tendency or pellet aggregation was observed during the application of the films. Moreover, the sedimentation problem could be eliminated. Nevertheless, due to the hygroscopic property of this substance, the release profile of the coated drug substances could be changed (9,10). Some techniques have also been applied to reduce the tackiness of polymeric films. For example, Yuasa et al. suppressed the agglomeration of coated particles in fluidized bed coating system by adding various amounts of 14 kinds of salts in the Hofmeister series into the HPMC aqueous coating solution (11,12). However, this method could not be applied in the case of aqueous dispersions due to the difference in film formation mechanism between polymer solution and dispersion system. Harris et al. added the process of overcoating the pellets with a water-soluble film after the coating with pseudolatex system. The curing time was reduced and the pellets did not exhibit the tackiness associated with the non-overcoated preparation (13).

The use of surfactants as effective anti-tacking agents seems to start from the work of Petereit et al (14), who found that some hydrophobic non-ionic emulsifiers having HLB values between 2.5 and 7 showed a positive result in reducing the tackiness of acrylic polymer films. Glyceryl monostearate (GMS), a common excipient with an HLB value of 3.8 (15), showed an excellent anti-sticking property with only a little amount of 2-10% w/w (based on dry polymer). Besides GMS, sorbitan esters, a series of mixtures of partial esters of sorbitol and its mono- and di-anhydrides with fatty acids, are widely used in cosmetics, food products, and pharmaceutical formulations as lipophilic nonionic surfactants. They are mainly used in pharmaceutical formulations as emulsifying agents in the preparation of creams, emulsions, and ointments for topical application and are generally regarded as nontoxic and nonirritant materials (16). It is possible that some surfactants in a group of sorbitan esters can show similar anti-sticking property as GMS.

Among various types of aqueous polymeric dispersions, acrylate polymers and their derivatives, collectively known as Eudragit® polymers, were the first synthetic polymers used in pharmaceutical coatings as aqueous polymeric dispersion (17). They have been used as pharmaceutical coatings for over 30 years (18). These films have excellent mechanical strength, good flexibility, and good aesthetic qualities (19). Processing of some Eudragit polymeric dispersions is frequently associated with extreme tackiness during the coating operation, especially the Eudragit NE30 D, a copolymer of ethyl acrylate (EA) and methyl methacrylate (MMA) at a ratio of 2:1. There have been many previous studies investigated the adhesive properties of acrylate polymer films on substrates (20-25). Some focused on tack behavior of coating solutions and the measurement (26-32). Only little work, however, aimed at the tackiness of acrylate polymer films and its mechanism. Therefore, trying to reduce the tackiness of the acrylate films and knowing their mechanisms is a promising task.

Plasticization is a process to lower glass transition temperature ($T_g$) of the polymer, resulting in many property changes, such as mechanical properties, permeability, solubility and adhesiveness (21,33-35). However, this process can also lower the MFT as the inter-diffusion of the polymer molecules occurs easier when the $T_g$ is lowered. External plasticizers are high boiling liquids or solids that can lower the $T_g$ of the polymers. For the plasticizer to be effective, it must be compatible with other ingredients in the formulation and must also be permanent, both initially and during storage (36). Nevertheless, some experiments showed that fairly water-soluble plasticizers could leach out from the films and cause change in the drug release (37-40). Some plasticizers caused instability of the coating dispersion due to physical interactions with other ingredients (41,42). Time for plasticization of each plasticizer also varies from a few hours to more than one day (43,44). Type and concentration of plasticizers also have significant effects on the drug release pattern (45-51).

Apart from introducing external plasticizer, internal plasticization by directly modifying the chemical structure is another method to lower the $T_g$ and MFT of the polymer. The advantage of this method is that the drawback of using the external plasticizer could be eliminated. The whole time and step of the coating process are also shortened. However, change in the polymer properties must be carefully investigated, as this would always happen.

Among the polymers used for the enteric coating, methacrylic acid copolymer type C dispersion USP (Eudragit® L 30D-55, Kollicoat® MAE 30D, Eastacryl® 30D) has been acceptable as an effective enteric film former for many decades. This copolymer comprises of methacrylic acid (MA) and ethyl acrylate (EA) at a ratio of 1:1. Although the $T_g$ of this polymer is around 107 $^oC$, its MFT is only around 27 $^oC$. In the event the MFT is far lower than the $T_g$, this could be contributed to the effect of the dispersing agent (water) that can act as a temporary plasticizer (4). Since the MFT is still slightly higher than the optimal MFT for the coating, 10-20 % plasticizer (based on polymer mass) is required in the coating formulation. However, it is possible that only minor change in the chemical structure might lower the MFT of the polymer to an optimal level for the coating. If so, an external plasticizer might be no longer required in the coating formulation. Many previous studies focused on the application and properties of Eudragit L30D-55 (40,52-57). Some studies compared this copolymer with other commercial copolymers for enteric coating purpose (58-61). Only few studies, however, started from synthesizing new copolymers for pharmaceutical purpose (62-63). Therefore, the development of new copolymers having better properties for pharmaceutical coating is a challenging task

The work in this study was divided into two main parts. The first part was an investigation of the anti-tacking property of selected surfactants. The objectives were as follows:

1. To find the surfactants from a series of sorbitan esters which have good anti-tacking property for the acrylate polymer films.

2. To study the properties and mechanisms of the surfactants in reducing the tackiness of the acrylate polymer films.

3. To study the effects of the new anti-tacking agents on the release of drug from the pellets coated with the acrylate polymer films.

The second section was to develop a new aqueous colloidal dispersion of acrylic copolymers. The objectives were as follows:

1. To synthesize new acrylic copolymer latices which have good film forming property.

2. To evaluate the properties of the films obtained from the synthesized latices.

3. To study the enteric property of the tablets coated with the synthesized latices.

# CHAPTER 2
# LITERATURE REVIEW

## **Aqueous polymeric film coating** (33, 64, 65)

Film coating is an important process to develop the dosage forms. The objective is to apply a thin polymer film onto the surface of a solid substrate in order to improve the physical and chemical properties. The substrates here may be tablets, capsules, pellets, granules, or particles. Typically, the polymer film thickness is approximately 25 to 100 μm and is normally created by spraying. Nowadays, the spraying conditions can be optimized by an automatic coating machine, which gives much better film smoothness and homogeneity. Recently, the fluid-bed spraying process has also been introduced and become important for the coating of smaller particles.

In the past, most of the spraying process was based on the organic solvent systems and the polymer was dissolved in one or a combination of organic solvents. However, when film coating was employed more and more as a number of the dosage forms to be produced increased, the organic solvents became a problem due to the high cost of air pollution management. A number of water-soluble film formers were introduced, such as cellulose derivatives. For example, methylcellulose (MC), hydroxypropyl cellulose (HPC), and hydroxypropyl methylcellulose (HPMC) were employed in the grades of low molecular weight to reduce the viscosity of the coating solutions. In 1972, methacrylic acid copolymers were introduced as enteric-film formers (66). A pseudolatex of ethylcellulose was consecutively developed in 1977 (67). Micronized HPMCP (HP®55 F) was recommended for enteric coating formulations in water. An aqueous cellulose acetate phthalate (CAP) pseudolatex (Aquateric®) was introduced by FMC (Philadelphia) in 1983 (68). Polyvinyl acetate phthalate (PVAP) was launched to the market as an aqueous dispersion by Colorcon under the trademark Coateric®. Recently hydroxypropyl methylcellulose acetate succinate (HPMCAS) has become available as an aqueous colloidal coating material (Aquot®) (37). Permeable coatings can be also prepared from aqueous dispersions of ammoniomethacrylate copolymers (Eudragit® RL/RS 30D) (69). In principle, all-

important coating materials used today can be in the form of aqueous formulations. Generally, the polymers can be divided into two classes: water-soluble polymers and water-insoluble or pH-dependent soluble polymers.

**Formulation of films from polymeric solutions**

In the case of an aqueous solution system, the internal structure of the film formed by the coating essentially depends on the rate of solvent evaporation, which is controlled by the latent heat of vaporization. Film formation generally comprises initial rapid evaporation of solvent from the atomized droplets of coating liquid, causing an increase in polymer concentration and contraction in volume of the droplets. Following by further loss of solvent from the film at a slower rate which is now controlled by the rate of diffusion of solvent through the polymer matrix. Then, the polymer molecules are immobilized at the "solidification point". After that, the rate of solvent evaporation is very much slow. Solvent loss from the polymer matrix is governed by the amount of space (or the free volume) between the polymer molecules. As solvent loss continues, the glass-transition temperature ($T_g$) of the polymer films increases and the free volume decreases. Finally, the free volume becomes so small that the further solvent loss is almost impossible. Theoretically, the absolute loss of the solvent can take place only when the polymer is heated up to above its $T_g$. However this condition rarely occurred during the coating with most polymers, thus it is not so easy to obtain solvent-free films from commonly used polymers.

**Formation of films from aqueous polymeric dispersions**

Film formation from aqueous polymeric dispersions is clearly different from that in the case of solution. It requires coalescence of polymer particles into a continuous film. Water evaporation is a rapid process, whereas coalescence of the polymer takes much more time and may extend for several weeks or months, especially when the formulations are not so appropriate. The mechanism of film formation from an aqueous polymeric dispersion is quite complex, and many theories have been proposed to explain the process. In conclusion, this process involves rapid evaporation of water, causing the particles of dispersed polymer to be brought into close contact with one another. After that, the pressure was developed until be able to overcome repulsive forces between particles and cause deformation of the polymer particles. The gradual

coalescence of the polymer particles finally occurs as a result of the movement of polymer molecules across the interfaces between particles.

**Film coating materials:**

**Polymers**

The polymer or film former is the most important ingredient in the film-coating formulations. It directly affects the final properties of the coating. The evolution of the coating therefore depends upon the innovation of new polymeric coating materials. Generally, polymers are not well-defined substances. As in case of macromolecules, difference in molecular weight, resulting in different properties is available. Therefore, grades of polymers (as determined by viscosity or molecular weight) have to be specified for using. Batch-to-batch variation also often occurs as a result of the polydisperse nature.

For the conventional film-coating which the main purpose is to improve product appearance or dosage form stability. The most popular class of polymers used is cellulose derivative such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) etc. Since most of them can be dissolved in both water and organic solvent, thus the coating has been shifted to aqueous system. Polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) are not frequently used as the major film formers in the formulations. The films obtained from PVP are brittle and hygroscopic, whereas PEG films are waxy, hygroscopic and soft. They are more appropriate to be pore formers or plasticizers in the formulations. In Europe, the acrylic polymers are extensively employed. Dimethylaminoethyl methacrylate-methacrylic acid ester copolymer is soluble only at low pH and is favored to use for taste masking of the tablets. Ethyl acrylate-methyl methacrylate copolymer is water-insoluble, and is available as aqueous latex-coating systems.

For the enteric coating which the objective is to maintain the dosage forms in the stomach, but allow them to break down in the small intestine, the coating polymers must be resistant to the gastric juice in the stomach which pH is approximately 1, and be readily soluble when pH of the gastro-intestinal fluid reaches approximately 6.8 in the small intestine. The examples of the polymers used for this purpose involve cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose phthalate (HP), and hydroxypropyl methylcellulose acetate succinate

(HPMCAS). For the group of synthetic polymers, methacrylic acid copolymers are most favorable, such as mathacrylic acid-ethylacrylate (1:1) copolymer, methacrylic acid-methyl methacrylate (1:1, 1:2) copolymers.

In case of sustained-release purpose of the coating, the polymeric film-formers are normally insoluble but permeable in water. Therefore, aqueous dispersion coatings are favorable for this purpose. The examples of these polymers are ethylcellulose, shellac, polyvinylacetate, and acrylic ester copolymers.

**Plasticizers**

Most of the polymers used in pharmaceutical film coating are amorphous. One characteristic of these polymers is that as the temperature is lowered, the $T_g$ is reached. The polymers will be in a glassy state and behave like an organic glass. The hardness, stiffness, brittleness and toughness increase dramatically in this state. Because the $T_g$s of many polymers used in film coating are high and exceed the coating temperature, it is often necessary to reduce the $T_g$s of these polymers, especially in the formulations of aqueous polymeric dispersions which the polymer coalescence strongly depends upon the polymer mobility that is directly related to the $T_g$. The process to reduce the $T_g$ of the polymer is known as plasticization. Plasticizers reduce the $T_g$s of amorphous polymers and also improve flexibility, which is one of the main properties of the films. The basic properties of the plasticizer are permanence and compatibility. That is the plasticizer should have low volatility and stays permanently among the polymer molecules. Compatibility means that the plasticizer must be miscible with the polymer. In another word, the polymer-plasticizer intermolecular forces should be similar to those exist in the polymer molecules themselves.

In principle, plasticizers can be classified into two categories: internal and external plasticizers. Internal plasticizing involves the chemical modification of a basic polymer to alter the physical properties of the polymer. Changes in the degree of substitution, the type of substitution, and the polymer chain length influence the physical characteristics of the polymeric film. However, the formulator always has to manipulate with the commercial polymers that are available, therefore the film properties are often altered by the addition of external plasticizers. The external plasticizer can be another polymer, a nonvolatile liquid, or even an aqueous solvent. The plasticizer changes the polymer-polymer interactions and improves the flexibility

of the film by relieving molecular rigidity. The examples of plasticizers are propylene glycol, glycerol, polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate etc. Several insoluble plasticizers may be incorporated in combination with one or more water-soluble plasticizers for the water-soluble polymer formulations. Some of these ingredients are hygroscopic and retain water in the films. Water itself can be an effective plasticizer, but the concentration will vary depending on environmental temperature and relative humidity. Similarly, the properties of the film will be affected by the change of the storage conditions.

**Opaquants and colorants**

In case of the conventional film coating, to improve the elegance of the dosage forms, color is always added in the coating formulations. As the appearance of the product is the only product property a customer can assess, color uniformity and color stability are extremely important. The colorant can be either solubilized in the solvent system or suspended as insoluble particles. The colorants used in the coating formulations are generally provided by certified Food, Drug and Cosmetic (FD&C) or Drug and Cosmetic (D&C) dyes and lakes. These are synthetic colorants. Lakes are prepared from dyes by precipitating the colorant with alumina or talc carriers. Lakes are water-insoluble and provide the most reproducible tablet colors. Commercially available lakes generally contain 10 to 30% dye contents, but some lakes may contain up to 50%. Although the lakes are water-insoluble, the dye can be removed from the carrier through the use of solvent systems that dissolve the dye. The inorganic colorants and opaquants are chemically very stable. However, most of them lack color intensity. The natural colorants are less stable than the synthetic dyes and lakes. The most stable natural colorants are caramel and carmine.

Commercial color concentrates and film-coating concentrates are available in the market. They provide convenience and less batch-to-batch color variation. To achieve reproducible colors, the insoluble colorants must be milled, and matched with a color standard. The two commercial materials for aqueous film coating are Opaspray® (an opaque color concentrate for film coating) and Opadry® (a complete film coating concentrate), available from Colorcon.

**Supplemental coating ingredients**

Some other ingredients are always added into the coating formulations to stabilize or improve the products. The ingredients used in a film are generally tasteless, hence, sometimes flavors or sweeteners are added to enhance the esthetic properties of the products or to mask unpleasant odors or tastes. Surfactants may be introduced to solubilize some ingredients, to reduce the surface tension of the coating formulations, and to facilitate dissolution of the films. The stability of some colorants can be significantly improved by the addition of antioxidants such as ascorbic acid or alpha tocopherol. Preservatives may be added in case the ingredients in the formulations are prone to microbial growth. Antimicrobials that are routinely used include parabens, sorbic acid, and benzoates.

## **Polymethacrylate coating systems** (4, 19)

Copolymer latices consisting of methacrylic acid (MA), methyl methacrylate (MMA), or ethyl acrylate (EA) have been introduced for a long time in paints and food packaging industries. In early 1970s, copolymers of EA with MA for enteric coating of pharmaceutical dosage forms were developed by Lehmann and Dreher (66). The neutral ester copolymer poly(EA-MMA) 2:1 was used in the coating of particles for sustained-release preparations, and used with high amounts of hydrophilic additives in the coating of tablet cores for protective purpose with fast disintegration (70). Hydrophilic copolymers containing quaternary ammonium groups could be transformed into latex-like aqueous dispersions by direct emulsification of the bulk polymers in hot water (71). The films obtained from these copolymers exhibit good mechanical strength, good flexibility, and good aesthetic quality (19). At present, these acrylic polymers known as Eudragit® are widely used in the coating of pharmaceutical dosage forms. The following is a review of the structures, properties and applications of these copolymers.

**Methacrylic acid copolymers**

Copolymers of MMA and EA as ester components with MA are used as enteric coatings because they contain carboxylic groups that are transformed to carboxylate groups in the pH range of 5-7 by salt formation with alkali or amines. In pure water and diluted acids they form water-insoluble films resistant to gastric juice. Their

dissolution pH depends primarily on their content of carboxylic groups. Poly(MA-MMA) 1:1 (Eduragit L 100) dissolves at pH 6; poly(MA-MMA) 1:2 (Eudragit S 100), above pH 7. When the ester component is EA which is more hydrophilic in case of poly(MA-EA) 1:1 (Eudragit L 30 D-55, Eudragit L 100-55), the films dissolves above pH 5.5. All of these products are produced by emulsion polymerization in water, and the solid powders are obtained by spray drying. The products are described in USP XXI/NF XVI in the monograph Methacrylic Acid Copolymers and are distinguished by their MA content as types A, B and C. Type A contains 46.0-50.6% MA units (dry basis) and is equivalent to MA-MMA 1:1 copolymer (Eudragit L 100) with a molecular weight of 135,000. Type B contains 27.6-30% MA units and is equivalent to MA-MMA 1:2 copolymer (Eudragit S 100) with the same molecular weight. Both polymer powders are soluble in isopropanol, acetone, methanol, ethanol, and mixtures of alcohol-water. With the addition of 5 mol % of alkali or organic bases, the polymer powders can be redispersed in water to latices with approximately 30% solids. Type C is in a latex form and is equivalent to MA-EA 1:1 copolymer (Eudragit L 30 D-55) with a molecular weight of 250,000. The latex has a solids content of 30% and contains some emulsifiers. The commercial product Eudragit L 100-55 is prepared by spray drying of Eudragit L 30 D-55. The powder can be redispersed in water by the addition of 3-5 mol % alkali of organic bases to obtain latices with 30-40% solids. After film formation, both latices have the same gastroresistant effects and show the same dissolution properties. Scheiffele et al. (72) compared MA-EA 1:1 copolymer latex with other enteric film formers such as HPMCAS, HPMCP, CAP and found that MA-EA 1:1 copolymer had the smallest particle size and particle size distribution. The isolated films also did not display any tack.

Copolymers of methacrylic acid are brittle, so addition of plasticizer is essential to get effective enteric coatings without cracks. The film formation is also improved, especially in latex systems. The softening effect of plasticizer on the polymeric latex particles results in a lower MFT. As the dispersing agent (water) can act as a temporary plasticizer, the MFTs of aqueous dispersions of these copolymers are low compared with their $T_g$s. For example, the $T_g$ of MA-EA 1:1 copolymer is at 107 $^oC$, whereas the MFT is at 27 $^oC$. Poly(MA-EA) 1:1 can be applied in the form of a latex under normal working conditions, with the addition of 10-20% plasticizer, and good

film formation can be obtained. The polymers containing MMA as a comonomer (Eudragit L 100, Eudragit S 100) show very high $T_g$s and also high MFTs. To achieve good film formation and also enteric properties of coating under usual working conditions, 40-50% triethyl citrate must be added (73). The effects of other plasticizers such as dibutyl sebacate, dibuthyl phthalate, triacetin on the film formation, film properties, and drug release of the dosage forms have also been extensively studied (37, 74-77). In some cases, stabilizing agents are used in latex formulations of methacrylic acid copolymers and they are preferably noionic emulsifiers such as sorbitan esters, which are also used in the emulsion polymerization process. They also act as plasticizers and are normally incorporated in the formulations to improve their compatibility. Sorbitan esters are also useful as stabilizer in the redispersion process of polymer powders to anionic methacrylate latexes, but foam is often generated. This can be controlled by the addition of very small amounts of antifoaming agents such as silicone.

Some solid additives acting as glidants or anti-tacking agents are recommended in all coating formulations to reduce sticking effects during film formation and drying. The most effective glidant is talc, which also improves the smoothness of the film. An amount of 25% calculated on a dry polymer basis is sufficient. With equal amounts of talc and polymer, opaque coatings are obtained. Gastroresistance and enterosolubility of the films are not affected by the addition of talc, in most cases improved. With very high amounts of talc, i.e., more than 200% based polymer weight, the permeability of the films is increased and dissolution in intestinal fluid delayed. Glyceryl monostearates (GMS) provide an excellent alternative to talc or magnesium stearate as glidants (14). Due to its high efficacy, only 2-15% GMS based on dry polymer is necessary to get comparable effect. Polymethacrylates exhibit high pigment binding capacity. Up to approximately 2 parts of solid additives can be incorporated in 1 part of dry polymer without any significant changes on the film characteristics such as mechanical stability, gloss, or the dissolution properties. Magnesium stearate, which is often used in organic coating formulations instead of talc, is incompatible with these latices. This is because of the reaction between magnesium ions and the carboxylic groups of the polymers.

The films obtained from methacrylic acid copolymers are hard and brittle, since their $T_g$s are high as discussed above. Addition of plasticizer is necessary to increase the flexibility up to more than 15% elongation at break. Another method to extend the flexibility is the combination with a soft polymer such as poly(EA-MMA) 2:1. The films obtained from these latex mixtures become flexible. However their tensile strength decreases (78). The permeability of these films to water vapor is low compared with cellulose derivatives for enteric coating (79). List and Laun (80) found that the permeability was even lower with films from latices than with films from organic solutions. The stability of methacrylic acid copolymers against hydrolysis is very high. Dry films are also chemically stable up to about 150°C (4).

The main application of the methacrylic acid copolymers is the enteric coating of tablets or multiparticulate dosage forms such as pellets, granules, or powders. The tablets to be coated should have a minimum hardness of 50 N and a friability of less than 0.1%. Enteric coatings require 3-5mg/cm$^2$ of dry polymer, which is equivalent to ~30 μm film thickness. The inclusion of pigments and other additives in the given amounts will not affect enteric properties of the films. Lehmann and Petereit (81) studied the drug release from tablets, pellet, and granules coated with Eudragit L 100 and Eudragit S 100 and found that the coated cores showed excellent resistance to simulated gastric fluid. Less than 5% of drug was released at pH up to 6.8 from preparations coated with Eudragit S 100. Release at pH 7.2-7.5 was complete within 30-45 min. Dissolution between pH 6 and 7 could be controlled by mixing these latices together. Methacrylic acid copolymers also have been studied with various drug cores such as diclofenac pellets, ketorolac tromethamine tablets, phenytoin sodium microcapsules, pancreatin pellets, theophylline microcapsules, chlorpheniramine maleate tablets, ibuprofen in soft gelatin capsules, nitroglycerin tablets, bisacodyl pellets, theophylline granules, aspirin crystals, and metronidazole pellets (82-93). Pulsatile release tablets could also be developed by coating the cores with ethylcellulose/Eudragit L (94). The compaction properties of the pellets coated with Eudragit L 30D-55 were determined by Felton et al. (95). The effect of various excipients on the protection of coated pellets was also investigated by Menendez and Sakr (96).

Occasionally, protective coatings are required. When these copolymer latices are applied in small amounts, about 1 mg/cm$^2$, which are not sufficient to resist gastric juice, and when some disintegrants are incorporated into the tablet core to stimulate breaking up of the film by swelling, such coatings give very good moisture protection, and disintegration time of the coated cores is retarded for only about 10-30 minutes in gastric fluid.

**Methacrylate ester copolymers** (97)

The products in this group can be classified into 2 minor classes: neutral methacrylate ester copolymer and hydrophilic methacrylate ester copolymers. These copolymers are insoluble in pure water, dilute acids, buffer solutions, or digestive fluids over the entire pH range.

Poly(EA-MMA) 2:1 (Eudragit NE 30 D) is a neutral methacrylate ester which is an aqueous latex produced by emulsion polymerization. The molecular weight is around 800,000. The latex contains 30% solid including some emulsifier. The polymer Eudragit NE 30D is not available as a solid. A sticky powder that tends to form lumps can be prepared by freeze-drying. The polymer has no functional groups and is practically neutral. Therefore the films obtained are insoluble in water and in aqueous buffer solutions over the entire physiological pH range. However they can swell in water and give permeable membranes. The permeability is independent of the pH. Since the solid powder prepared by freeze-drying or other drying processes is very sticky, it is not commercially available. The polymer obtained from the latex is used mainly for sustained-release and transdermal drug formulations. The MFT of the latex is around 5 °C, and a soft, flexible film is formed at room temperature without any plasticizer. Normally no reactions or absorptive effects are observed when the polymer comes into direct contact with drug substances, so it is a very useful material for embedding drugs, for granulation processes, and for protective coatings. Changes in pH do not alter the properties of the polymer, and the latex is not very sensitive to the incorporation of drugs or excipients. The pigment binding capacity of the polymer is very high, so that up to ~2-3 parts by weight of additives can be incorporated in 1 part by weight of dry polymer without affecting the film properties. The latex is compatible with talc, titanium dioxide, color lakes, iron oxide pigments, and magnesium stearate, when these additives are suspended in water before mixing with the latex. Optimal

stability is in the pH range of 7-8.5, but the latex can also be acidified if necessary by adding dilute acid slowly under moderate stirring. Many solid additives are useful as lubricants (glidants, anti-tacking agents) to reduce the stickiness of the polymer during the film forming process and during storage. A minimum of approximately 25% of such additives calculated on dry polymer basis should be used in the formulations. To increase the permeability of film layers or to increase the disintegration tendency of matrix structures of drug formulation, several water-soluble or water–swellable substances can be added, such as sucrose, lactose, and other saccharides, starch, micronized cellulose, polyvinylpyrrolidone, polyvinylalcohol, and carbowaxes . Colloidal silica is effective as an additive to prevent sticking of small coated particles during storage, especially at elevated temperatures and high humidity. Disinfection was achieved by adding 5 ppm of active chlorine in the form of hypochlorite solution. Preservatives are not recommended due to the risk of incompatibility with components in the formulation.

The hydrophilic methacrylate ester copolymers are created from the introduction of hydrophilic quaternary ammonium groups into the structure by copolymerization with trimethylammonioethyl methacrylate chloride (TAMCI). The permeability of methacrylic ester copolymers was modified. Films of poly(EA-MMA-TAMCl) 1:2:0.2 are more permeable and films of poly(EA-MMA-TaMCl) 1:2:0:1 are less permeable than those of poly(EA-MMA) 2:1. The copolymers are produced by bulk polymerization and are commercially available as solid granules (Eudragit RL 100, Eudragit RS 100) or as milled polymer powder. When the solid polymer are directly emulsified in hot water without any additive, the formation of a latex-like aqueous dispersion is caused by the hydrophilic ammonium groups. The commercial aqueous dispersions with 30% polymer content (Eudragit RL 30D, Eudragit RS 30 D) contain 0.25% sorbic acid as a preservative but no emulsifier. The MFTs of these dispersions are between 40 °C and 50 °C, thus the addition of 10-20% plasticizer is necessary to reduce the MFT to below 20 °C. The most effective plasticizers are triethyl citrate and triacetin. PEG is not effective on the MFT. Water-insoluble plasticizer could be added in the form of emulsions in a 1% aqueous solution of polysorbate 80. In this case the migration of the plasticizer into the polymer phase take some time to come to equilibrium (98). Mild stirring of the mixture of plasticizer emulsion and the latex is

recommended for about 24 h. There is obviously some influence of added plasticizer on the permeability of the resulting films. The addition of plasticizer is important to increase the flexibility of the films but also to lower the MFT which facilitates coating processes under moderate conditions. The compatibility of these latex-like dispersions with the widely used additives: talc, titanium dioxide, pigments, and others is generally acceptable and very similar to that described above for the neutral poly (EA-MMA) 2:1 latex. Particle shape and size of the pigments also influence the release properties of the pellets coated with Eudragit RS 30D (99). The pH of the dispersion, which is normally in the range of 5-6, should be kept nearly constant and additives added preferably in the form of aqueous suspensions or solutions of the same pH.

The films obtained from methacrylate ester copolymer latices are soft and more flexible than those obtained from the methacrylic acid copolymers. Poly (EA-MMA) 2:1 especially is a very soft and flexible material and any added plasticizer will cause undesirable sticking effects in film coating processes. The flexibility of the films from this polymer is approximately 600% in term of elongation at break. Sticking of coated substrates can occur during storage above 45 °C or at high humidity even around 40 ° C. On the other hand, latices of this polymer are very useful as granulating agents and as soft components in latex mixtures.

The films of poly (EA-MMA-TAMCI) are less flexible. Even with 10% plasticizer they show some brittleness. Addition of 20% plasticizer results in a considerable increase in the elongation of break whereas tensile strength at break is lowered. The amount of quaternary ammonium groups, despite their low content in the neutral ester in the polymer chain, has high influence on the permeability of the films. The diffusion rate of dissolved drug molecules through membranes of poly (EA-MMA-TAMCI) 1:2:0.2 (Eudragit RL 30D) is so high that the release from coated tablets or particles with a film thickness of 10-30 μm is very fast and normally reaches nearly 100% within 10-30 min. Such films can be used as fast-disintegrating protective coatings. The less hydrophilic film of poly(EA-MMA-TAMCI) 1:2:0.2 (Eudragit RS 30D) contains only half of this amount of quaternary ammonium groups and strongly retards the dissolution of the coated cores. The diffusion rate through such films depends on the specific nature of the drug molecules, such as molecular size, steric structure effects, and interactions with water as a solvent, and eventually on

the polymer film microstructure. The permeability of films can be influenced by the added phasticizer (100). Hydrophobic phasticizers such as tributylacetyl citrate and dibutyl phthalate show the lowest permeability. Triethyl citrate, triacetin and tributyl citrate show medium values, while triethylacetyl citrate and diethyl phthalate give higher permeability. Films from aqueous dispersions are less permeable than those from organic solution. The permeability and drug release properties of the films are significantly influenced by the application conditions (101,102). The product temperature is especially important for optimal film formation. Most effective and reproducible retardation of theophylline release from pellet cores was achieved in fluid bed equipment at 25-30 °C, which was 10-20 °C above the MFT of the coating formulation. The retarding effects of films from poly (EA-MMA) 2:1 (Eudragit NE 30D) are similar to those of RS films, so that it corresponds to RS-RL mixtures of approximately 9:1-8:2 with respect to the diffusion of drugs. Whereas Eudragit RL coatings give comparable moisture protection but less retardation effects than Eudragit NE 30D. Baert and Remon (103) found that the water vapor permeation rates of Eudragit NE 30D were dependent on film composition and thickness and thermal treatment.

Eudragit RS 30D and RL 30D can be mixed together in any proportion. In addition, it is also possible to mix these polymers with the Eudragit NE 30D (104, 105). It is recommended that for this purpose some neutral surfactant be added as stabilizer to the emulsifier-free Eudragit RL/RS dispersions. One to three grams of polysorbate or isononylphenylpolyoxyethylene glycol ether are sufficient to stabilize 100 g of 30% dispersions. Before mixing, the Eudragit NE30D is first brought to pH 5-6 by the addition of small amounts of diluted acid. Mixing is best achieved by slowly pouring one dispersion under moderate stirring into the other. There is no limitation on the mixing ratio. The main purpose of mixing these ester polymers is to modify the permeability and to use the soft poly(EA-MMA) 2:1 as a polymeric plasticizer to optimize film formation and mechanical properties. For the same purposes, this polymer can be used in mixtures with ethylcellulose latices. High-speed stirrers are not necessary for mixing and can sometimes cause coagulation of the latex system when high shearing forces are generated. Incorporation of air bubbles and foam formation should be prevented. Precautions should be taken when mixing

anionic dispersions such as methacrylic acid copolymer latices with the Eudragit RS 30D or RL 30D to reduce the interactions between the ionic groups in the polymers. The mixture can be used within the next 2 days though a soft sediment is formed within a few hours. The agglomerates are normally not larger than ~2 μm, but they can be resuspended easily by moderate stirring and form acceptable films under the normal working condition. Mixed films of anionic and hydrophilic polymers are sometimes useful when the solubility of the coated drug substance decreases with increasing pH, which is observed mainly with salts of weak amines. In mixed films the enterosoluble component dissolves in neutral to weakly alkaline intestinal fluid, the permeability of the coating increases and compensates for the reduced solubility of the drug, so that a more constant release rate over the whole pH range might be achieved. For this purpose mixtures of anionic polymers with the neutral poly(EA-mmA) 2:1 (Eudragit NE 30D) as described earlier can also be used. The mechanical properties as well as drug permeation of the films from these latex mixtures have been extensively studied (106, 107).

For coating of tablets, Eudragit RL 30D is used mainly for protective layers and for coloring. Some delayed disintegration and sustained-release effects are expected if Eudragit RS 30D or NE 30D are used, since they form films with low permeability. Also, incorporation of disintegrants into the tablet cores will stimulate disintegration and rupture of the water-insoluble film coatings. Eudragit NE 30D has recently been introduced to prepare microporous membranes on potassium chloride tablets (108). Nearly constant release pattern was achieved using calcium phosphate as a pore-forming material, which is soluble at low pH. Floating minitablets could be developed by coating with the mixture of Eudragit NE 30D and RS 30D (109). Eudragit RS 30D can also be applied to develop pulsatile drug delivery system based on soft gelatin capsules (110). For sustained-release coating of small particles, formulations the poly (meth)acrylic ester latices can be applied in similar formulations and processing conditions as in the case of tablet coating (111). Coated particles encapsulated with a highly effective membrane may contain only 10-20% of coating material and can be put into capsules or compressed into disintegrating tablets. Several batches of coated particles with different release profiles can be mixed to optimize the release pattern or to produce more convenient formulations. The drug dissolution rates from the

substrates coated with Eudragit NE 30D or Eudragit RS/RL or the mixtures of these copolymers have been studied with several drug cores such as ferrous fumarate granules, theophylline pellets, theophylline granules, thiamine hydrochloride granules, indobufen pellets, phenylpropanolamine hydrochloride pellets, diclofenac sodium microcapsules, josamycin and acetaminophen granules, indapamide pellets, 5-aminosalicylic acid tablets, and verapamil hydrochloride pellets (112-122).

## **Polymer latex film formation** (123-125)

The understanding of the latex film formation process is essential for one who involves in the coating industries such as paints, adhesives, paper coatings, textile finishes, and pharmaceuticals. In the area of pharmaceutical science, in order to understand better about the drug diffusion through the polymer film obtained from the latex, it is helpful to understand how the film is formed. The formation of a latex film involves the coalescence of the individual latex particle, which is dependent on the minimum film-forming temperature (MFT) of the given polymer. And this is directly related to the elastic modulus and the viscosity of the polymer. The MFT is defined as the lowest temperature at which film formation can occur as determined by visual observation of cracking or whitening (126). If the latex is cast below its MFT, it will form cracking films or powder compact. As the particle coalescence depends on the polymer chain mobility, which is directly related to the $T_g$ of the polymer, therefore the $T_g$ and the MFT of the given polymer are relatively closed in values. However, a broad difference between $T_g$ and MFT has been observed in some cases. For example, the comonomers that enhance the hydrophilicity of the polymer such as methyl or ethyl acrylate may reduce the MFT below the $T_g$ by allowing water to act as a temporary plasticizer (127,128). The latex particle size also influences the MFT, although this is not always the case (129-131).

Figure 1 exhibits the steps of film formation from the polymer latex. In conclusion, the film formation starts from the evaporation of water, which is a dispersing medium. As water evaporates, the interfacial tension between water and the polymer particles drives the particles to come into intimate contact with one another. If the driving force overcomes the electrostatic/steric repulsive forces, the particle deformation followed by complete coalescence will occur. Capillarity generated by the

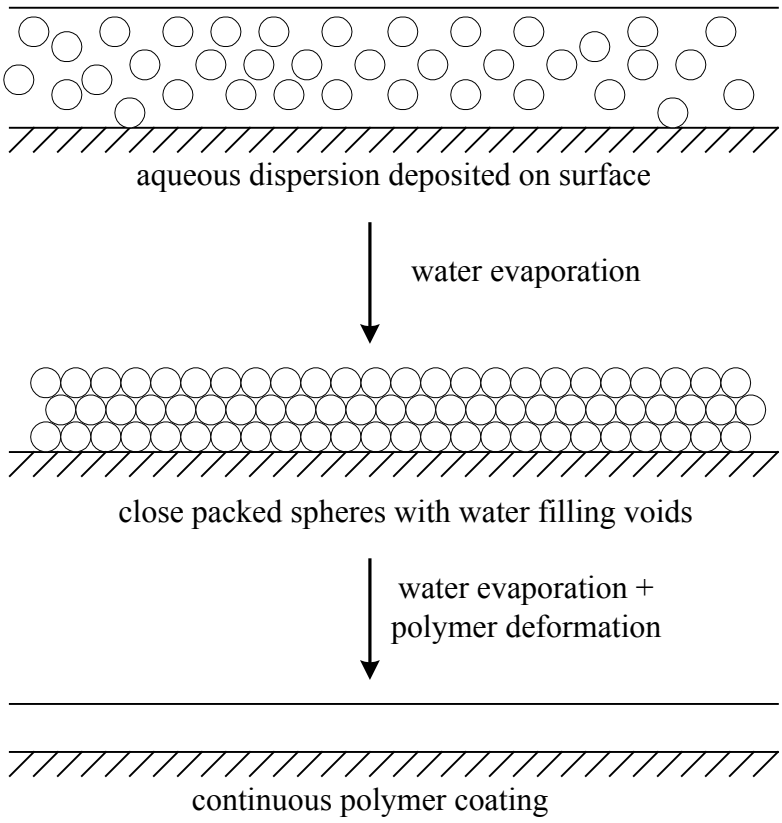



Figure 1. Schematic representation of film formation from polymer latex

high surface tension of water is the main driving force to fuse the particles. Vanderhoff et al. (132,133) described the process of film formation by dividing it into three stages as follows (Figure 2):

**Stage I: evaporation and particle concentration**

This stage takes the longest period of the whole process. It starts from the evaporation of water from the latex, resulting in the concentrated latex. The evaporation rate is similar to the evaporation rate of pure water or of water containing small amount of electrolyte and surfactant. This stage lasts until 60-70% volume fraction of the polymer is reached or until the latex's liquid-air interface begins to decrease as a result of solid film formation. Before the drying process, the latex particles can move independently due to the Brownian motion. After the latex is concentrated, the particle movement is restricted once a large volume of water is evaporated.

**Stage II: particle deformation**

This stage starts from the time that the latex particles begin to come into irreversible contact. Although the evaporation rate of water per unit area of the latex surface remains constant in this stage, the overall rate of evaporation greatly declines. The deformation of the particles can then occur in this stage. Over the years there have been a number of theories considering about the driving forces for the latex particle deformation. These theories involve dry sintering (134,135), capillary theory (136), wet sintering (137-139), piston-like compression (140), and inter-particle cohesion promoted by surface forces (141). Among these theories, dry sintering is the first theory that was proposed by Dillon et al. Sintering is originally a term used to describe a reduction in surface area of the particles which is driven by polymer-air interfacial tension. Dillon suggested that the energy required for the coalescence of polymer spheres results from the surface tension of the polymer generated by the negative curvature of the particle surface (Laplace forces) and may be described by Frenkel equation:

$$\theta^2 = \frac{3\gamma t}{2\pi\eta r}$$

where $\theta$ = angle of deformation (seen in Figure 3), $\gamma$ = polymer surface tension, $t$ = time, $\eta$ = polymer viscosity, and $r$ = particle radius

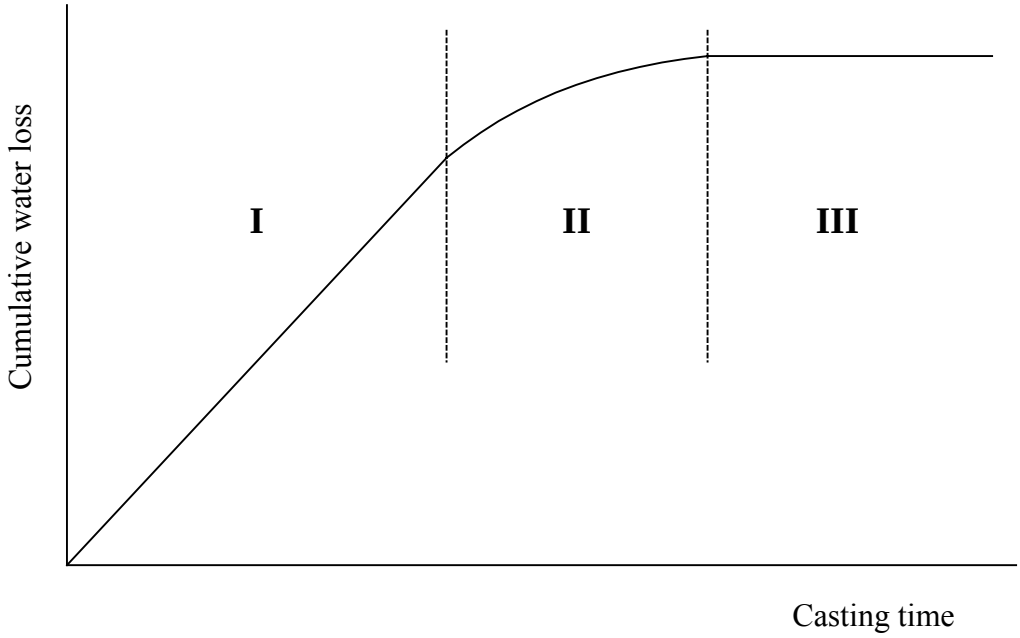



Figure 2. Schematic plot of the water loss occurring on latex drying

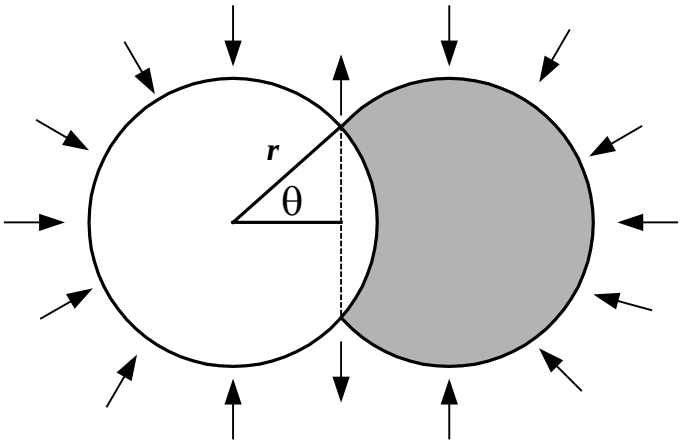



Figure 3. A cross-section of sintered latex particles

The level of coalescence is determined by the angle of deformation. It can be noted that a low polymer surface tension promotes the coalescence where as the phenomenon is retarded as the polymer viscosity is higher or the particle size is larger.

Besides dry sintering, Brown proposed capillary theory, which states that the deformation of the particles is driven by the water-air interfacial tension in the interstitial capillary system between the particles, during drying. He suggested that this force could both promote and inhibit the coalescence process. In summary, the coalescence occurs when the capillary force (resulting from the surface tension of the interstitial water caused by the formation of small radii of curvature between the particles as the water evaporates) overcomes the forces of resistance to deformation.

**Stage III: polymer chain diffusion across particle boundaries**

This stage begins from the initial formation of a continuous film. The remaining water in the film still evaporates via the remaining channels among the particles. However, the rate of water removal in this stage is very slow and may be reduced by film additives, which are impermeable or hydrophilic. In this final stage, a soft latex becomes more homogeneous and the mechanical properties are enhanced as the interdiffusion of the polymer chains occurs. This polymer interdiffusion may be called maturation, autohesion, or further gradual coalescence (FGC), and may require several hours or even days depending on the polymer hardness and working conditions. Particle interfaces tend to become less distinct in this stage. A drastic change in film properties between stage II and III can be observed as the brittle cohered particles become more ductile due to polymer chain entanglement.

## **Theory of adhesion and tack** (142,143)

The mechanism of adhesion has been studied for years. Several theories have been proposed to explain adhesion phenomena. These theories are based on the knowledge about surface science, polymer characteristics and also the interaction between polymers and surfaces. However, there is no unifying theory that can illustrate all adhesive bonds. At present, there are four main mechanisms or theories proposed to describe adhesion phenomenon. They are adsorption and surface reaction, diffusion theory, electrostatic theory, and mechanical interlocking. As the bonding of two materials using an adhesive is the net result from the mechanical (physical) and chemical forces, when discussing about these theories of adhesion, it is not possible to separate these forces from one another although these theories are controversial in some circumstances. The concise explanations of these theories are as follows:

**Adsorption theory**

Among the theories of adhesion, this theory is the most generally accepted theory on the adhesion between adhesive and adherend. It states that adhesion results from intimate intermolecular contact between two materials, and involves surface forces that develop between the atoms in the two surfaces. The most common surface forces that form at the adhesive-adherend interface are van der Waals forces. In addition, acid-base interactions and hydrogen bonds (generally considered a type of acid-base interaction) may also contribute to the adhesion forces. These forces are referred to as secondary bonds. To obtain good physical adsorption, the materials must be under intimate contact so that van der Waals forces or acid-base interaction or both can occur. Therefore, good wetting is necessary. According to Dupre equation:

$$W_A = \gamma_1 + \gamma_2 - \gamma_{12} \quad (1)$$

i.e. the work of adhesion of a liquid to a solid ($W_A$) is equal to the sum of the surface free energies of liquid and solid less the interfacial free energy. However, the latter value is not directly measurable except in the case of two liquids. Therefore the Young equation in which a diagram is obtained form a model of a drop of liquid on a solid (Figure 4) is introduced. That is

$$\gamma_{sv} = \gamma_{sl} + \gamma_{lv} \cos \theta \quad (2)$$

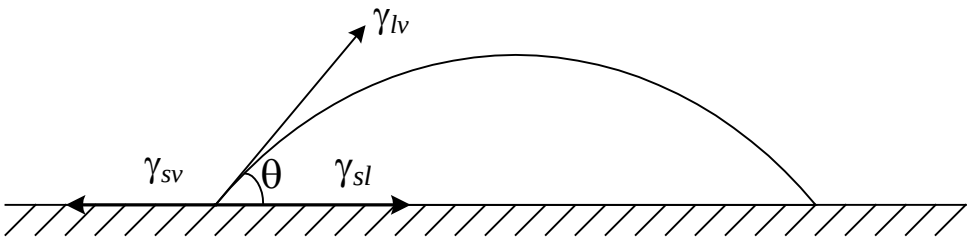



Figure 4. Contact angle and tensions for liquid drop on solid surface

where $\gamma_{sv}$, $\gamma_{sl}$ and $\gamma_{lv}$ are interfacial tensions between solid-vapor, solid-liquid, and liquid-vapor, respectively. $\theta$ is contact angle. By equating $\gamma_{sv}$ with $\gamma_1$ and $\gamma_{lv}$ with $\gamma_2$, equation (1) and (2) can be combined to obtain the Young-Dupre equation:

$$W_A = \gamma_{lv} (1+ \cos \theta) + \pi \quad (3)$$

Where $\pi$ is a spreading pressure and equal to $\gamma_s$-$\gamma_v$. It has been assumed that for solids of low surface free energy such as polyolefins and fluorinated polymers, the spreading pressure $\pi$ is negligible. While on surface of solids with high surface free energy most liquids will spread spontaneously and hence $\cos \theta = 1$ and equation (3) becomes:

$$W_A = 2\gamma_{lv} + \pi \quad (4)$$

Since work of cohesion ($W_C$) = $2\gamma_{lv}$, hence $W_A$ is always larger than $W_C$. This indicates that failure in an adhesive joint is cohesive failure in adhesive or adherend rather than adhesive failure. The use of the Young-Dupre equation is limited to the systems where the contact angle is finite and the spreading pressure is negligable. Such systems are those in which normal adhesives are ineffective.

In some circumstances, surface reactions may occur and involve in adhesive bond strength. These chemical interactions can be explained by the chemisorption or chemical bonding theory. The chemical bonding mechanism suggests that primary chemical bonds may form across the interface. Chemical bonds or primary forces are strong and make a significant contribution to the intrinsic adhesion in some cases. For example, primary chemical forces have energies ranging between 60-1100 kJ/mol, which are significantly higher than the bond energies that secondary forces have (0.08-5 kJ/mol). There is some evidence that covalent bonds are formed with silane coupling agents. Another possible sample is the reaction of an epoxide adhesive with a surface containing amine groups to give C-N bonds.

**Diffusion theory**

The diffusion theory attributes the adhesion of the polymer materials to the inter-diffusion of the polymer chains at the interface, so that the initial boundary eventually disappears (Figure 5). This theory requires that both the adhesive and adherend are polymers and such inter-diffusion will occur only if the polymer chains are mobile (i.e. the temperature must be above their $T_g$s) and compatible. Since most polymers such as polyethylene and polypropylene are incompatible despite their similar

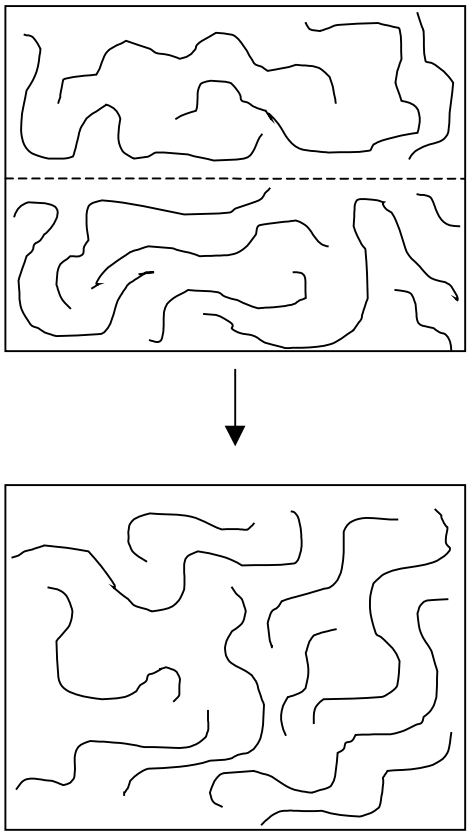


Figure 5. Diffusion theory of adhesion

chemical structures, this theory can usually be only applied to the rubbery polymers or when surfaces coated with adhesives are pressed together. The theory is limited to the polymer that the chain movement is restricted by its highly cross-linked, crystalline structure or when it is below the $T_g$.

To explain autohesive phenomenon of the polymers, several theories have been employed such as reptation (144), cooperativity (145) and entanglement coupling (146). Parameters influencing the diffusion process are contact time, temperature, molecular weight and physical form of the polymers.

**Electrostatic theory**

The basis of the electrostatic theory of adhesion is the difference in electronegativities of the materials in contact. Adhesive bond strength is attributed to the transmission of electrons across the interface creating positive and negative charges, which attract one another. For example, when an organic polymer is brought into contact with metal, electrons are transferred from metal into the polymer, creating an attractive electrical double layer and this accounts for resistance to separation of the adhesive and the substrate. The theory is extensively applied in the coating industry where the polymer particles are negatively charged and the piece to be coated is positively charged. However, many controversies have arisen around this theory due to the fact that the electrical double layer could not be identified without separating the adhesive bond. The theory is also unable to explain why dissimilar polymers are less adhesive than similar polymers despite their greater potential voltage differences. Some researchers also thought that the effect of the electrical double layer on the adhesive bond strength was overestimated.

**Mechanical interlocking**

The mechanical interlocking theory proposes that good adhesion occurs only when an adhesive penetrates into the pores, holes, and other irregularities of the adhered surface of the substrate, and locks mechanically to the substrate. The adhesive must not only wet the substrate, but also have a suitable fluidity to penetrate pores and any openings of the surface. Since good adhesion can take place between smooth surfaces as well, it is obvious that while interlocking helps promote adhesion; it is not really a mechanism that can be generally applied. Therefore this theory only explain for a few examples such as bonding of rubber to the textiles and paper. The

pretreatment applied on the surface of some substrates such as plastic can also enhance the adhesion. The pretreatment result in microroughness on the surface, which can improve bond strength and durability by providing mechanical interlocking. In addition, the greater bond strength due to the surface roughness may also result from other factors such as the formation of a larger surface, the improved kinetics of wetting, and the increased plastic deformation of the adhesive.

**Tack** (143,147)

Tack can be defined as:

(1) The ability of a material to stick to a surface on momentary contact and then to resist separation

(2) The tendency of a rubber to stick to itself rather than to other surfaces (autohesion, self-adhesion)

The measurement of tack comprises two steps. First, a probe is placed in contact with a tacky surface. This step is called “bonding”. Then the “debonding” step is the separation of the probe from the surface. If the material can wet or be adsorbed on the probe surface, the separation will be resisted. The value of tack is both thermodynamically and kinetically controlled. The thermodynamic control is evident when the probes used have different critical surface tension, whereas the dependence of tack on the time of contact and the load applied during contact is the kinetic control. Removal of the probe is also rate and temperature dependent and includes viscoelastic deformation of the bulk of the tacky material.

Unvulcanized natural rubbers and chloroprene rubber generally show high tack. The rubber must be sufficiently low viscous or have low molecular mass, in order to flow and wet the adherend under low pressure applied. However, the viscosity must be high enough so that there is some elastic resistance to the separation. Tack may be enhanced by the addition of tackifying agents such as coumarone-indene polymer, rosin or a phenol-formaldehyde resin.

## **Emulsion polymerization** (148,149)

Emulsion polymerization is a unique process employed for radical chain reaction and has great importance in the industry. It was first introduced during World War II to produce synthetic rubbers from 1,3-butadiene and styrene. The process involves the polymerization of monomer in the form of emulsion (i.e., colloidal dispersion). The reaction components differ from those employed in suspension polymerization in that the initiator is dissolved in the dispersion medium (usually water) instead of in monomer as in case of suspension polymerization. This process has several advantages. For examples, the physical state of the colloidal system makes it easy to control the process. Compared with bulk polymerization, the heat dissipation is better and the viscosity is much lower. The product obtained from the process, which is called latex, can be directly utilized without further separation of the colloidal polymer particles. Such applications include paints, coatings, finishes, and floor polishes. At present, emulsion polymerization is the predominant process for the commercial polymerization of vinyl acetate, methacrylates, vinyl chloride, acrylamide, and chloroprene.

### **Initiators**

In the process of emulsion polymerization, the initiators used must be water-soluble. These initiators include potassium or ammonium persulfate, hydrogen peroxide, 2,2'-azobis(2-amidinopropane) dihydrochloride. Partially water-soluble peroxides such as succinic acid peroxide and azo compound have also been used occasionally. Redox systems such as persulfate or hydrogen peroxide with ferrous ion, sulfite, or bisulfite ion are commonly used, especially in the industrial scale. The advantage of the redox systems is that they can give desirable initiation rates at temperatures below 50 $^{o}$C.

### **Surfactants**

The most commonly used surfactants in emulsion polymerization are anionic surfactants. These surfactants include fatty acid soaps, sulfates and sulfonates, such as potassium stearate, sodium palmitate, potassium laurate, sodium lauryl sulfate, sodium dodecylbenzene sulfonate. The sulfates and sulfonates are useful for the polymerization in acidic medium where soaps are not stable or in case that the products must be stable in acidic condition or toward the addition of heavy metals.

Nonionic surfactants such as poly(ethylene oxide), poly(vinyl alcohol) and polysorbates are frequently utilized in conjunction with anionic surfactants for improving the freeze-thaw and shear stability of the polymer or to help in controlling particle size and size distribution. Unlike anionic surfactants which stabilize the polymer particles by electrostatic repulsion force, nonionic surfactants enhance the colloidal stability via steric interference with the van der Waals attraction force between the particles. Nonionic surfactants are also useful in case the final product should be stable over a wide pH range. However, they are seldom used alone as their efficiency is less than that of the anionic surfactants. Generally, anionic surfactants are used at a range of 0.2-3% based on the amount of water, whereas nonionic surfactants are used at a range of 2-10%. Cationic surfactants are less frequently used as their efficiency is low. Also, they are more expensive than anionic surfactants. Increasing the surfactant concentration in the recipe results in the increase of particle number and the decrease of particle size. However, delayed addition of the surfactant after the nucleation is complete can improve particle stability, without affecting the particle number and size.

**Mechanism of polymerization**

A typical formulation for an emulsion polymerization comprises of monomer(s), dispersing medium, emulsifier, and water-soluble initiator. The dispersing medium is a liquid, usually water, in which other components are dispersed or dissolved. The ratio of water to monomer(s) is generally in the range of 70/30 to 40/60 (by weight). When the concentration of the emulsifier exceeds its critical micelle concentration (CMC), the excess molecules aggregate together to form small colloidal clusters called micelles. Normally, the CMC values of most surfactants are in the range of 0.001-0.1 mole/liter. The concentration of the surfactant in the formulation therefore exceeds the CMC. Typical micelles have dimensions of 2-10 nm with each micelle containing 50-150 surfactant molecules. The surfactant molecules are arranged in a micelle with their hydrocarbon portions pointed toward the interior of the micelle and their ionic parts point outwards to the aqueous phase. When a water-insoluble or slightly water-soluble monomer is added, a very small fraction dissolves in the continuous aqueous phase. Some but still small portion enters the interior hydrocarbon portions of the micelles. The largest portion (>95%) is dispersed as monomer droplets which are stabilized by

surfactant molecules absorbed on their surfaces. The monomer droplets are generally much larger than the monomer-containing micelles. Hence, the micelles are far greater in number than the monomer droplets. A simplified schematic representation of an emulsion polymerization system is shown in Figure 6.

At the beginning of the reaction, primary free radicals formed from the initiator react with monomers in the aqueous phase to produce oligomeric radical species which then diffuse into the monomer-swollen micelles to initiate polymerization. The entry of the radicals into the monomer droplets is very unlikely as the micelles are much more than the monomer droplets. Propagation within the micelles is supported by absorption of monomer from the aqueous phase, and the monomer from the droplets then diffuses toward the aqueous phase to maintain equilibrium. When the monomer-swollen polymer-particles become larger, they absorbed surfactant molecules from the micelles that have not undergone initiation to maintain their colloidal stability. The reaction progresses until reaching the point at which all micelles are completely consumed (usually below 10% conversion). This is the end of particle nucleation (i.e. interval I). The number, $N_p$, of latex particles per unit volume of latex then remains constant. Polymerization within these particles still continues and is supported by the diffusion of monomer as described above. The rate of diffusion of monomer exceeds the rate of polymerization so that the concentration, $[M]_p$, of monomer within a particle remains constant. Finally, the monomer droplets are completely consumed and the end of the period of constant rate is reached (interval II). Thereafter, $[M]_p$ and the rate of polymerization decrease continuously as the remaining monomer present in the particles is polymerized (interval III). The three intervals of emulsion polymerization are shown the conversion curve in Figure 7.

If $\bar{n}$ is the average number of radicals per latex particle, then the corresponding number of moles of radicals is $\bar{n}/N_A$, where $N_A$ is the Avogadro constant. Thus the rate of polymerization in an average particle is $k_p[M]_p(\bar{n}/N_A)$ and so the rate of polymerization per unit volume of latex is given by

$$R_p = k_p[M]_p(\bar{n}/N_A)\, N_p \qquad (5)$$

As the particles are very small, two radical species can only exist independently within a particle for very short periods before reacting together. Therefore termination can be

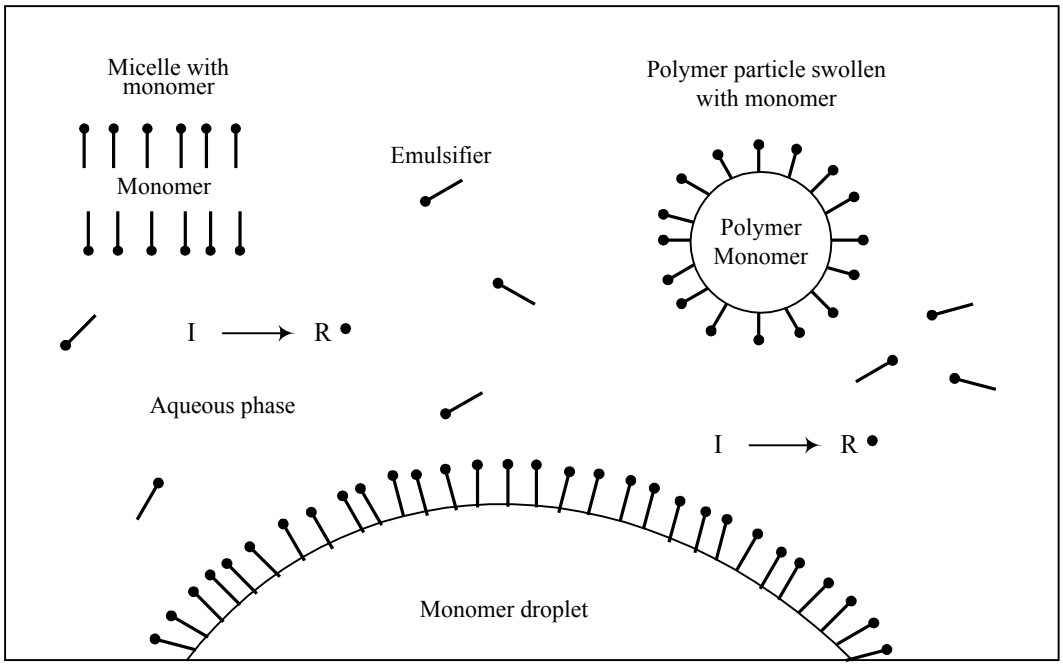



Figure 6. Schematic representation of an emulsion polymerization system (from ref. 149)

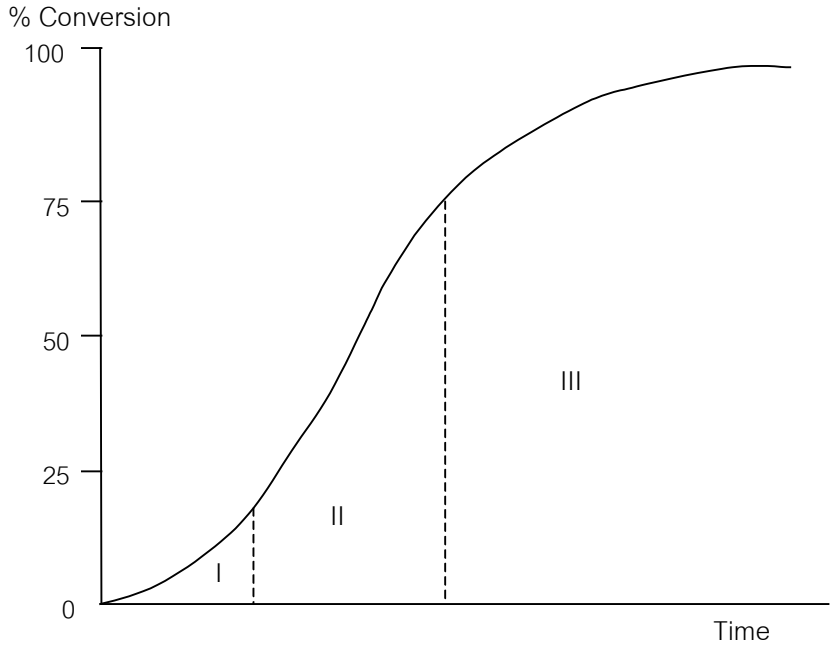



Figure 7. Variation of percent conversion with time for emulsion polymerization

considered to occur immediately after the entry of a second radical species into a particle containing a single propagating chain radical. The particle then remains inert until the entry of a new radical initiates the propagation again. Therefore, on average, each particle contains one propagating chain radical for half the time of its existence and none for the remaining half. Under these conditions $\bar{n} = ½$ and

$$R_p = \frac{k_p[M]_p N_p}{2N_A} \quad (6)$$

Moreover, if the rate of formation of radical species from the initiator is $\rho_i$ then the average time interval between consecutive entries of radicals is $(N_p/\rho_i N_A)$. Since each propagating chain radical adds molecules of monomer at a rate $k_p[M]_p$, the number-average degree of polymerization of the polymer formed is given by

$$\overline{\chi_n} = k_p[M]_p(N_p/\rho_i N_A) \quad (7)$$

Equations (6) and (7) are best applied to interval II when $[M]_p$ and $N_p$ are constant. They show that both $R_p$ and $\overline{\chi_n}$ can be increased by increasing $N_p$. Because simultaneously propagating chain radicals are segregated into separate particles, high molecular weight polymer is obtained at high polymerization rate.

The important features of emulsion polymerization are the good heat dissipation, relatively low viscosity of the products at high polymer concentrations, and the ability to control particle morphology.

# CHAPTER 3
# MATERIALS AND METHODS

## Materials

1. Eudragit® NE 30D (Röhm Pharma GmbH, Germany)
2. Eudragit® RS 30D (Röhm Pharma GmbH, Germany)
3. Eudragit® RL 30D (Röhm Pharma GmbH, Germany)
4. Triethyl citrate (TEC, Morflex Chemical Co., USA)
5. Acetyltributyl citrate (ATBC, Morflex Chemical Co., USA)
6. Glyceryl monostearate (GMS, Fluka Chemie, Switzerland)
7. Sorbitan monooleate (Span®80, Fluka Chemie, Switzerland)
8. Sorbitan monostearate (Span®60, Fluka Chemie, Switzerland)
9. Sorbitan monopalmitate (Span®40, Fluka Chemie, Switzerland)
10. Sorbitan monolaurate (Span®20, Fluka Chemie, Switzerland)
11. Talc (Merck, Germany)
12. Theophylline anhydrous (Shanghai Wandai Pharmaceutical Co.,China)
13. Microcrystalline cellulose 101 (JRS GmbH, Germany)
14. Povidone K30 (BASF, USA)
15. Lactose anhydrous (The Lactose Company, New Zealand)
16. Methacrylic acid (Fluka Chemie, Switzerland)
17. Ethyl acrylate (Fluka Chemie, Switzerland)
18. Hydroxyethyl methacrylate (Fluka Chemie, Switzerland)
19. Potassium persulfate (Fluka Chemie, Switzerland)
20. Sodium lauryl sulfate (Fluka Chemie, Switzerland)
21. Polysorbate 80 (Fluka Chemie, Switzerland)
22. Paracetamol (Mallinckrodt, USA)
23. FlowLac® (Meggle, Germany)
24. Sodium starch glycolate (Edward Mendell, USA)

25. Magnesium stearate (Merck, Germany)
26. Sodium hydroxide (Fluka Chemie, Switzerland)
27. Hydrochloric acid 37% (Fluka Chemie, Switzerland)
28. Potassium biphthalate (Fluka Chemie, Switzerland)
29. Acetic acid, glacial (Fluka Chemie, Switzerland)
30. Sodium acetate trihydrate (Fluka Chemie, Switzerland)
31. Potassium dihydrogen phosphate (Fluka Chemie, Switzerland)
32. Trisodium phosphate dodecahydrate (Fluka Chemie, Switzerland)
33. Methanol (Sigma-Aldrich Chemie, Germany)
34. PTFE protective overlay (Cole-Parmer Instrument Co., USA)

## Instruments

1. Fourier transform infrared spectrometer (FTIR Spectrum One, Perkin-Elkmer, USA)
2. Tensile tester (TA.XT plus, Stable Micro Systems, England)
3. Optical microscope (Zeiss, Germany)
4. Dynamic mechanical Analyzer (GABO Qualimeter, Germany)
5. pH meter (Orion®, USA)
6. Homogenizer (Ultra Turrax®, Germany)
7. Extruder (Pharmaceutical & Medical Supplies Co., Thailand)
8. Spheronizer (Pharmaceutical & Medical Supplies Co., Thailand)
9. Fluidized bed coater (Pharmaceutical & Medical Supplies Co., Thailand)
10. Dissolution test apparatus (VK 7000, Vankel Industries, USA)
11. UV/visible spectrophotometer (VK 50 UV-Vis, Vankel Industries, USA)
12. LS particle size analyzer (Coulter® N4MD, USA)
13. Viscometer (Brookfield® DV-II+, USA)
14. Differential scanning calorimeter (DSC 7, Perkin-Elmer, USA)
15. Temperature gradient bar (designed to conform to ASTM D2354 standard)
16. V-shape blender (Pharmaceutical & Medical Supplies Co., Thailand)
17. Powder mixer (Pharmaceutical & Medical Supplies Co., Thailand)
18. Single-stroke tableting machine (Yeo Heng Co., Thailand)
19. Sieve shaker (Fritsch, Germany)

20. Thickness gauge (Minitest 600, Erichsen, Germany)
21. Tablet hardness tester (VK 200, Vankel Industries, USA)
22. Micrometer (Vankel Industries, USA)
23. Friabilator (Vankel Industries, USA)
24. Disintegration tester (VK 100, Vankel Industries, USA)
25. Perforated coating pan (Pharmaceutical & Medical Supplies Co., Thailand)

## Methods

### 1. Investigation of the anti-tacking property of selected surfactants

#### 1.1 Preparation of the polymer dispersions

The polymer dispersions with various concentrations of surfactants were prepared. The formulations are shown in Table 1 and Table 2. The surfactants were first prepared in a form of dispersion by homogenizing in water for 15 minutes at temperatures above their melting points. The surfactant dispersions were then added into the Eudragit NE 30D and Eudragit RS 30D dispersions to obtain the polymer dispersions with 5%, 10% or 15% w/w surfactants (based on polymer mass). For the Eudragit RS 30D, the polymer was plasticized first with 30%w/w ATBC for 48 hours. The weight of the dispersions was adjusted to 15% solid content with water prior to stirring for 15 minutes. The polymer dispersions containing 15%, 50% and 100%w/w talc were also prepared.

#### 1.2 Preparation of the sprayed films

The films were produced by using a pneumatic nozzle that intermittently sprayed the polymer dispersions onto a sheet of PTFE laid on a glass plate. The dispersions were stirred continuously when spraying. The films were formed on the surface of the PTFE sheet by the intermittently application of warm air. The spray position was constantly changed in order to obtain films with a uniform thickness. After the films, with an approximate thickness of 0.25 mm, had been obtained they were kept under warm air until they felt dry to the touch and then were removed from the PTFE sheet. The films were stored over silica gel until required for the tests.

Table 1. Formulation of Eudragit NE 30D dispersions

| Component (g) | Formulation | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| Eudragit NE30D | 50 | 47.6 | 43.5 | 33.3 | 25.0 | 47.6 | 45.4 | 43.5 | 47.6 | 45.4 | 43.5 | 47.6 | 45.4 | 43.5 | 47.6 | 45.4 | 43.5 | 47.6 | 45.4 | 43.5 |
| Talc | - | 0.71 | 1.96 | 5.0 | 7.5 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |
| GMS | - | - | - | - | - | 0.71 | 1.37 | 1.96 | - | - | - | - | - | - | - | - | - | - | - | - |
| Span 80 | - | - | - | - | - | - | - | - | 0.71 | 1.37 | 1.96 | - | - | - | - | - | - | - | - | - |
| Span 60 | - | - | - | - | - | - | - | - | - | - | - | 0.71 | 1.37 | 1.96 | - | - | - | - | - | - |
| Span 40 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.71 | 1.37 | 1.96 | - | - | - |
| Span 20 | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | 0.71 | 1.37 | 1.96 |
| Purified water | 50 | 51.7 | 54.6 | 61.7 | 67.5 | 51.7 | 53.2 | 54.6 | 51.7 | 53.2 | 54.6 | 51.7 | 53.2 | 54.6 | 51.7 | 53.2 | 54.6 | 51.7 | 53.2 | 54.6 |
| Solid content | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Polymer mass | 15 | 14.3 | 13.0 | 10.0 | 7.5 | 14.3 | 13.6 | 13.0 | 14.3 | 13.6 | 13.0 | 14.3 | 13.6 | 13.0 | 14.3 | 13.6 | 13.0 | 14.3 | 13.6 | 13.0 |
| Content of anti-tack (%) (based on polymer mass) | - | 5 | 15 | 50 | 100 | 5 | 10 | 15 | 5 | 10 | 15 | 5 | 10 | 15 | 5 | 10 | 15 | 5 | 10 | 15 |

Table 2. Formulation of Eudragit RS 30D dispersions

| Component (g) | Formulation | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Eudragit RS30D | 38.4 | 37.0 | 35.7 | 37.0 | 35.7 | 37.0 | 35.7 | 37.0 | 35.7 | 37.0 | 35.7 |
| ATBC | 3.5 | 3.3 | 3.2 | 3.3 | 3.2 | 3.3 | 3.2 | 3.3 | 3.2 | 3.3 | 3.2 |
| GMS | - | 0.56 | 1.1 | - | - | - | - | - | - | - | - |
| Span 80 | - | - | - | 0.56 | 1.1 | - | - | - | - | - | - |
| Span 60 | - | - | - | - | - | 0.56 | 1.1 | - | - | - | - |
| Span 40 | - | - | - | - | - | - | - | 0.56 | 1.1 | - | - |
| Span 20 | - | - | - | - | - | - | - | - | - | 0.56 | 1.1 |
| Purified water | 58.1 | 59.1 | 60 | 59.1 | 60 | 59.1 | 60 | 59.1 | 60 | 59.1 | 60 |
| Solid content | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Polymer mass | 11.5 | 11.1 | 10.7 | 11.1 | 10.7 | 11.1 | 10.7 | 11.1 | 10.7 | 11.1 | 10.7 |
| Content of anti-tack (%) (based on polymer mass) | - | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 |

### 1.3 Determination of the tackiness of the films

The films were cut into 2.5 X 7.0 $cm^2$ sections and backed with cotton cloth. Two test films were pressed together under a 200-g weight and stored at 40$^oC$ for 1 hour. After this treatment, the samples were cooled to room temperature (23$^o$±2$^o$C), 50±5% R.H. for 1 hour and T-peel tests were performed using a tensile tester (TA.XT plus, Stable Micro System). The films were peeled from each other through one end at a cross-head speed of 15 mm/min. The force-displacement diagrams were recorded. The average values obtained from the constant force portions of the diagram were used to represent the peel forces. At least five specimens were tested for each sample.

### 1.4 Analysis of film compositions

#### 1.4.1 Spectroscopic study

The surface components of the test films were examined with a Fourier transform infrared spectrometer (FTIR Spectrum One, Perkin Elmer) equipped with an attenuated total reflection accessory (FTIR-ATR). Zinc selenide crystal (refractive index 2.4) having an incidence angle of 45$^o$ was used to give a total of 16 reflections. The scanning range was 650- 4000 $cm^{-1}$ and the approximate penetration depth was 1.6 micron at 1000 $cm^{-1}$. Each sample was scanned for four times and the spectrum was recorded at a resolution of 4 $cm^{-1}$

#### 1.4.2 Microscopic study

A thin film was prepared by spreading a drop of polymer dispersion on a glass slide prior to drying at 40$^oC$ for 3 hours. The morphological characteristics of the films were investigated under an optical microscope (Zeiss®, Germany) using transmittance mode. The images of the films were captured and scanned into a computer.

### 1.5 Mechanical properties of the films

#### 1.5.1 Storage modulus

Dynamic mechanical measurements were carried out on DMA (GABO Qualimeter®, Germany) in tension mode. The sample films were cut into 8.5X30 $mm^2$ sections and clamped between two grips of the machine. The gauge length was 20 mm. The samples were tested at a constant frequency of 10 Hz, under room temperature. The static strain was 20% and the dynamic strain was varied from 0.10% to 10.00%. The modulus of the samples was calculated from the program of the machine.

### 1.5.2 Film flexibility

The flexibility of the films was determined from their elongation property. A static tensile test was performed using a tensile tester (TA.XT plus, Stable Micro System) according to ASTM-D882. The sample width was 15 mm and the gauge length was 25 mm. The cross-head speed was 50 mm/min. The stress-strain profiles were recorded and the elongation at break of the films was calculated. The average of at least five measurements for each sample was reported.

## 1.6 Preparation of theophylline pellets

The pellets containing theophylline were prepared for the batch size of 10 kg. The formulation is shown in Table 3. Theophylline anhydrous, microcrystalline cellulose, and lactose were mixed in a 20:50:25 ratio for 20 minutes in a mixing container. A 5% PVP K30 (based on total mixture) was dissolved in a suitable amount of water and the solution was then added to the powder mixture. The moistened mass was extruded through a 1mm-diameter screen and the extrudates were spheronized by setting the spheronization speed and residence time at 950 rpm and 15 min., respectively. The wet spheronized pellets were then dried at 60 $^{o}$C for 24 hours. The dried pellets were sieved using a sieve shaker and the pellets with diameter between 0.71-1.25 mm were collected for further coating process.

## 1.7 Evaluation of the pellets

### 1.7.1 Determination of drug content

Standard curves of anhydrous theophylline in methanol and 0.1 N HCl were prepared. Theophylline approximately 12.5 mg was accurately weighed, dissolved in the solvent and diluted to 50 ml in a volumetric flask. Appropriate dilutions were then made to obtain standard solutions of 2.5, 5, 10, 20 μg/ml. The absorbance of the drug solutions was determined in 1-cm quartz cell at the maximum absorption wavelength of 271 nm with a UV/visible spectrophotometer using methanol or 0.1 N HCl as a blank. The absorbance was plotted against the drug concentrations and a linear regression was performed by the software.

The drug content in the pellets was determined by extraction with methanol. The pellets equivalent to about 20 mg of theophylline were accurately weighed, ground and transferred into a volumetric flask. Methanol was added into the flask and the mixture was stirred overnight to ensure a complete extraction. The solution was

Table 3. Formulation of theophylline pellets

| Component | Content (%) |
|---|---|
| Theophylline anhydrous | 20 |
| Microcrystalline cellulose 101 | 50 |
| Lactose | 25 |
| PVP K 30 | 5 |

filtered through a filter paper and assayed spectrophotometrically after an appropriated dilution with methanol.

### 1.7.2 Drug dissolution

The USP 26 rotating paddle method (37±0.5 $^{o}$C, 50 r.p.m., 900 ml 0.1 N HCl, n = 3) was used to study the drug release from the coated pellets. The weight of pellets used was equivalent to about 20 mg of theophylline. The automated dissolution-testing machine comprised of a dissolution apparatus, eight-channel peristaltic pump and a UV/visible spectrophotometer equipped with six 1.0-cm quartz cells (VK 7010, Vankel). The instrument was programmed to draw the sample automatically at predetermined time intervals by means of a peristaltic pump, which delivered the samples to the quartz flow cells of the spectrophotometer operating at 271 nm. The concentration of theophylline was detected and the drawn samples were returned to the dissolution vessels.

## 1.8 Preparation of coating dispersions

The formulations of coating dispersions are shown in Tables 4 and 5. Eudragit RS30D/RL30D was plasticized by stirring with 20% TEC (based on polymer mass) for 2 hours whereas Eudragit NE30D was used without plasticization. 100% of talc or 5% of each surfactant (based on polymer mass) were incorporated into the acrylic dispersions. The polymer content was then adjusted to 12.5% w/w by diluting with water. The dispersions were gently stirred for 15 minutes prior to coating.

## 1.9 Preparation of coated pellets

The coating dispersions were sprayed onto 600 g of the theophylline pellets in a fluidized bed coater (Thai coater®, Wurster insert, PMS Co., Thailand). The coating condition is shown in Table 6. The beads were coated until a theoretical polymer weight gain of 10% was obtained. After the coating, the coated beads were cured in an oven at 40$^{o}$C, 24 hours for the Eudragit NE30D formulations, and at 60$^{o}$C, 24 hours for the Eudragit RS30D/RL30D formulations.

## 1.10 Evaluation of coating efficiency

After the coated pellets were cured, the weight of total coated pellets was measured. The weight increase was calculated to determine the coating efficiency.

$$\text{Coating efficiency} = \frac{\text{weight increase of coated pellets}}{\text{weight of solid in coating dispersion}} \times 100$$

Table 4. Formulation of Eudragit RS 30D/RL 30D coating dispersions

| Component (g) | Formulation | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Eudragit RS30D | 100 | 160 | 180 | 180 | 180 | 180 |
| Eudragit RL30D | 100 | 40 | 20 | 20 | 20 | 20 |
| Triethyl citrate | 12 | 12 | 12 | 12 | 12 | 12 |
| GMS | 3 | 3 | 3 | - | - | - |
| Span 60 | - | - | - | 3 | - | - |
| Span 40 | - | - | - | - | 3 | - |
| Talc | - | - | - | - | - | 3 |
| Purified water q.s. | 480 | 480 | 480 | 480 | 480 | 480 |

Table 5. Formulation of Eudragit NE 30D coating dispersions

| Component (g) | Formulation | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Eudragit NE30D | 200 | 200 | 200 |
| GMS | 3 | - | - |
| Span 60 | - | 3 | - |
| Span 40 | - | - | 3 |
| Purified water q.s. | 480 | 480 | 480 |

Table 6. Operating conditions for the coating of theophylline pellets

| Condition | Formulation | |
|---|---|---|
| | Eudragit NE30D | Eudragit RS30D/RL30D |
| Batch size (g) | 600 | 600 |
| Nozzle diameter (mm) | 1.0 | 1.0 |
| Atomization pressure (bar) | 1.8 | 1.8 |
| Spray rate (g/min) | 2-7 | 2-7 |
| Inlet air temperature ($^{o}$C) | 30 | 40 |
| Product temperature ($^{o}$C) | 26-28 | 32-35 |
| Curing temperature ($^{o}$C) | 40 | 60 |
| Curing time (h) | 24 | 24 |

### 1.11 Evaluation of the coated pellets

#### 1.11.1 Determination of drug content in coated pellets

The drug content in the coated pellets was determined by extraction with methanol. The method was the same as that used to determine the drug content in the cores. The pellets equivalent to about 20 mg of theophylline were accurately weighed, ground and transferred into a volumetric flask. Methanol was added into the flask and the mixture was stirred overnight to ensure a complete extraction. The solution was filtered through a filter paper and assayed spectrophotometrically after an appropriated dilution with methanol. The residual drug content in the pellets after dissolution study was determined in the same manner.

#### 1.11.2 Dissolution studies

The USP 26 rotating paddle method (37±0.5 $^{o}$C, 50 rpm, 900 ml 0.1 N HCl, n = 3) was used to study the drug release from the coated pellets. The weight of pellets used was equivalent to about 20 mg of theophylline. The method and equipment was the same as that used to determine the drug dissolution from the core pellets.

### 1.12 Stability study

The stability of the drug release rate was examined. The coated pellets were kept at room temperature and at 40 $^{o}$C for at least 6 months. Change in drug release profiles after the storage was determined by dissolution tests.

## 2. Synthesis and evaluation of new acrylic copolymers

### 2.1 Latex synthesis

Two series of copolymer latices with a variety of monomer ratios were synthesized using semi-batch polymerization technique. The compositions of the latices are listed in Table 7. For the batch size of 460 g, synthesis was carried out in a three-neck round bottom flask equipped with reflux condenser, nitrogen inlet tube and magnetic stirrer. A picture of the reaction apparatus is shown in Figure 8. To start the reaction, 20% of the monomer mixture was poured into water containing sodium lauryl sulfate and polysorbate 80 and the emulsion was kept at 80 $^{o}$C in the presence of nitrogen gas. Potassium persulfate was dissolved in 20 ml of water and heated to 80$^{o}$C prior to adding into the emulsion to initiate the reaction. The remainder of the monomer mixture was then gradually dropped into the emulsion at a feed rate of 0.6 ml/min. The reaction was allowed to proceed for 6 hours. At the end of the reaction,

Table 7. Composition of latices with variable monomer ratios

| Component | Weight (%) |
|---|---|
| Monomers | 29.00 |
| MA:EA = 1:2, 2:3, 1:1, 3:2, 2:1 | |
| MA:HEM:EA = 4:1:5, 4:2:4, 5:1:4 | |
| Potassium persulfate | 0.12 |
| Sodium lauryl sulfate | 0.20 |
| Polysorbate 80 | 0.70 |
| Deionized water | 70.00 |


Figure 8. Photograph showing the reaction apparatus for the latex synthesis

the product was allowed to cool down and passed through a fine steel mesh to remove the grit formed during the reaction. The sample dispersion with a known weight was dried at 80 $^{o}$C to constant weight, and the solid contents were calculated.

### 2.2 Latex characterization

#### 2.2.1 Particle size analysis

The average size of the polymer particles in the latex was measured using an LS particle size analyzer (Coulter® N4MD). The dispersions were diluted down to approximately 0.1 % (w/w) before the measurement.

#### 2.2.2 pH measurement

pH of the latices was measured by a pH meter.

#### 2.2.3 Viscosity measurement

The viscosity was measured using a viscometer (Brookfield® DV-II+) at 25 $^{o}$C with shear speed of 100 rpm.

#### 2.2.4 Measurement of the minimum film-forming temperature

The minimum film-forming temperature **(**MFT) was determined using an MFT bar designed to conform to the ASTM D2354 standard. The apparatus consisted of a temperature gradient bar fabricated from stainless steel, an oil bath, a dry ice-isopropanol bath, air supply system, and a PMMA plastic cover. Borders were made on the main board by attaching plastic bars so that the dispersions could be poured. A temperature gradient was generated by putting one side of the bar into a dry ice-isopropanol bath. The other side was exposed to room temperature (25 $^{o}$C) or an oil bath. The temperature of the oil bath was set so that the bar temperature of the oil side was approximately 45 $^{o}$C. The flow rate of drying air was 10 L/min. After the temperature gradient reached equilibrium, 15 ml of the dispersion was poured on the bar and covered. The dispersion was dried in approximately 2 hours under this condition. The MFT was determined as the minimum temperature where the film was clear and free of cracks.

### 2.3 Preparation of cast films

The polymeric films were prepared by casting the latices on a PTFE sheet mounted on a leveled glass plate prior to drying in an oven at 60 $^{o}$C for 48 h. The dried films were kept over silica gels at room temperature before further experiments.

### 2.4 Film characterization

#### 2.4.1 Glass transition temperature

The thermal property of the cast films was evaluated using differential scanning calorimeter (DSC 7, Perkin Elmer). The heating rate was 20 $^{o}$C/min. The $T_g$s were determined as the midpoint of the transition of the heat flow.

#### 2.4.2 Infrared spectroscopy

The sample films were ground into powder. The powder samples were prepared in a form of KBr disk by compaction. The weight ratio of KBr to sample was approximately 100. Fourier transform infrared spectra were recorded with a FTIR spectrometer (Spectrum One, Perkin Elmer). Sixteen scans were collected for each sample at a resolution of 4 $cm^{-1}$ over the wavenumber region 450-4000 $cm^{-1}$.

#### 2.4.3 Mechanical properties of the films

Elongation at break, tensile strength, and modulus of the cast films were determined using a tensile tester (TA.XT plus, Stable Micro Systems) according to the method in ASTM D882. The films were cut into a standard dumbbell-shape (type V). The gage length was 7.62 mm. The cross-head speed was 10 mm/min. At least five specimens for each sample were tested.

#### 2.4.4 Rate of film dissolution

Rate of film dissolution was determined in 500 ml of buffer solution (pH 5.0, 5.5, 6.0, and 6.8) by stirring with a paddle in the release device at 37 $^{o}$C for 2 hours. Speed of stirring was 75 rpm and the size of the specimens was 2x2 cm (n=3). Rate of film dissolution = weight loss of film/(area of film x time required for dissolving).

### 2.5 Preparation of paracetamol core tablets

In this study paracetamol was selected as a model drug. The compositions of the cores are listed in Table 8. Ten kg of the cores was prepared. The ingredients of the formulation were sieved and mixed together in a V-shape blender for 10 minutes prior to compressing into round, convex tablets with a diameter of 9.7 mm.

### 2.6 Evaluation of the core tablets

#### 2.6.1 Weight variation

Weight variation of the core tablets was determined by weighing 20 tablets individually using an electronic precision balance. The average weight and standard deviation were calculated.

Table 8. Composition of paracetamol cores

| Ingredients | mg |
|---|---|
| Paracetamol | 50 |
| FlowLac® 100 | 278 |
| Microcrystalline cellulose Type 101 | 60 |
| Sodium starch glycolate | 10 |
| Magnesium stearate | 2 |
| Total | 400 |

### 2.6.2 Tablet hardness

Twenty tablets of the cores were measured for the hardness individually using a tablet hardness tester. The average value and standard deviation were calculated.

### 2.6.3 Friability

The friability of twenty core tablets was measured using Roche type friabilator. The drum was rotated at 25 rpm for 4 minutes. Loss of the tablet weight with respect to the initial value was calculated as percent friability.

### 2.6.4 Disintegration time

The disintegration time of the core tablets was determined in 0.1 N HCl and in phosphate buffer pH 6.8 using disintegration tester USP. Six tablets were measured individually. The average disintegration time and standard deviation were calculated.

### 2.6.5 Calculation of the surface area

Thickness of the tablets was measured by a micrometer. The surface area was calculated by the following equation:

$$\text{Surface area} = \pi \times (d \times h + d^2/2)$$

where d and h are the diameter and thickness of the tablet, respectively.

### 2.6.6 Determination of the drug content

Standard curves of paracetamol in 0.1 N HCl and in phosphate buffer pH 6.8 were prepared. Paracetamol approximately 200 mg was accurately weighed, dissolved in the solvent and diluted to 1,000 ml in a volumetric flask. Appropriate dilutions were then made to obtain standard solutions of 2, 6, 10, 15, 20 μg/ml. The absorbance of the drug solutions was determined in 1-cm quartz cell at the maximum absorption wavelength of 243 nm with a UV/visible spectrophotometer using 0.1 N HCl or phosphate buffer as a blank. The absorbance was plotted against the drug concentrations and a linear regression was performed by the software.

The drug content in the core was determined by extracting with 0.1 N HCl. Twenty tablets were ground. Then transfer an accurately weighed portion of the powder, equivalent to about 10 mg of paracetamol, to a 1,000-ml volumetric flask. 0.1 N HCl was added into the flask and the mixture was stirred overnight to ensure a complete extraction. The solution was filtered through a filter paper and assayed spectrophotometrically at the wavelength of 243 nm.

### 2.7 Coating of the cores

Fifty percent talc (based on dry polymer weight) was added to the synthesized latex. The polymer content was adjusted to 15% (w/w) by diluting with water. The coating dispersion was continuously stirred prior to and during the coating. In each case, the dispersion was continuously sprayed by a spray gun onto the pre-warmed cores in a perforated coating pan (Thai Coater®, PMS Co., Thailand). The coating parameters are shown in Table 9. The dispersion was applied onto the cores until the desired amount of the dry polymer on the tablet surface was obtained. After the coating, the coated tablets were subsequently dried at 30-33 $^{o}$C in the coating pan for 15 min.

The coating efficiency from each formulation was determined. The loss of coating was calculated from the difference between coating quantity and the increase in tablet weight. The stickiness of the films was also examined from the agglomeration of the tablets after the coating.

### 2.8 Examination of coated tablets

#### 2.8.1 Enteric property of the coated tablets

Resistance to gastric fluid of the coated tablets was determined from the increase in weight after 1 and 2 h in 0.1 N HCl under the disintegration test, according to USP 26 (n=6). The disintegration time in buffer solution pH 6.8 was also determined.

#### 2.8.2 Dissolution study

Dissolution rate was determined according to method B, USP 26 rotating paddle dissolution apparatus (1,000 ml of medium, 37 $^{o}$C, 50 rpm, n = 6). Samples were taken after 30, 60, 90, and 120 min during the acid stage and at 10-min interval during the buffer stage. The samples were subjected to spectrophotometric determination at 243 nm.

Table 9. Operating conditions for the coating of paracetamol cores

| Equipment parameters | |
|---|---|
| Batch size | 2 kg |
| Coaing pan speed | 10 rpm |
| Nozzle diameter | 1.0 mm |
| Atomizing pressure | 1.5 bar |
| Inlet air temperature | 50-55 $^{o}$C |
| product temperature | 30-35 $^{o}$C |
| Spray rate | 4-8 g/min |

# CHAPTER 4
# RESULTS AND DISCUSSION

## 4.1 Investigation of the anti-tacking property of selected surfactants

### 4.1.1 Effect of surfactants on the film tackiness

In the present study, four hydrophobic surfactants : Span 80, Span 60, Span 40, and Span 20, were tested for their anti-tacking property compared with talc and GMS, the well-known anti-tacking agents. T-peel tests were used to determine the tackiness of the test films. The force required to peel the pressed films from each other would represent the level of the film tackiness, at least for a comparative study (6). In order to assess the effects of the additives on the tackiness of the polymer films, the films were prepared by spraying, the same process as is used in the coating of the drug substrates. If the films are prepared by casting, the incorporated additives could sediment or move towards the film surface during the evaporation and film formation periods, which would make the structure of the cast films different from that of the films coated on the substrates.

The peel forces of the Eudragit NE 30D films and Eudragit RS 30D films containing various additives are summarized in Tables 10 and 11, respectively. Under the same condition used in the peel tests, the peel force of the pure Eudragit NE 30D film was 11.0 N, whereas this value of the pure Eudragit RS 30D film was 5.6 N. The peel force of the Eudragit NE 30D film was higher than that of the Eudragit RS 30D film, indicating that Eudragit NE 30D was more tacky than Eudragit RS 30D. This result corresponds to the thermal property of the polymers. The glass transition temperature ($T_g$) of Eudragit NE 30D is –8 $^oC$ (4). This polymer is soft and is in a rubbery state at room temperature. The polymer molecules can move and diffuse across the film surface easily, which makes the film very tacky. This polymer also does not require plasticizer for the film formation process. In case of Eudragit RS 30D, this polymer has $T_g$ at about 55 $^oC$ (4) and is in a glassy state at room temperature.

Normally, 20-30 %(w/w) plasticizer (based on polymer mass) is required for the film formation of this polymer. In this experiment, 30 % (w/w) acetyltributyl citrate (ATBC) was added to promote film formation during the spray process. However, the film obtained was still less tacky than the Eudragit NE 30D film.

The ability to reduce the film tackiness of talc and GMS is compared and shown in Figure 9. Talc could not significantly decrease the tackiness of the films when less than 50 % (w/w) was used. An obvious change was noticed only when up to 100 % was used. In contrast, only 5 % of GMS could lower the peel force significantly. This indicates the more powerful anti-sticking property of GMS over talc. This result is correspondent with the application of these materials as anti-tacking agents. Practically, the amount of talc in the coating formulation is not less than 20 %. In case of a very tacky film former, such as Eudragit NE 30D, the amount used may be up to 200 % (150). In contrast, the amount of GMS used is much less. Normally, not more than 10 % is used in the formulation. The results from this experiment also indicate that the peel test is an effective method for comparing the tackiness of the polymers.

Figures 10 and 11 demonstrate the effects of the surfactants on the tackiness of the Eudragit NE 30D and Eudragit RS 30D films, respectively. The results show that GMS, Span 60 and Span 40 could markedly reduce the tackiness of both films, and the film tackiness was lower when higher concentrations of these surfactants were used. In case of Span 80 and Span 20, both of these surfactants could greatly decrease the tackiness of the Eudragit NE 30D film when only 5 % was used, and their efficiencies were higher than GMS, Span 60 or Span 40. However, when the concentration was increased, the film tackiness did not decrease further. The efficiencies of these surfactants in the Eudragit NE 30D film at 5 %, 10 % and 15 % were not significantly different.

For the Eudragit RS 30D film, the effect of Span 80 and Span 20 on the film tackiness was opposite. Both these surfactants could not decrease the tackiness of this film. Moreover, the film tackiness was higher when 10 % of the surfactants was used. These results indicate that the mechanism of Span 80 and Span 20 that affect the film tackiness may be different from that of GMS, Span 60 and Span 40. The mechanism of these surfactants on the film tackiness was studied in the ensuing steps of these experiments.

Table 10. Peel forces of the Eudragit NE 30D films containing additives

| Additives | Peel force (N, mean (S.D.) | | | | | |
|---|---|---|---|---|---|---|
| | % w/w (based on polymer mass) | | | | | |
| | 0 | 5 | 10 | 15 | 50 | 100 |
| Talc | 11.0 (0.6) | 11.1 (0.6) | 9.9 (0.2) | 11.5 (1.0) | 10.8 (2.1) | 4.9 (1.2) |
| GMS | 11.0 (0.6) | 6.4 (0.9) | 2.8 (0.7) | 0.6 (0.3) | - | - |
| Span 80 | 11.0 (0.6) | 3.3 (0.3) | 2.1 (0.6) | 2.4 (0.3) | - | - |
| Span 60 | 11.0 (0.6) | 6.9 (0.5) | 4.2 (0.8) | 3.2 (0.5) | - | - |
| Span 40 | 11.0 (0.6) | 6.4 (0.8) | 5.1 (0.2) | 1.6 (0.2) | - | - |
| Span 20 | 11.0 (0.6) | 2.9 (0.5) | 2.4 (0.2) | 2.8 (0.5) | - | - |

Table 11. Peel forces of the Eudragit RS 30D films containing additives

| Additives | Peel force (N, mean (S.D.) | | |
|---|---|---|---|
| | % w/w (based on polymer mass) | | |
| | 0 | 5 | 10 |
| GMS | 5.6 (0.4) | 0.9 (0.1) | 0.6 (0.1) |
| Span 80 | 5.6 (0.4) | 5.1 (0.5) | 8.1 (0.3) |
| Span 60 | 5.6 (0.4) | 2.4 (0.3) | 1.7 (0.2) |
| Span 40 | 5.6 (0.4) | 3.5 (0.4) | 2.0 (0.3) |
| Span 20 | 5.6 (0.4) | 5.2 (0.3) | 8.9 (0.6) |

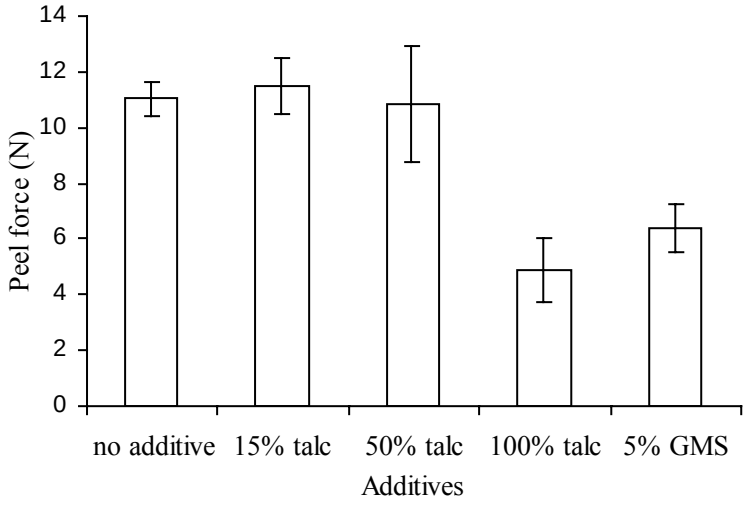



Figure 9. Effect of talc and GMS on the tackiness of Eudragit NE 30D films

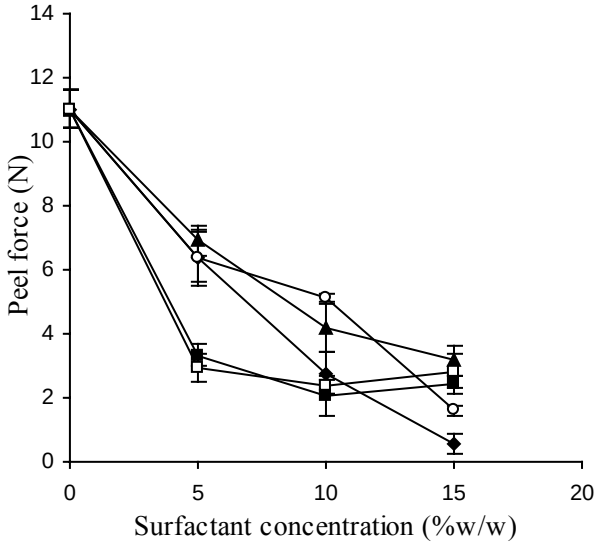



Figure 10. Effect of surfactants on the tackiness of Eudragit NE 30D. ♦, GMS; ■, Span80; ▲, Span60; ○, Span40; □, Span20

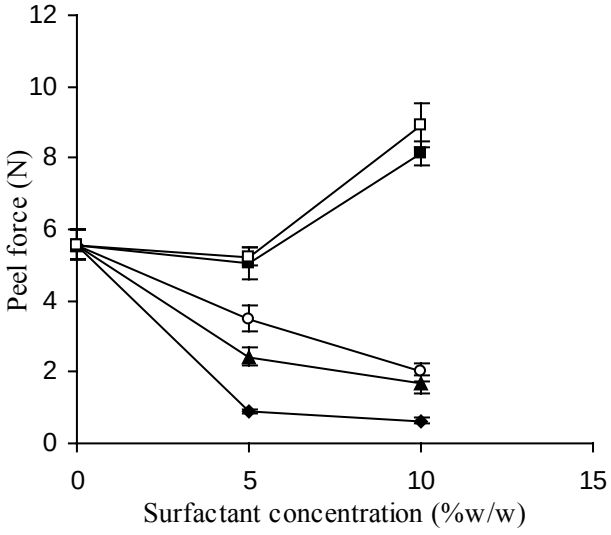



Figure 11. Effect of surfactants on the tackiness of Eudragit RS 30D films. ♦, GMS; ■, Span80; ▲, Span60; ○, Span40; □, Span20

### 4.1.2 Components of the films

#### A. Spectroscopic study

To investigate the structure of the film surface before and after incorporating the additives, changes in the IR spectrum of the film surface were studied by FTIR-ATR technique. The ATR-IR spectra of the Eudragit NE 30D film and the Eudragit RS 30D film are shown in Figures 12 and 13, respectively. The intensive peaks at about 1730 $cm^{-1}$ were found in both polymers. These peaks are attributed to the C=O stretching of the ester groups in the polymer structure, as these polymers are composed of ethyl acrylate and methyl methacrylate (151). Figure 14 exhibits the IR spectrum of talc with the characteristic peaks at 1017 and 669 $cm^{-1}$, whereas the spectrum of glyceryl monostearate (GMS) is shown in Figure 15. As this substance is an ester of glycerol and stearic acid, the broad band around 3400 $cm^{-1}$, which is attributed to the O-H stretching of the OH groups of glycerol could be obviously detected. Figures 16,17,18 and 19 exhibit the spectra of Span 80, Span 60, Span 40 and Span 20, respectively. The spectra of these materials are very similar, as all of them are fatty acid esters of sorbitan. The difference is only the kind of fatty acid that is esterified. The broad bands due to the O-H stretching which indicates the presence of the OH groups in the sorbitol sugar can also be found.

If the structure of the polymer film surface was interfered by the additives, the ATR-IR spectrum would be changed. The change in the spectrum should then indicate the level of the interference of the additives. Figure 20 exhibits the spectra of the Eudragit NE 30D film, talc and the films with various concentration of talc. It can be noticed that the spectra of the films containing talc are not significantly different from that of the original talc-free film, when less than 50% talc was incorporated. The characteristic peaks of talc at 669 $cm^{-1}$ and 1017 $cm^{-1}$ become evident, only when 100 %w/w of talc was added. On the contrary, when considering the change in the spectra between 2800 and 3000 $cm^{-1}$ of the films containing GMS in Figure 21, the characteristic peaks of GMS at 2849 $cm^{-1}$ and 2916 $cm^{-1}$ are clearly observed, even though only 5 %w/w of GMS was incorporated. This indicates that within the same concentration, GMS has much more influence on the structure of the film surface than talc. Moreover these findings were correspondent with the results from the peel test, which indicated that only 5 % GMS in the films could reduce the film tackiness

significantly, whereas at least 50% must be used in case of talc. These results indicate that the ability of the additives in reducing the film tackiness is related to their ability to change the structure of the film surface

Figures 22,23,24 and 25 show the ATR-IR spectra of the films containing Span 80, Span 60, Span 40 and Span 20, respectively. In case of the films containing Span 60 or Span 40, change in the spectra can be seen in both Eudragit NE 30D and Eudragit RS 30D even only 5% was added. The peaks of the surfactants are more dominant when their concentrations in the films increase. These findings were similar to those found in GMS. However, in the case of Span 80 and Span 20, the spectra of the Eudragit RS 30D films did not change significantly after incorporating the surfactants. This was related to the results from the peel tests, which showed that Span 80 and span 20 could not reduce the tackiness of the Eudragit RS 30D films. In addition, it was found that the surfaces of the Eudragit NE 30D films containing Span 80 or Span 20 were very oily to the touch. This indicated the presence of Span 80 and Span 20 at the film surface since both of these surfactants are liquids. It is possible that the solubility of Span 80 and Span 20 in the polymers is limited and some insoluble portions could be exuded to the surfaces to become a layer of surfactant covering the film surfaces (152). This resulted in a notable reduction of the film tackiness, as shown in the peel tests, even though only 5% of them were used. This assumption was proven by wiping the surfaces of the films two to three times with cotton wool and comparing the ATR-IR spectra of the film surfaces before and after wiping. The results are shown in Figure 26. It can be noticed that the spectra of the film surfaces before and after wiping are different, indicating that some portions of the surfactant were possibly removed. Nevertheless, the exudation of these surfactants was not evidently found in the Eudragit RS 30D films. This difference might be because Eudragit NE 30D is more hydrophilic than Eudragit RS 30D (4). In case of the incorporation of sorbitan esters which are hydrophobic surfactants, the surfactants would be less compatible with Eudrait NE 30D than with Eudragit RS 30D.

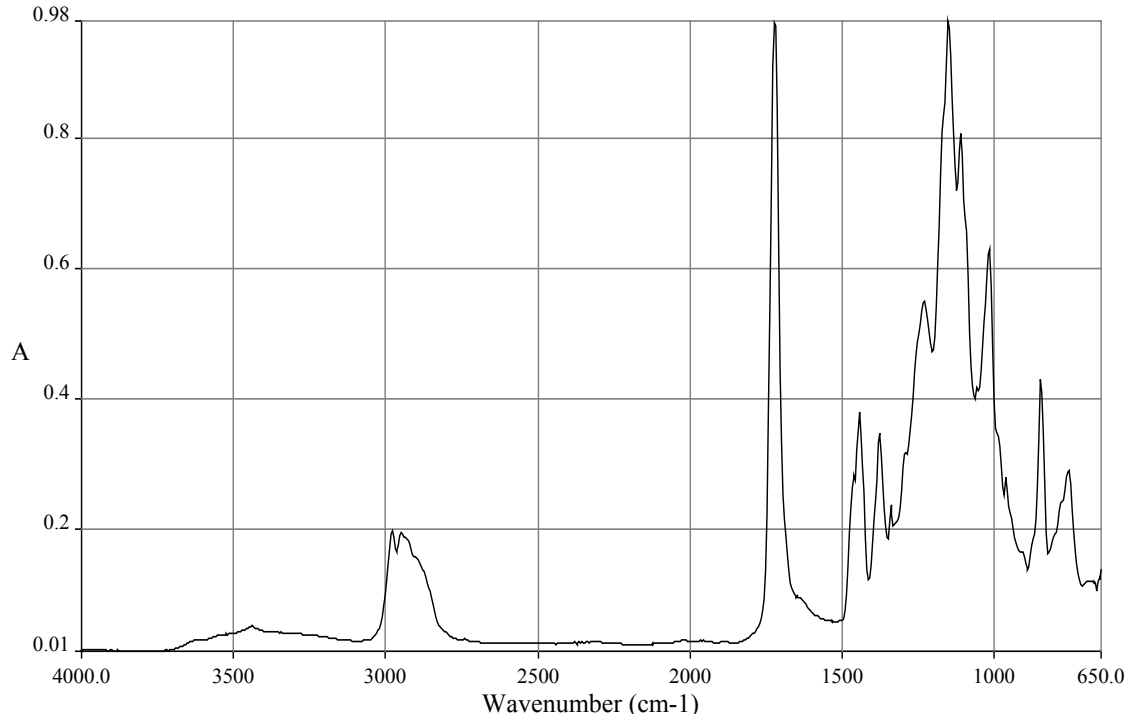



Figure 12. ATR-IR spectrum of Eudragit NE 30D film

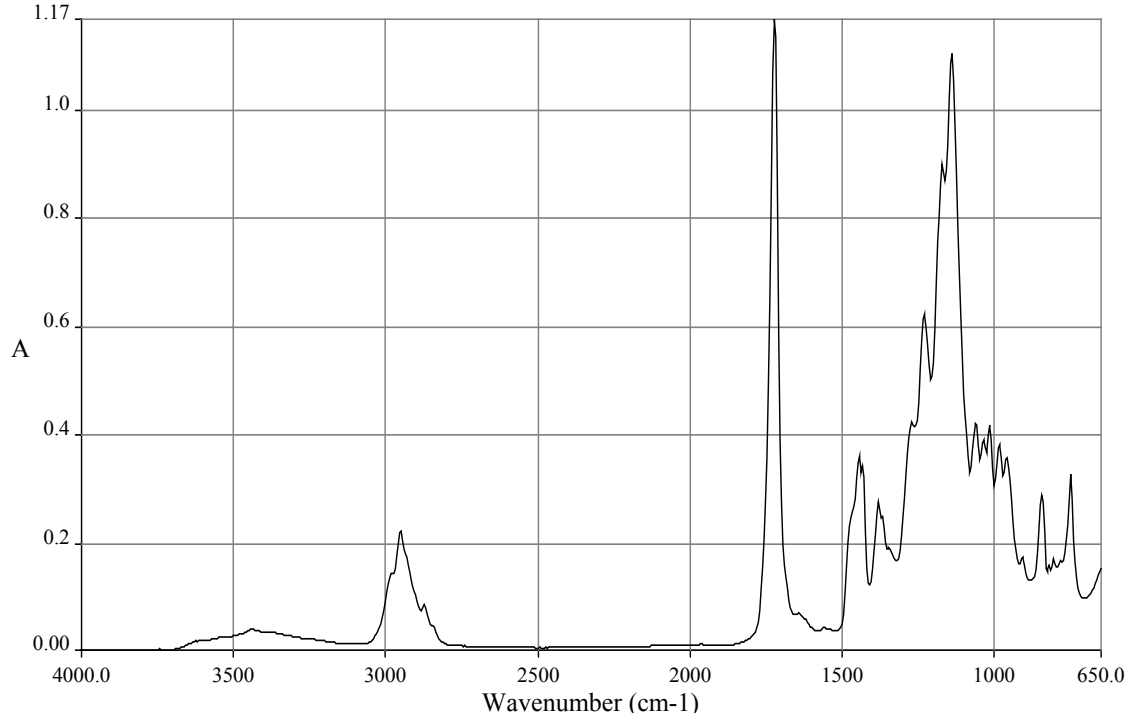



Figure 13. ATR-IR spectrum of Eudragit RS 30D film

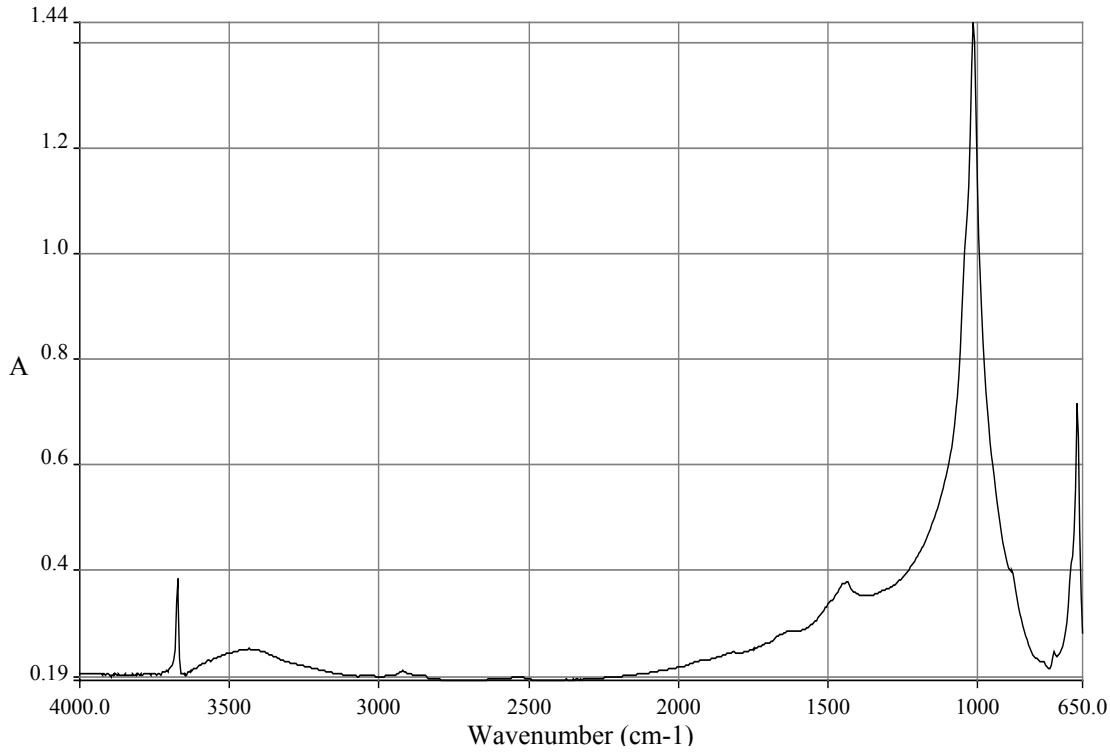



Figure 14. IR spectrum of talc

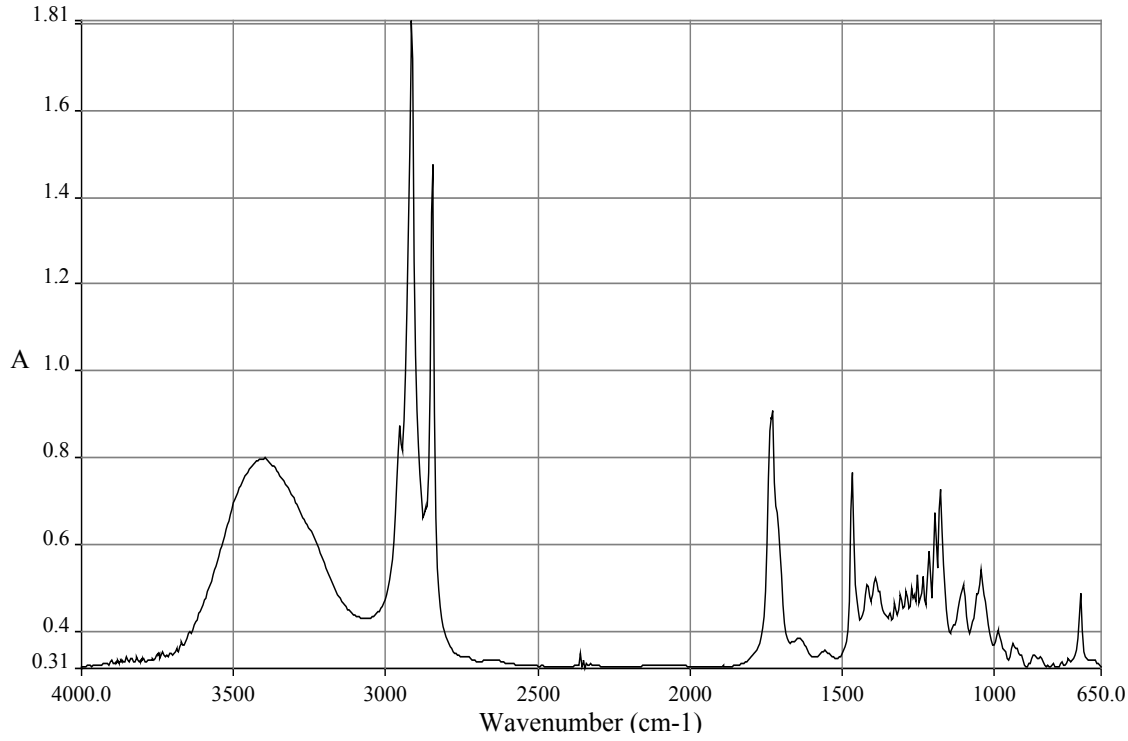



Figure 15. IR spectrum of glyceryl monostearate

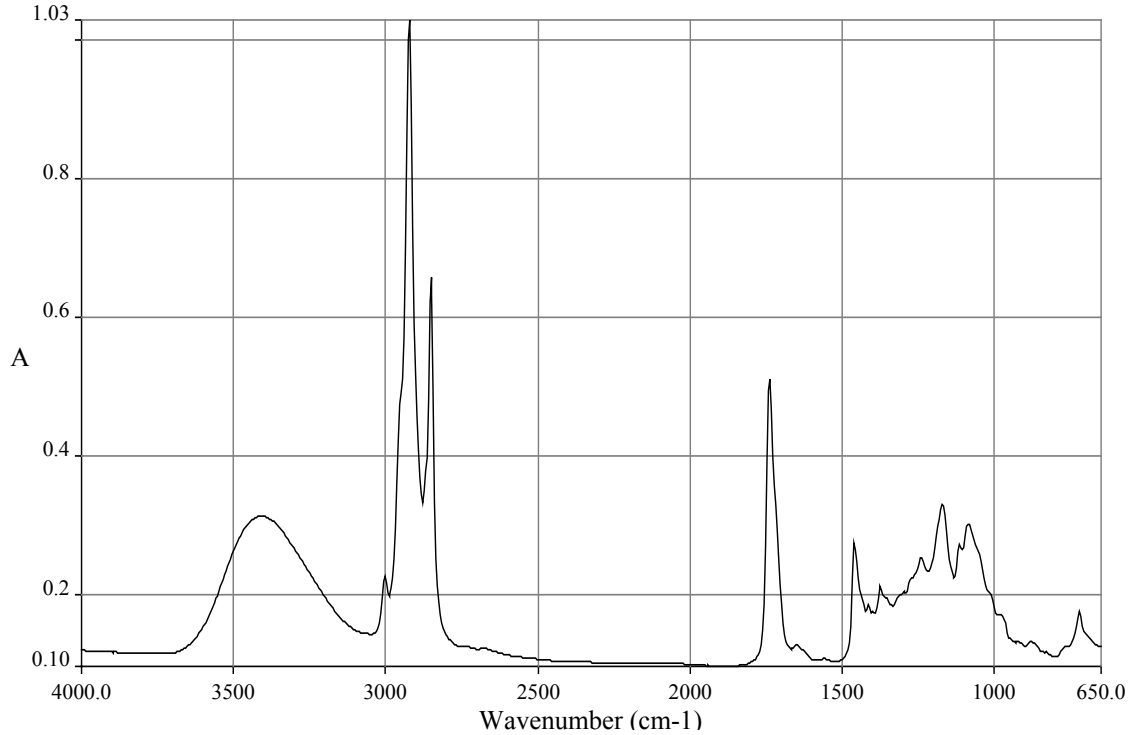



Figure 16. IR spectrum of Span 80

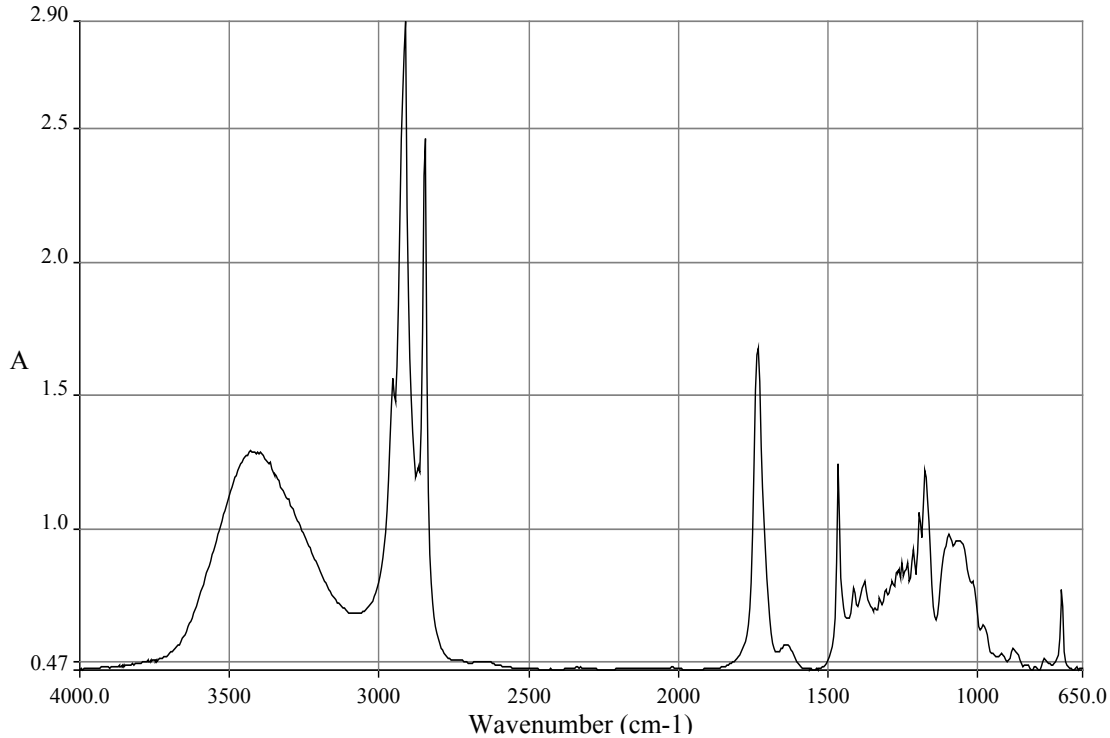



Figure 17. IR spectrum of Span 60

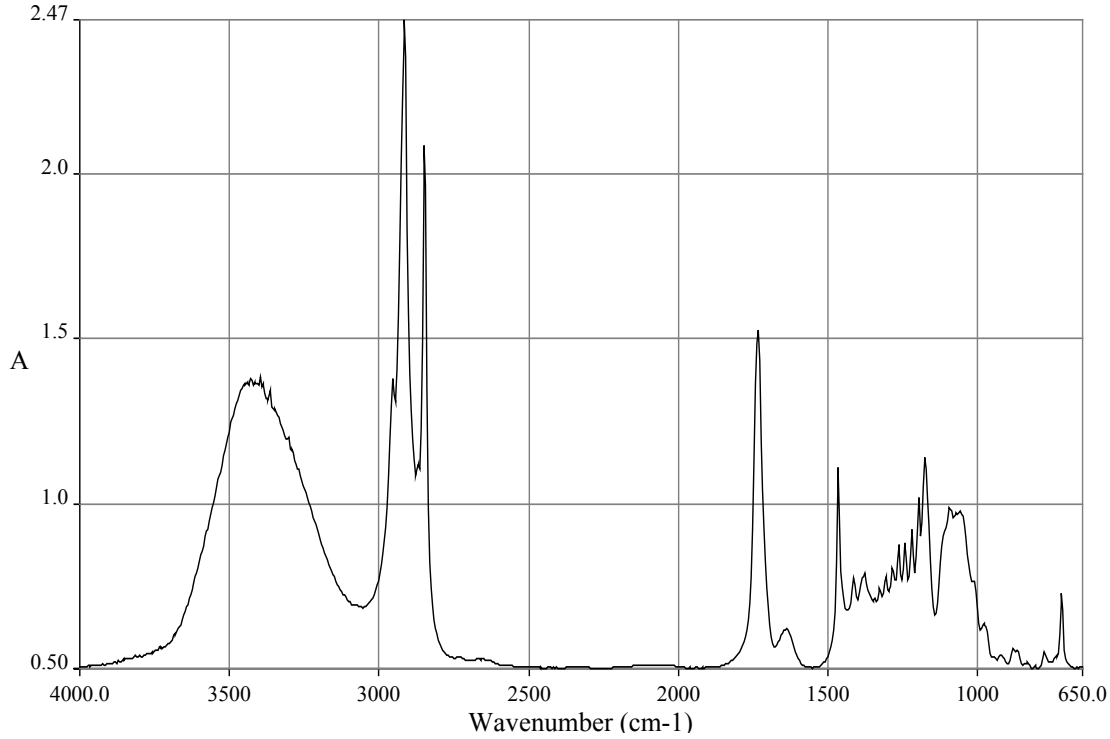



Figure 18. IR spectrum of Span 40

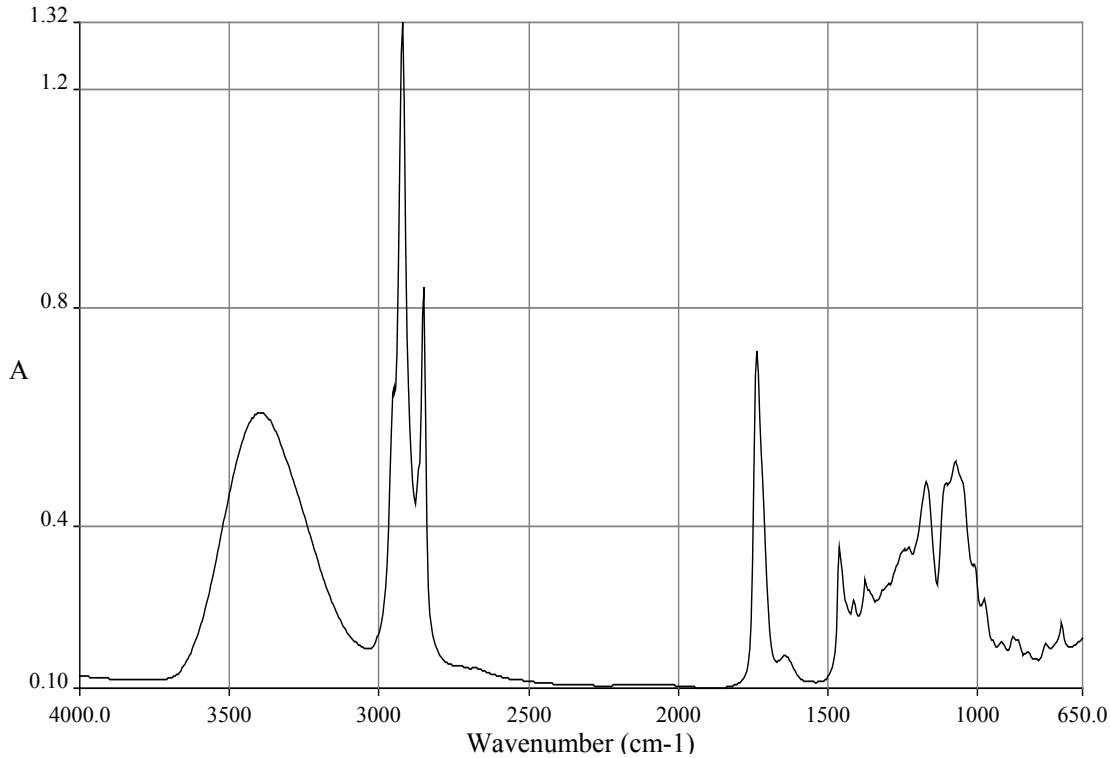



Figure 19. IR spectrum of Span 20

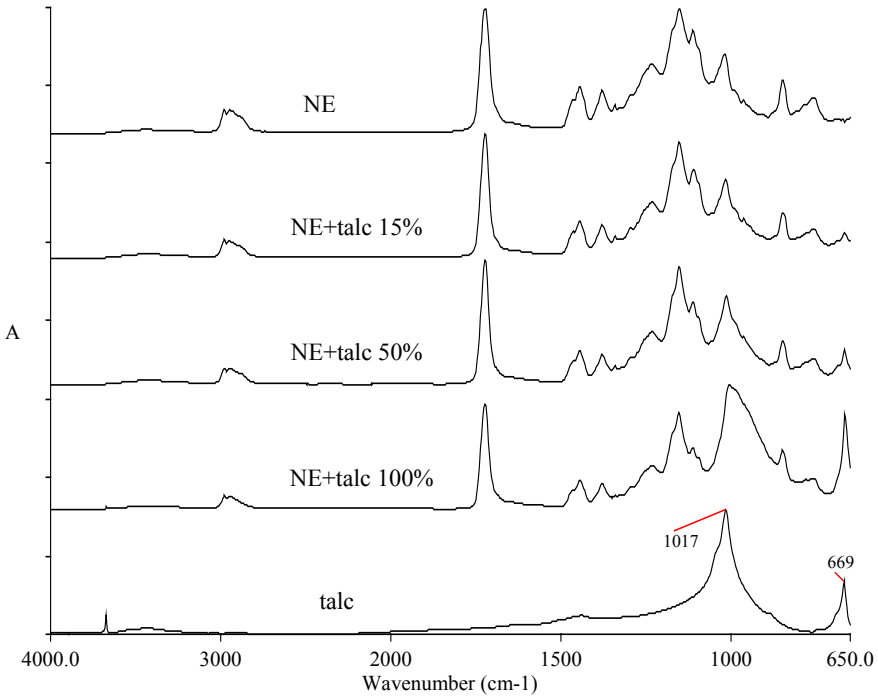



Figure 20. ATR-IR spectra of Eudragit NE 30D films containing talc

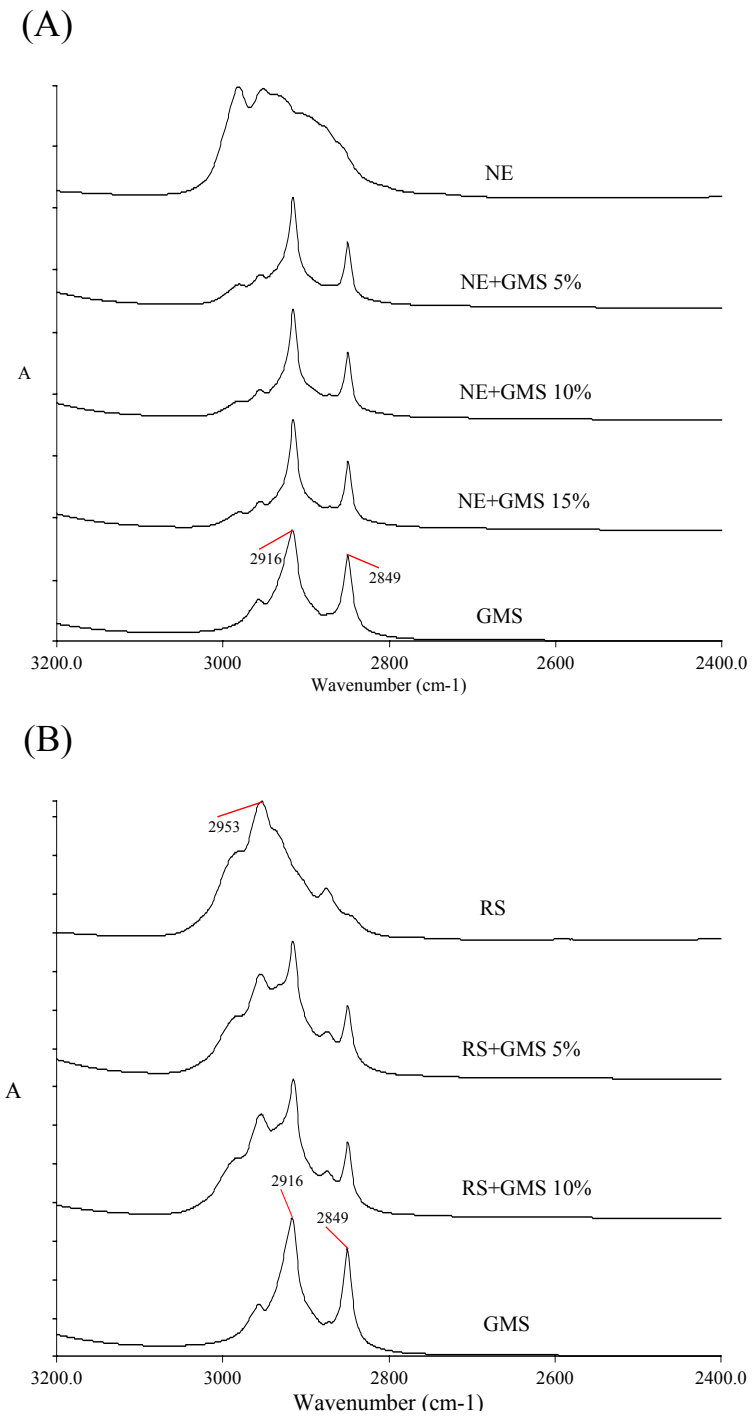



Figure 21. ATR-IR spectra of Eudragit NE 30D films (A) and Eudragit RS 30D films (B) containing glyceryl monostearate (GMS)

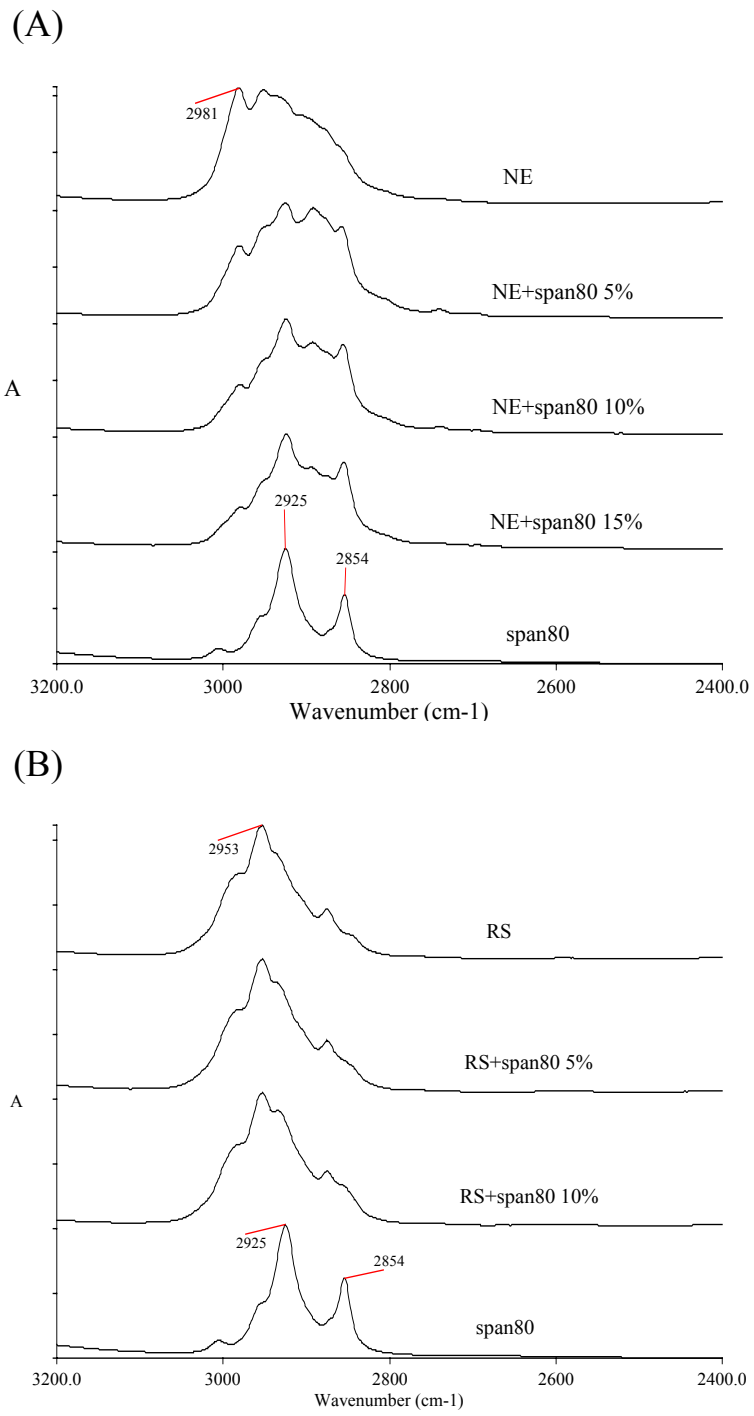



Figure 22. ATR-IR spectra of Eudragit NE 30D films (A) and Eudragit RS 30D films (B) containing Span 80

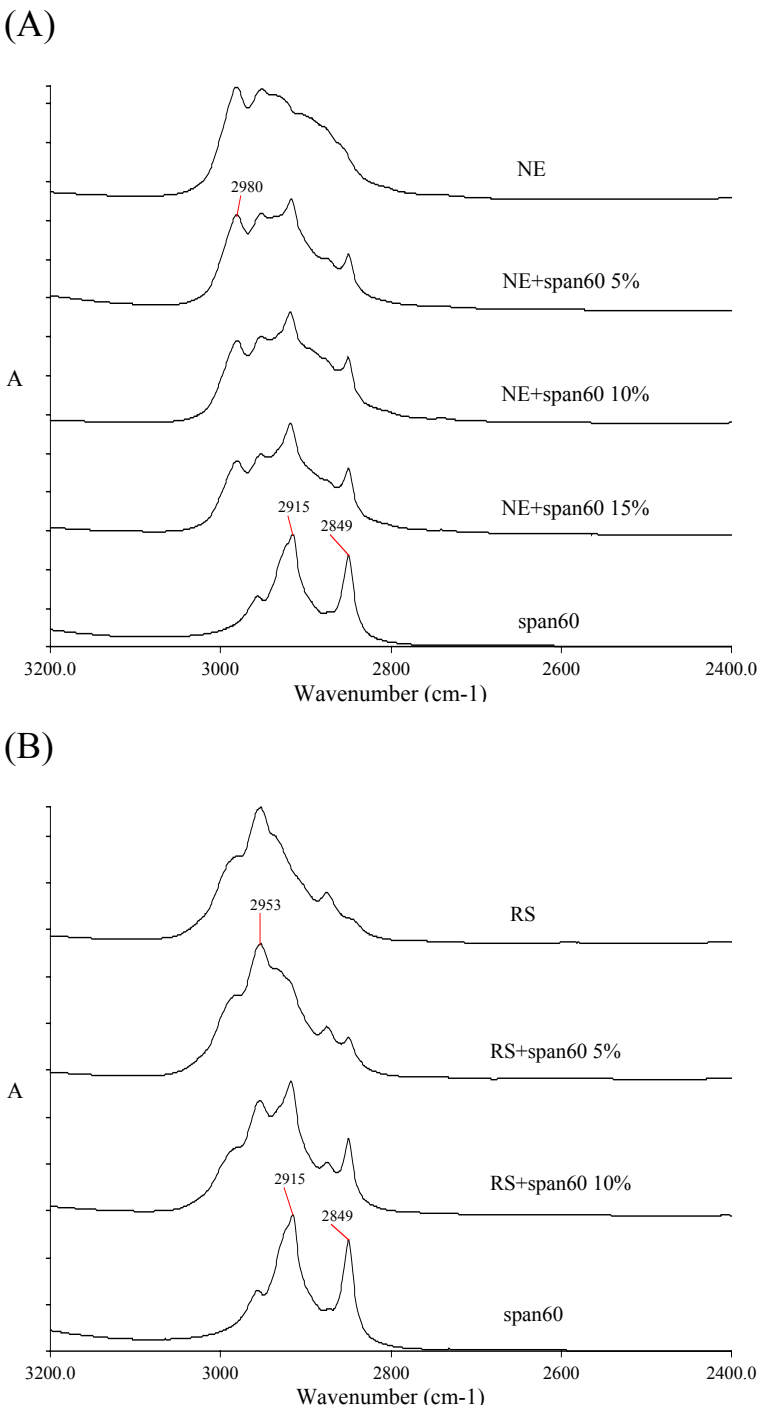



Figure 23. ATR-IR spectra of Eudragit NE 30D films (A) and Eudragit RS 30D films (B) containing Span 60

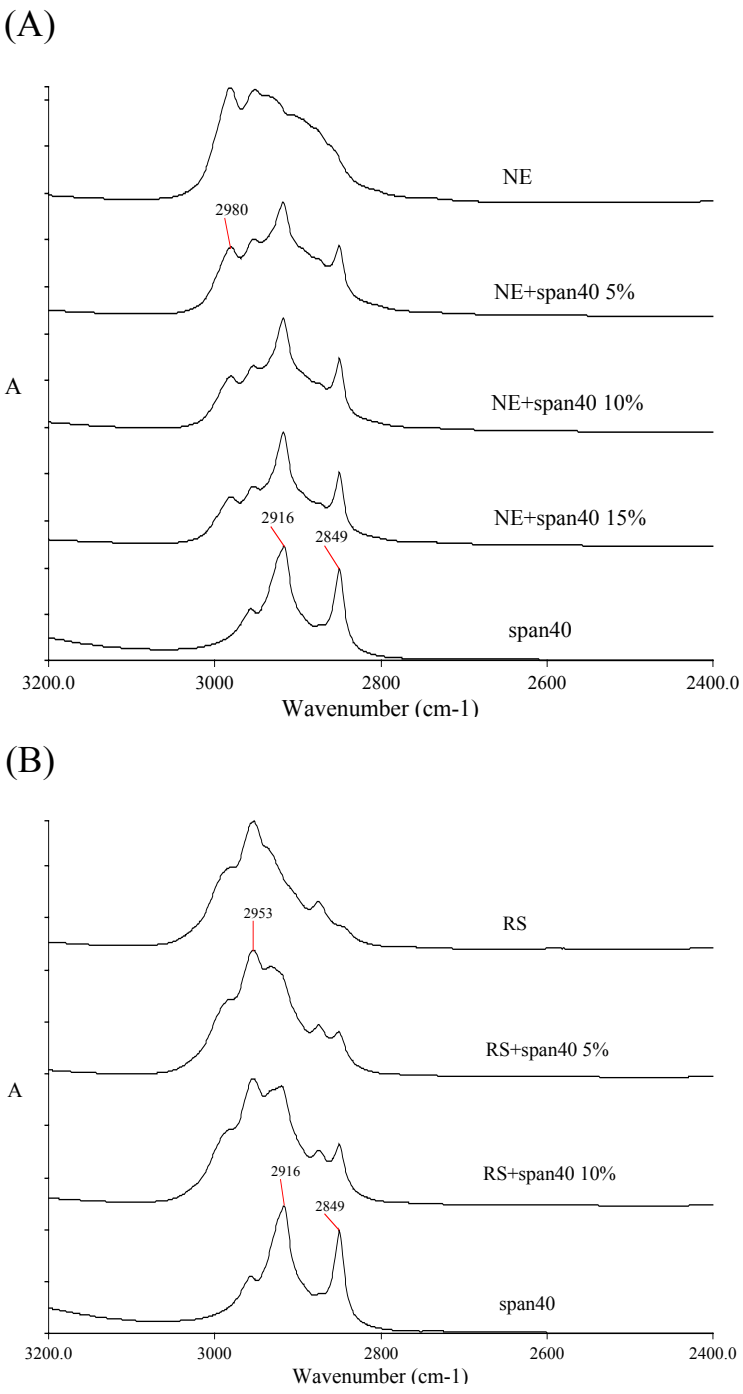



Figure 24. ATR-IR spectra of Eudragit NE 30D films (A) and Eudragit RS 30D films (B) containing Span 40

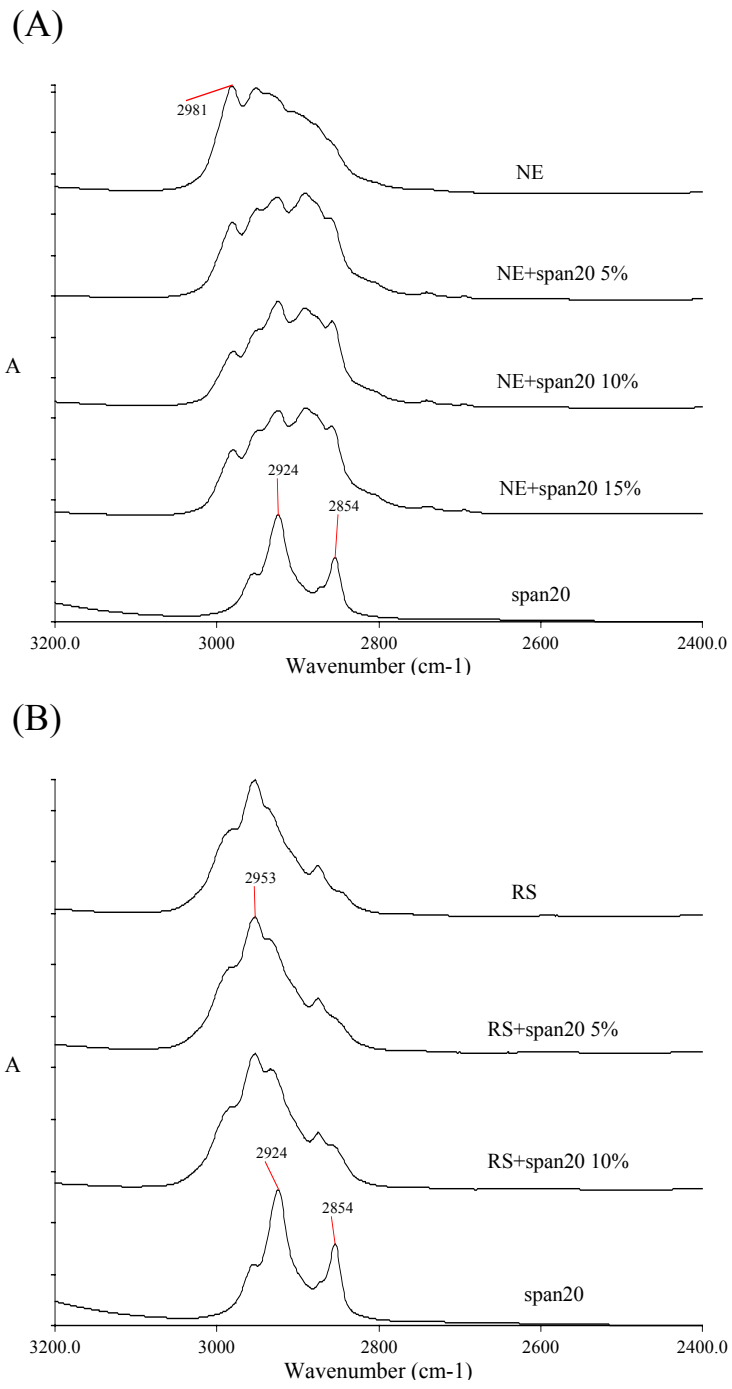



Figure 25. ATR-IR spectra of Eudragit NE 30D films (A) and Eudragit RS 30D films (B) containing Span 20

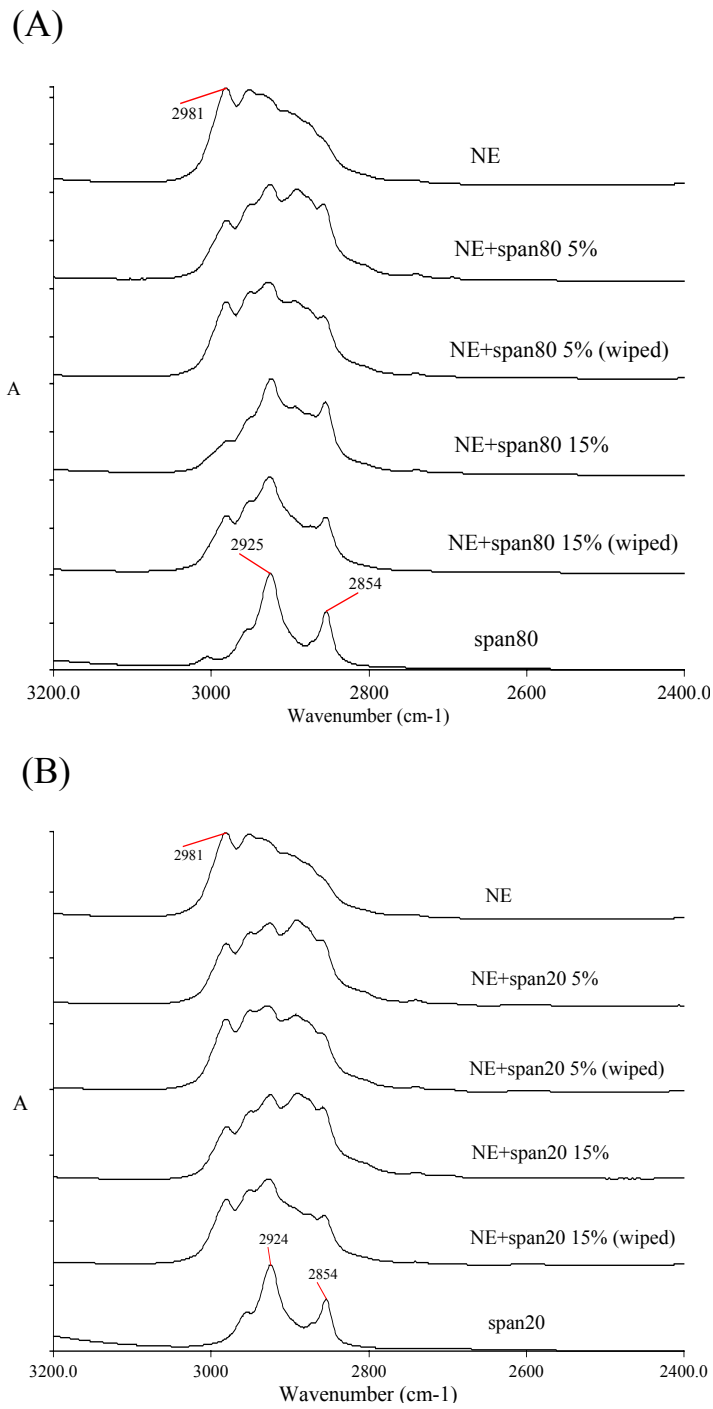



Figure 26. ATR-IR spectra of Eudragit NE 30D films containing Span 80 (A) and Span 20 (B) before and after wiping

**B. Microscopic study**

In this study, the characteristics of the films containing the additives were investigated under optical microscope. The images of the free Eudragit NE 30D film and the films with various concentration of talc are shown in Figure 27. It can be noticed that for the film containing 5 % talc, only a few particles of talc could be observed. When 50 or 100 % talc was incorporated, more particles could be seen and the area occupied by the polymer is less. This finding was consistent with the IR spectra of the films, which showed that the characteristic peaks of talc appeared evidently in the spectra only when more than 50 % talc was added. In contrast, when considering the images of the Eudragit NE 30D and Eudragit RS 30D films containing 5 % GMS as shown in Figure 28, the films show a lot of small GMS particles covering a large area of the films. Considering the fact that GMS is practically insoluble in water due to its low HLB (3.8), in the current experiment, GMS was homogenized in water at 65 $^{o}$C which is above its melting point (55-60 $^{o}$C) (16). As a result, the material turned into small liquid droplets and became solid when cooled. Thus the GMS particles were much smaller than the talc particles. Within the same volume, a large number of small particles can occupy a greater area than a small number of large particles. In addition, the specific gravity of GMS is 0.92, whereas this value of talc is approximate 2.7 (16). Therefore, within the same weight, the volume of GMS is about three times larger than that of talc. These microscopic images of the films were also in good agreement with the IR spectra, which showed dominant characteristic peaks of GMS. This indicates that the efficiency of the materials in reducing the tackiness of the films is related to their capability in reducing the contact area between the polymer. GMS can decrease more polymer contact area than talc, thus the ability to reduce film tackiness of GMS is greater.

The images of the films containing Span 80, Span 60, Span 40 and Span 20 are shown in Figures 29, 30, 31 and 32, respectively. One can notice that the images of the films containing Span 60 or Span 40 show a large number of additive particles dispersing throughout the film areas, similar to those of the GMS-containing films. This finding was correspondent with the results from the peel tests; that was Span 60 and Span 40 could reduce the tackiness of the Eudragit NE 30D and the Eudragit RS 30D film to the same extent as GMS. Since both these surfactants are waxy solid

substances like GMS, with a melting point 53-57 $^{o}$C for Span 60 and 43-48 $^{o}$C for Span 40 (16), therefore they can be dispersed into small particles by homogenizing in hot water similar to GMS. However, in case of the films containing Span 80 or Span 20, the images are different from those containing GMS, Span 60 or Span 40. Many droplets of the surfactants with various sizes can be obviously seen, especially in the Eudragit NE 30D films. As both these surfactants are hydrophobic liquid, although they were homogenized into small droplets, it was possible that during the film coalescence process, the surfactant droplets coalesced with one another to become larger droplets, and some might exude toward the film surface. The exudation of the surfactants appeared to occur more in Eudragit NE 30D film than in Eudragit RS 30D films. This can be noticed from the number of the droplets in Eudragit NE 30D films which are more than those in Eudragit RS 30D films, indicating that the surfactants might be less compatible with Eudragit NE 30D than with Eudragit RS 30D. All of the results from the optical microscopic study were correspondent with the results from the spectroscopic study.

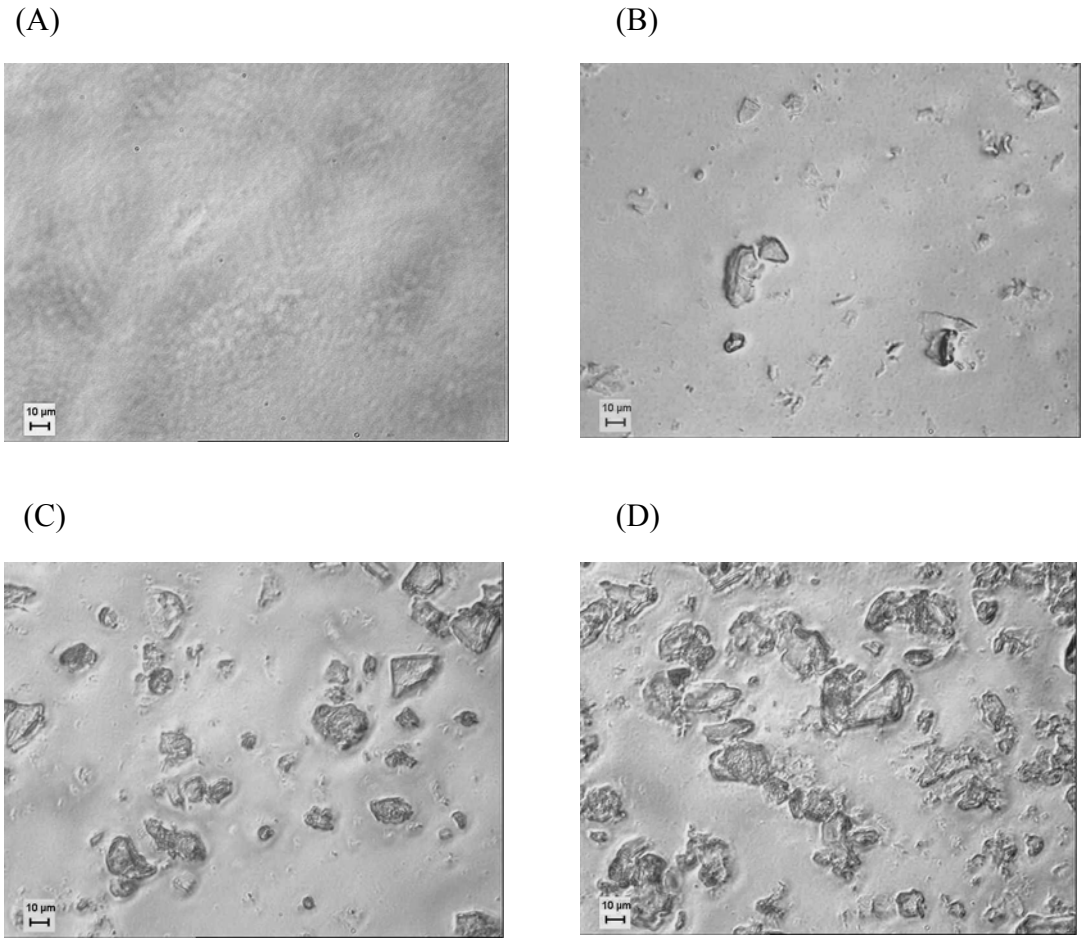
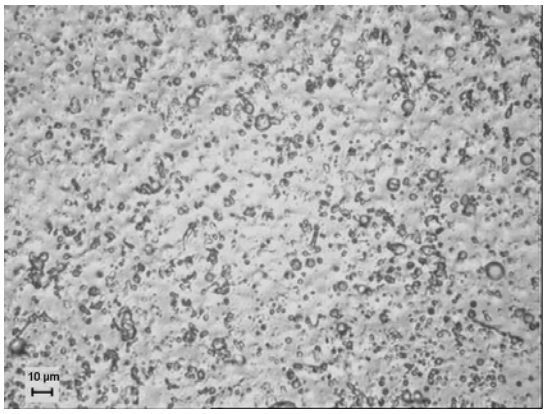



Figure 27. Optical microscopic images of Eudragit NE 30D films without additive (A) and the films containing: 5 % talc (B); 50 % talc (C) and 100 % talc (D)

(A)




(B)

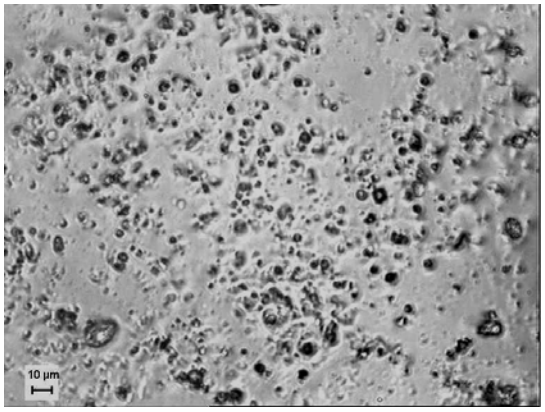
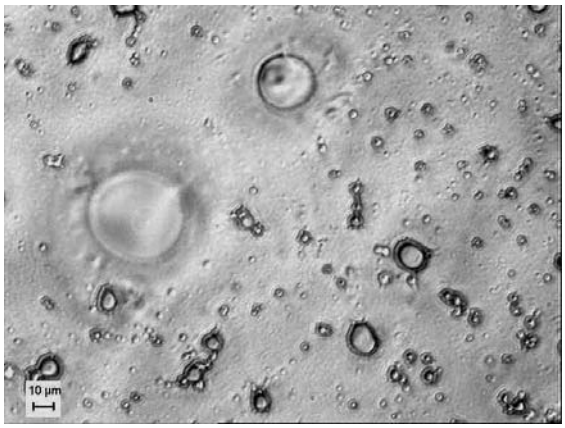



Figure 28. Optical microscopic images of Eudragit NE 30D film (A) and Eudragit RS 30D film (B) containing 5 % GMS

(A)




(B)

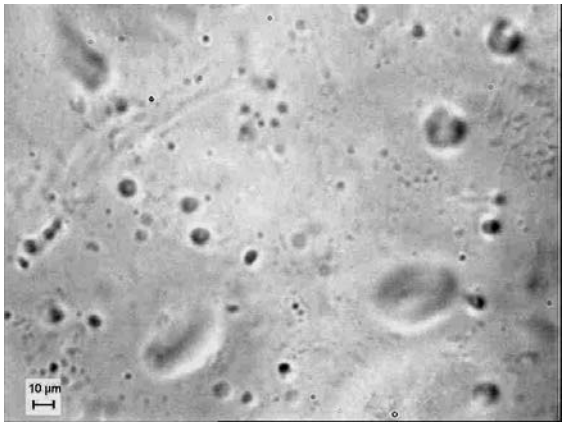
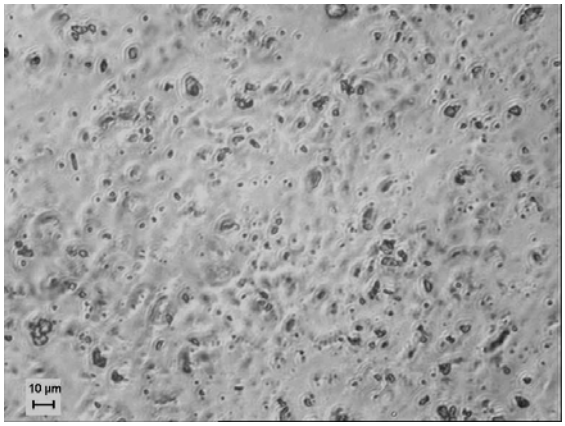



Figure 29. Optical microscopic images of Eudragit NE 30D film (A) and Eudragit RS 30D film (B) containing 5 % Span 80

(A)




(B)

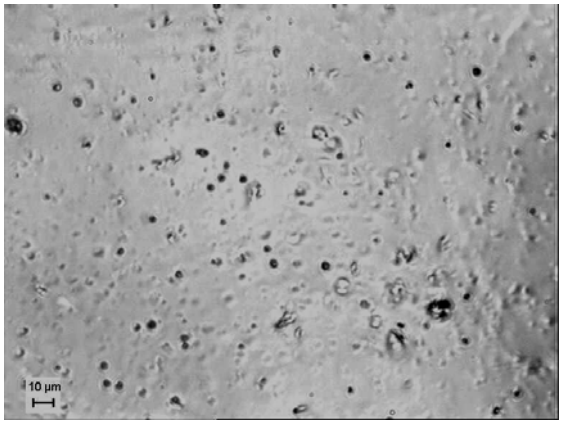
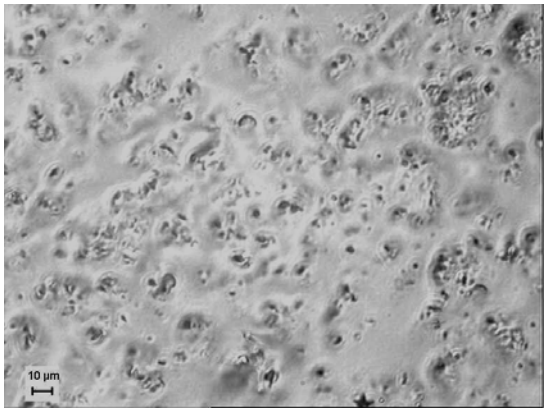



Figure 30. Optical microscopic images of Eudragit NE 30D film (A) and Eudragit RS 30D film (B) containing 5 % Span 60

(A)




(B)

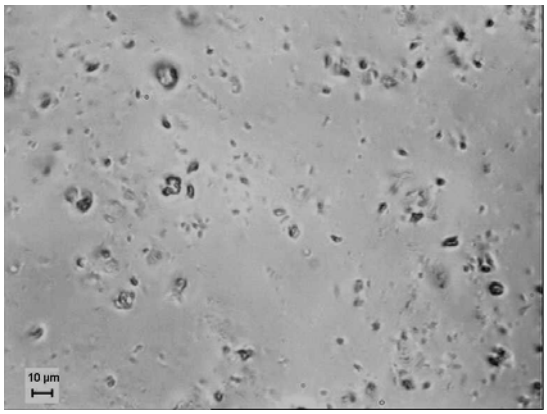
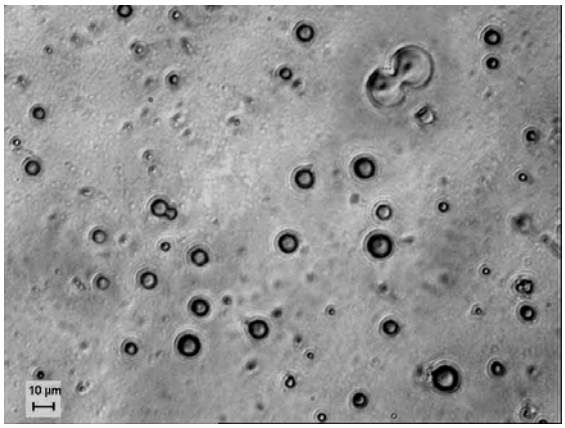



Figure 31. Optical microscopic images of Eudragit NE 30D film (A) and Eudragit RS 30D film (B) containing 5 % Span 40

(A)




(B)

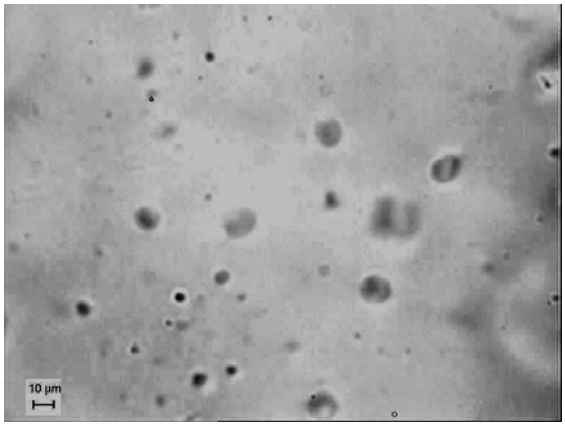



Figure 32. Optical microscopic images of Eudragit NE 30D film (A) and Eudragit RS 30D film (B) containing 5 % Span 20

### 4.1.3 Mechanical properties of the films

#### 4.1.3.1 Storage modulus

The achievement of intimate contact between the polymer surfaces requires deformation of the materials, which is related to the storage modulus (153). In other words, if the additives can soften the polymer films, the tackiness of the films would be higher as the contact between the polymer surfaces is more intimate, resulting in higher bond strength. Inter-diffusion of the polymer molecules across the surfaces may also occur. On the contrary, if the additives increase the polymer hardness, the tackiness would be lowered. It is known that the incorporation of the additives or fillers into the polymer matrix has a complex influence on the final physical and mechanical properties of the polymer (154). In the current study, the storage modulus of the films was measured by a dynamic mechanical analyzer at various strain levels, at room temperature and constant frequency. Figure 33 exhibits the storage modulus of the Eudragit NE 30D films and the Eudragit RS 30D films containing GMS. It can be noticed that GMS could increase the modulus of the Eudragit NE 30D films, whereas the modulus of the Eudragit RS 30D films was slightly lowered. However, GMS could reduce the tackiness of both Eudragit NE 30D and Eudragit RS 30D films. Therefore, the effect of GMS on the modulus of the films might be too small to affect the ability of GMS in reducing the film tackiness.

Figures 34, 35, 36 and 37 exhibit the moduli of the films containing Span 80, Span 60, Span 40 and Span 20, respectively. The results show that Span 60 and Span 40 had slight effects on the modulus of the films, whereas Span 80 and Span 20 could decrease the modulus of the films significantly. It was possible that some portion of these surfactants could dissolve in the polymer and behaved as plasticizer, resulting in the reduction of the polymer hardness (4). From these findings, it could be assumed that Span 80 and Span 20 could increase the film tackiness by decreasing the modulus of the films. However, in the case of the Eudragit NE 30D films, this effect was overcome by the existence of the surfactant layers at the film surfaces, which prevented the direct contact between the polymer at the surfaces.

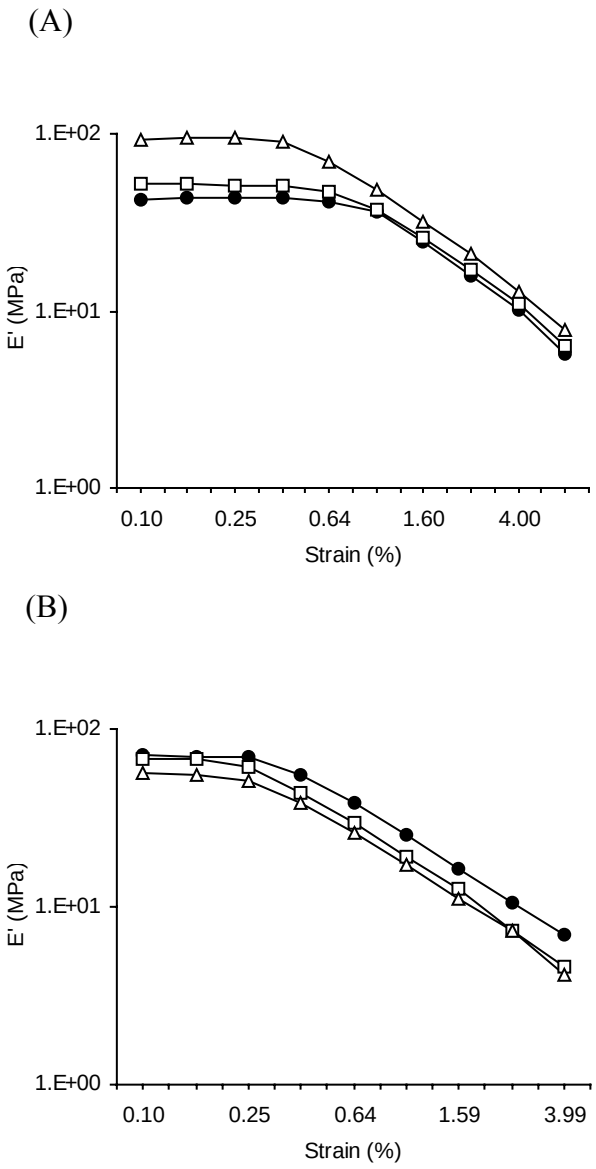
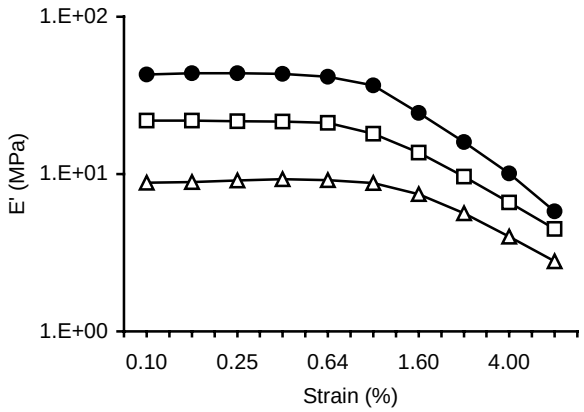



Figure 33. Storage modulus of Eudragit NE 30D films (A) containing no additive (•), 5% GMS (□), 15% GMS (Δ) and Eudragit RS 30D films (B) containing no additive (•), 5% GMS (□), 10% GMS (Δ).

(A)




(B)

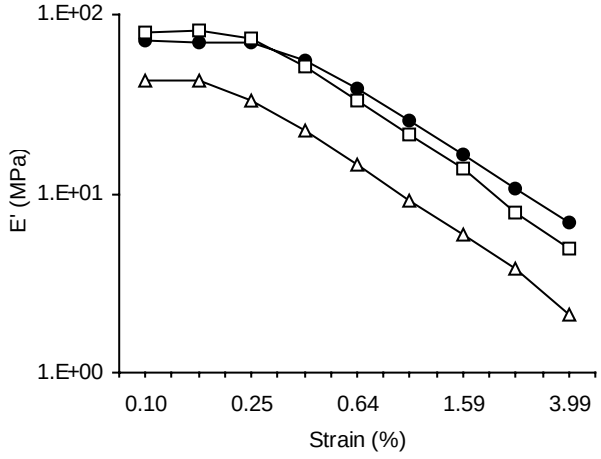



Figure 34. Storage modulus of Eudragit NE 30D films (A) containing no additive (●), 5% Span80 (□), 15% Span80 (Δ) and Eudragit RS 30D films (B) containing no additive (●), 5% Span80 (□), 10% Span80 (Δ).

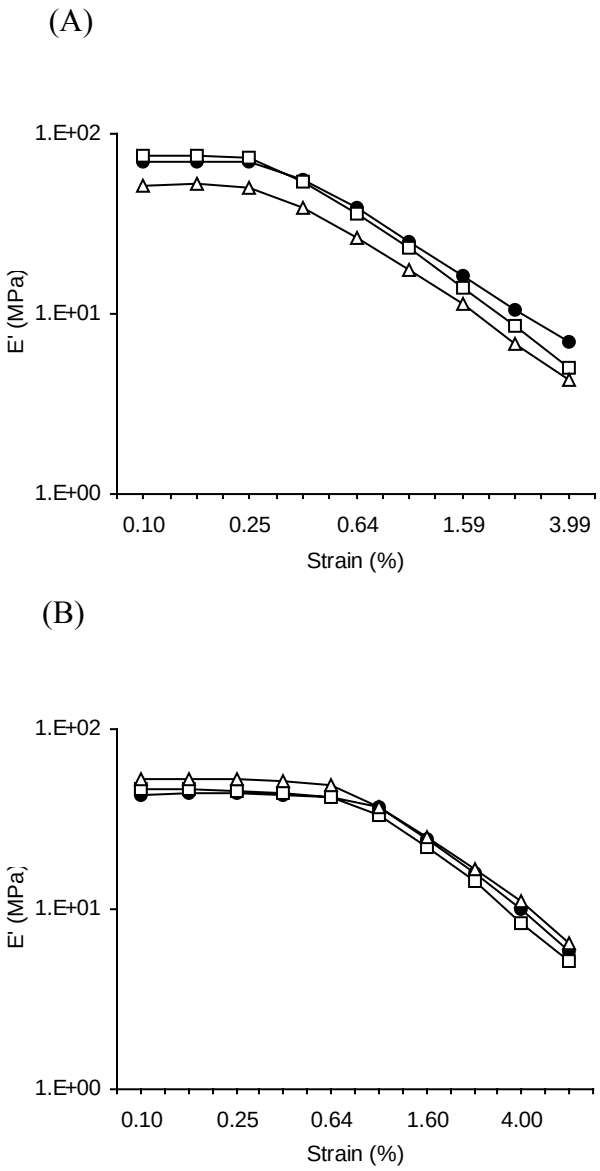



Figure 35. Storage modulus of Eudragit NE 30D films (A) containing no additive (•), 5% Span60 (□), 15% Span60 (Δ) and Eudragit RS 30D films (B) containing no additive (•), 5% Span60 (□), 10% Span60 (Δ).

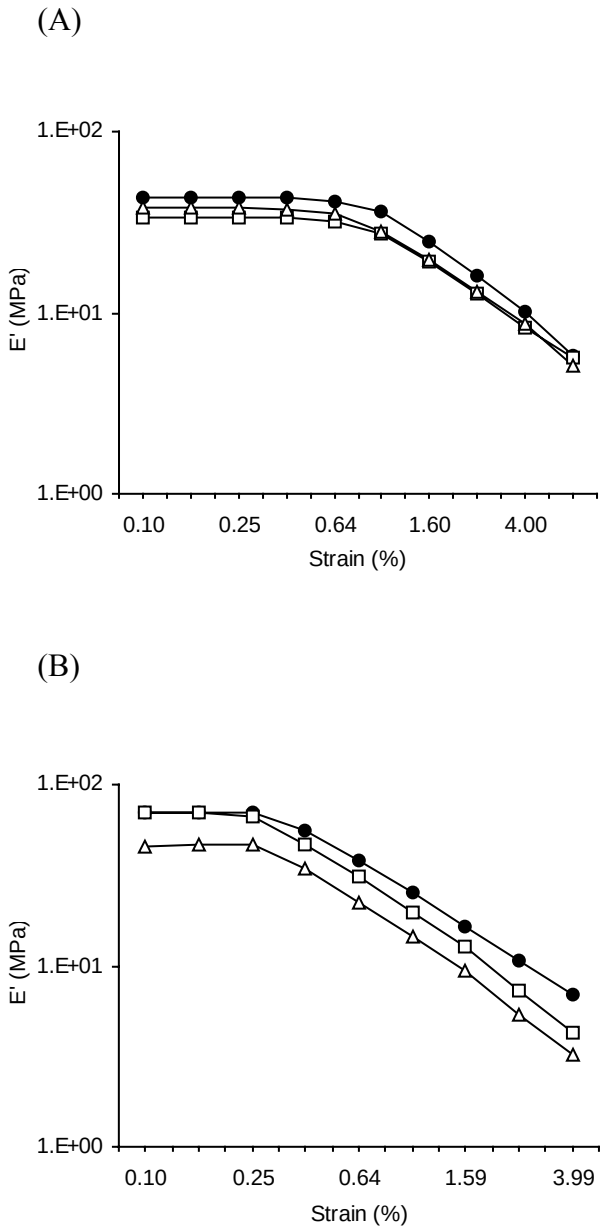



Figure 36. Storage modulus of Eudragit NE 30D films (A) containing no additive (●), 5% Span40 (□), 15% Span40 (Δ) and Eudragit RS 30D films (B) containing no additive (●), 5% Span40 (□), 10% Span40 (Δ).

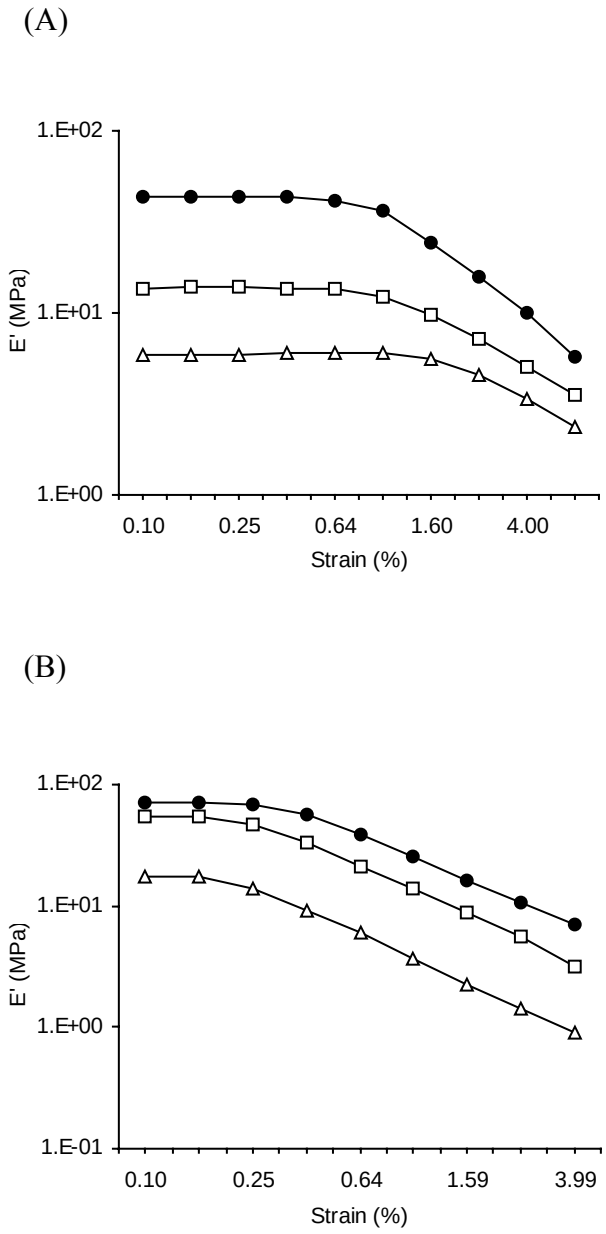



Figure 37. Storage modulus of Eudragit NE 30D films (A) containing no additive (•), 5% Span20 (□), 15% Span20 (Δ) and Eudragit RS 30D films (B) containing no additive (•), 5% Span20 (□), 10% Span20 (Δ).

#### 4.1.3.2 Film flexibility

Flexibility is also an important characteristic of the film coating on the drug substrates. A flexible film is more resistant to mechanical stress as well as being able to maintain the integrity of the coated substrates during passage down the gastrointestinal tract. A high level of talc in the coating formulation can greatly affect the film flexibility (150). The effects of talc and surfactants on the film flexibility were also examined in this study. Figure 38 shows the effect of talc on the elongation at break of the Eudragit NE 30D films. The result was in good agreement with the previous studies. When there was no additive in the film, the elongation at break was 607%, which was a very high value, indicating a high flexibility of the Eudragit NE 30D film. This property is due to the low $T_g$ of this polymer as described previously. And this is also related to the high tackiness of the polymer. After talc was added into the film, the elongation at break decreased dramatically, and the film nearly had no flexibility when 100% talc was added. As discussed formerly, to be an effective anti-tacking agent, high concentration of talc must be added into the formulation. Therefore, this result indicates the drawback of talc that it makes the film become more rigid. Compared with the use of the surfactants, the effects of GMS and Spans on the flexibility of the Eudragit NE 30D films are shown in Figure 39. It can be noticed that all these surfactants did not significantly decrease the elongation at break of the films, especially when less than 10%, which is the normal range of the application, was incorporated. In addition, in case of Span 80 and Span 20, one can notice that the flexibility of the films was higher. This might be due to some plasticizing effect of these surfactants that made the films softer and more flexible, as discussed previously.

Figure 40 shows the elongation at break of the Eudragit RS 30D films containing the surfactants. The elongation at break was 141% when there was no additive in the films, indicating that the Eudragit RS 30D film was less flexible than the Eudragit NE 30D film. This result was correspondent with their modulus and tackiness. In addition, all the surfactants used in this experiment also did not reduce the flexibility of the Eudragit RS 30D films. The findings were similar to those found in the Eudragit NE 30D films.

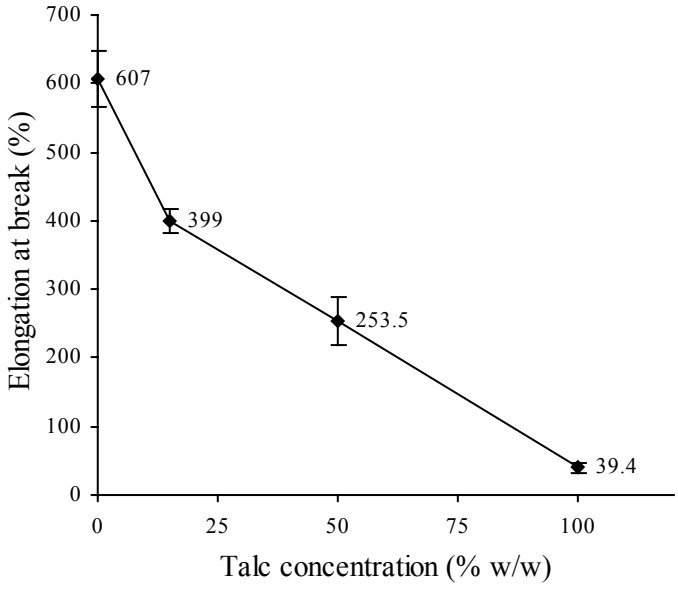



Figure 38. Effect of talc on the elongation at break of Eudragit NE 30D films

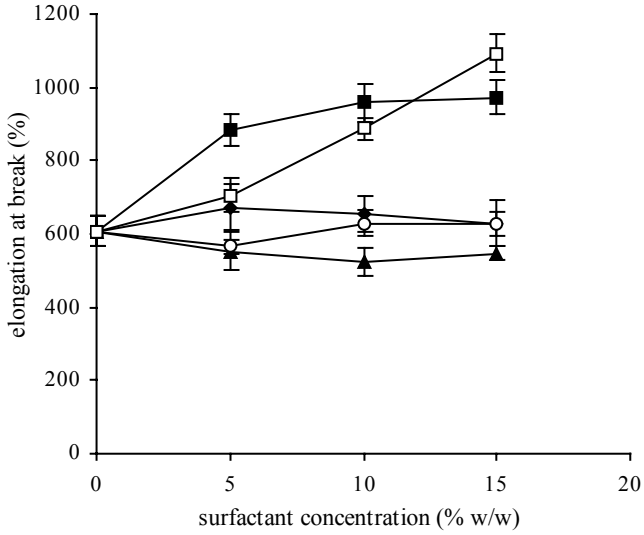



Figure 39. Effect of surfactants on the elongation at break of Eudragit NE 30D films.
♦, GMS; ■, Span80; ▲, Span60; ○, Span40; □, Span20

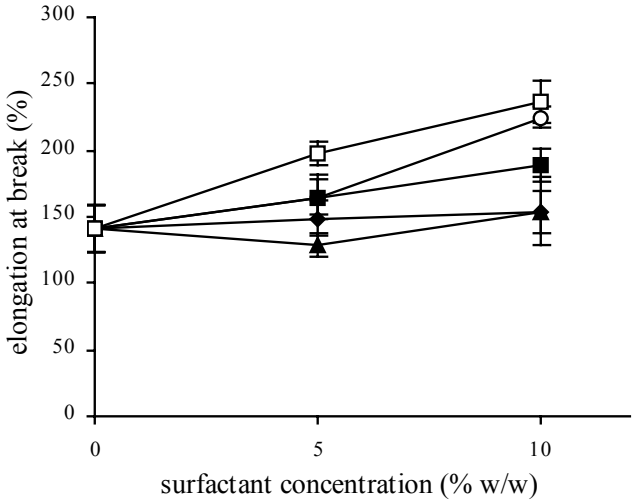



Figure 40. Effect of surfactants on the elongation at break of Eudragit RS 30D films.

♦, GMS; ■, Span80; ▲, Span60; ○, Span40; □, Span20

### 4.1.4 Evaluation of the core pellets

#### 4.1.4.1 Determination of the drug content

The content of theophylline in the core pellets was determined using UV spectrophotometry. The absorbances of various concentrations of the drug solution at wavelength 271 nm in methanol and in 0.1 N HCl are shown in Tables 12 and 13, respectively. The absorbances were plotted against the concentrations as shown in Figures 41 and 42. The relationships were linear with good correlation coefficients. The slope and y-intercept were calculated by linear regression analysis.

As theophylline has a good solubility (1:80) in alcohol, therefore in this experiment it was extracted from the pellets with methanol. The theophylline content in the pellets calculated from spectrophotometric measurement was 21.11 %

#### 4.1.4.2 Drug dissolution

One of the main objectives of this study was to evaluate the anti-tacking property of certain surfactants, therefore, the Eudragit NE 30D and the Eudragit RS 30D polymers, which are known for their tackiness, were used in this experiment. Although these polymers are water insoluble, they are water permeable. Therefore, they are often used to coat on the drug substrates to create a reservoir-diffusion controlled-release system. In this case, the permeation of the drug molecules through the polymer membrane is the process to control the drug release rate. If the polymer membrane loses its integrity, for example, by the mechanical damage from the separation of the agglomerated substrates, the membrane would no longer be able to control the release of the drug molecules. In order to determine the integrity of the polymer membrane coating on the drug substrates, the drug release rates between the core and the coated pellets should be significantly different. In other words, the drug release from the cores should be rapid. In this experiment, as theophylline, the model drug, has a fair solubility in water (1:120), thus the drug release rate from the cores was somewhat high. The release of theophylline from the pellets in 0.1 N HCl is shown in Figure 43. It can be seen that the drug was released almost 100 % within 30 minutes, indicating that the drug pellets prepared in this experiment were suitable for the study of the controlled release property of the polymer membranes.

Table 12. UV absorbance data of theophylline in methanol at 271 nm

| Standard concentration (μg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2.66 | 0.1452 |
| 5.32 | 0.2892 |
| 13.30 | 0.7102 |
| 21.28 | 1.1364 |
| 26.60 | 1.4561 |

Table 13. UV absorbance data of theophylline in 0.1 N HCl at 271 nm

| Standard concentration (μg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2.47 | 0.1374 |
| 4.95 | 0.2715 |
| 9.90 | 0.5310 |
| 14.14 | 0.7366 |
| 19.80 | 1.0150 |

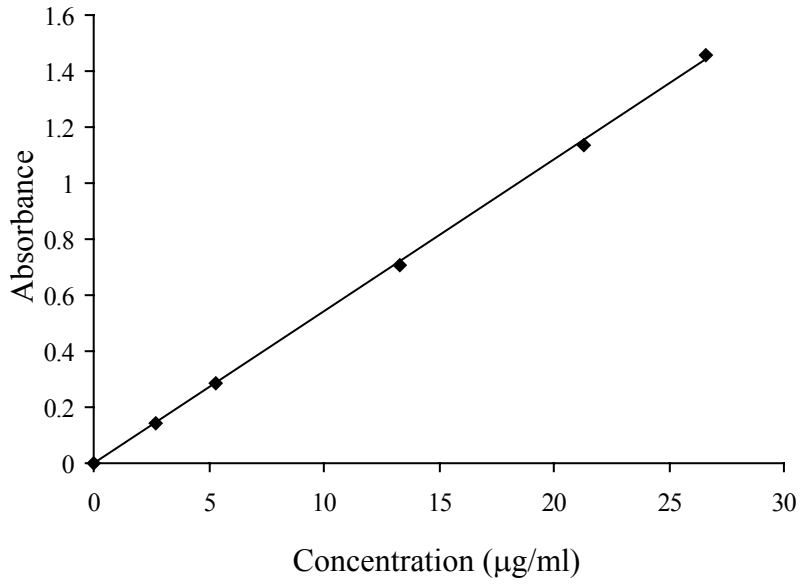



Figure 41. Standard curve of theophylline in methanol at 271 nm
($y = 0.05295\ x + 0.00620$, $r^2 = 0.99998$)

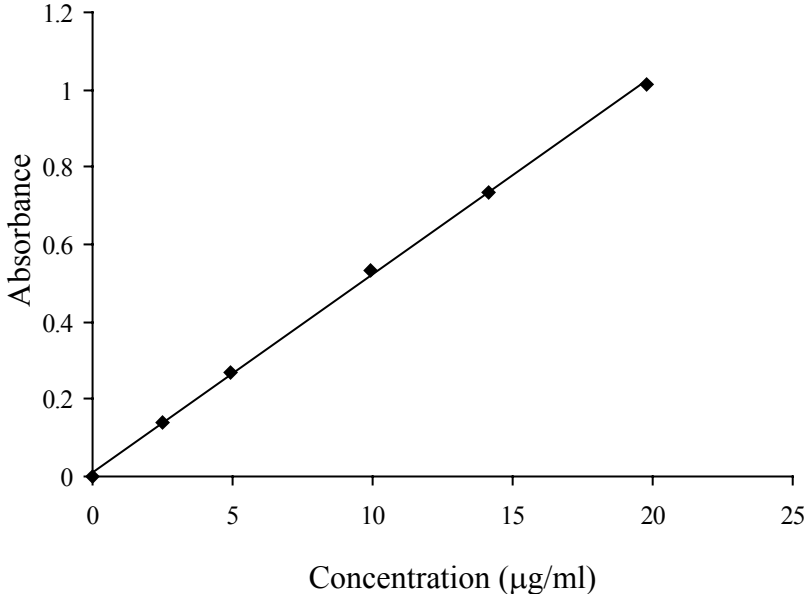



Figure 42. Standard curve of theophylline in 0.1 N HCl at 271 nm
($y = 0.05055\ x + 0.02000$, $r^2 = 0.99958$)

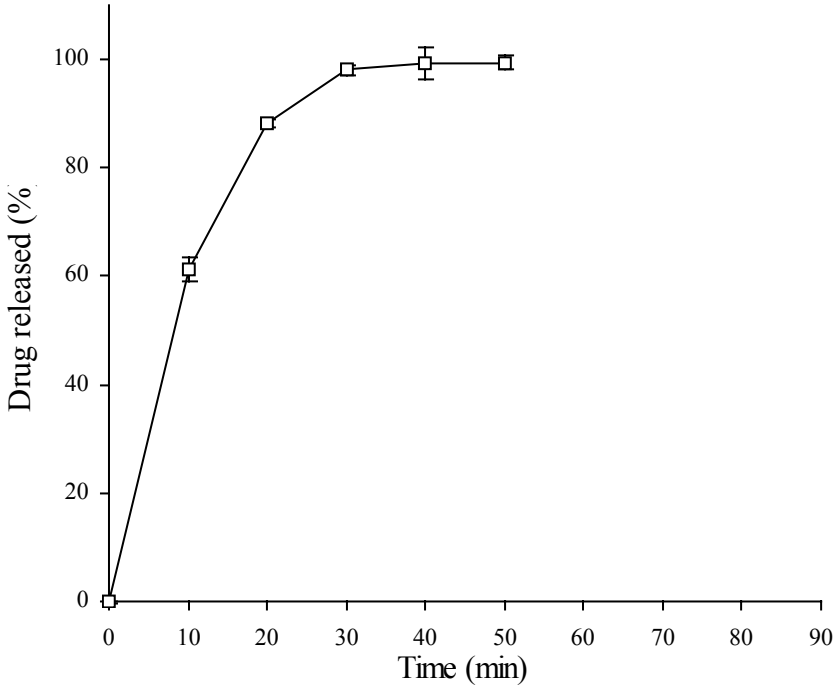



Figure 43. The drug release of the theophylline pellets in 0.1 N HCl

### 4.1.5 Evaluation of the pellet coating

#### 4.1.5.1 Anti-sticking property and the drug release

As the results obtained from the peel tests indicated that among the surfactants selected to test for their anti-sticking property, only GMS, Span 60 and Span 40 could reduce the tackiness of both Eudragit NE 30D and Eudragit RS 30D films. Therefore, in this experiment, these surfactants were used as anti-tacking agents in the Eudragit NE 30D and the Eudragit RS/RL 30D based-coating formulations for the coating of the theophylline pellets. Generally, Eudragit aqueous dispersions are usually diluted with water to contain approximately 15 % of total solids in the coating formulations (19). During this process, additives such as plasticizers, anti-tacking agents, pore formers, colorant, and/or fillers, are incorporated in the formulation to enhance processibility, to maximize aesthetic attributes, and to modify the release characteristics of dosage forms. In general, the effects of three variables on the drug release profiles are often studied. They are plasticizer type and concentration, the polymer ratio (in case of using the polymer blends as film formers), and the quantity of the coating dispersion, or in other words, the film thickness (155). Normally, Eudragit NE 30D does not require plasticizer to form a flexible film at normal coating temperatures as its $T_g$ is very low, whereas Eudragit RS/RL 30D polymers need to be plasticized to facilitate film formation due to the high $T_g$ values of the polymers (4). Substances used as plasticizers include triacetin, triethyl citrate, ethylene vinyl acetate, polyethylene glycol 200 to 8000, polyvinylpyrrolidone, and dibutyl phthalate (19). Among these plasticizers, triethyl citrate (TEC) is one of the most favorable. In this study, TEC was introduced to plasticize the Eudragit RS/RL 30D with the concentration of 20% w/w (based on polymer mass). As the aim of this study was focused on the property of the surfactants on the tackiness of the films, thus the study of the effect of plasticizer type and concentration on the drug release was beyond the scope of this study. However, the effects of film thickness or the coating level on the drug release were investigated. Figure 44 demonstrates the effect of the coating level on the drug release of the theophylline pellets coated with Eudragit NE 30D containing 5% w/w GMS. The result was as expected, as an increase in the coating thickness is accompanied by a decrease in release rate (156). The most significant effect responsible for such a relationship is the effective diffusional path length in the

coatings. In the absence of a tortuous path, thinner coatings have shorter diffusional length and are accomplished by faster release rate (19). It can be noticed that when the coating level increased from 5% to 10% w/w (based on pellet weight), the drug release after 12 hours decreased from 60% to 8%. The drug release profiles from the pellets coated with Eudragit NE 30D containing Span 60 and Span 40 are shown in Figures 45 and 46, respectively. The results are similar to those from the pellets coated with the polymer containing GMS. As the film thickness increased, the release rate decreased. The release rates at 6% or 8% coating level were slower than the rate at 5% coating level. However, they were faster than that at 10% coating level.

In order to prove the importance of the anti-tacking agent, in this experiment the pellets were also coated with Eudragit NE 30D without any anti-tacking agent. It was found that a severe agglomeration of the pellets occurred. As a result, the pellets could not flow in the coating chamber and the coating process had to stop after only an approximate 3 % of polymer weight gain was obtained. However, when the pellets were coated with the polymer containing 5 % GMS, Span 60, or Span 40, no agglomeration was observed during the coating process. The pellets could be freely fluidized in the coating chamber in every batch of the coating. After curing the coated pellets at 40 $^{o}$C for 24 hours to stabilize the drug release rate (157), only a slight agglomeration was observed, and the coated beads could be separated easily without film damage. This was confirmed from the sustained release profiles of the drug dissolution, which indicated the integrity of the polymer films. Therefore, the results from the experiments proved that Span 60 and Span 40 can be practically used as anti-tacking agents in the Eudragit NE 30D coating formulations similar to GMS.

Anti-sticking property of GMS, Span 60 and Span 40 was also tested for the Eudragit RS 30D formulations. In this study, the polymer blends derived from mixing Eudragit RS 30D and Eudragit RL 30D together at various ratios were used as the film formers. Both these polymers are copolymers of ammoniomethacrylate with a low content of positively charged quaternary ammonium groups. The cation density is 1 per 20 repeating units for Eudragit RL and 1 per 40 repeating units for Eudragit RS. Therefore, Eudragit RL 30D has higher water permeability and swellability than Eudragit RS 30D. To produce sustained release formulations with these two polymers, two major ways of influencing drug release are possible. They are the modification of

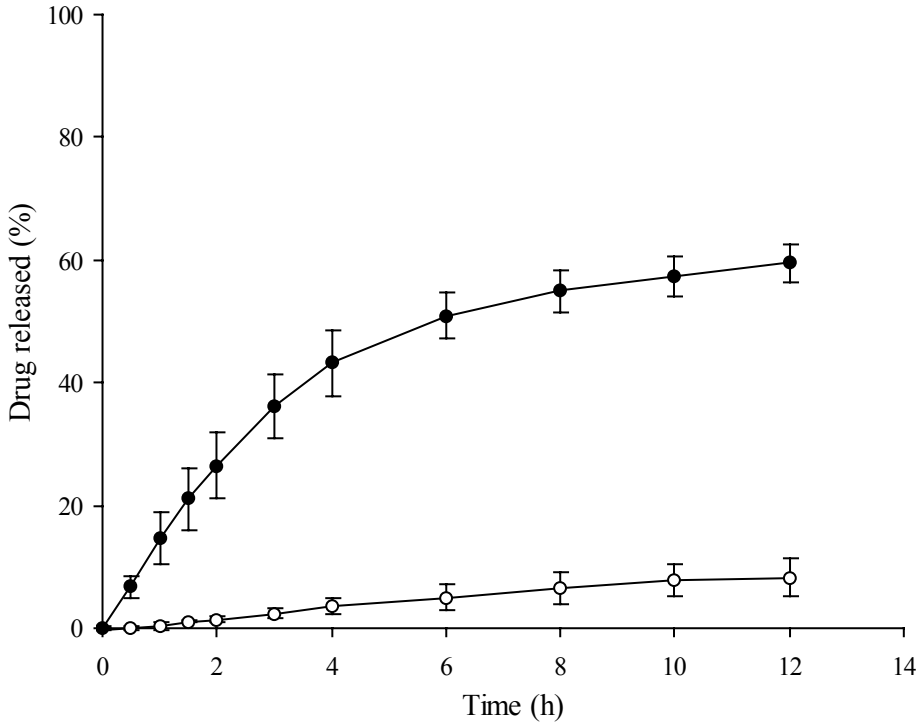



Figure 44. Dissolution of theophylline from pellets coated with Eudragit NE 30D containing 5 % GMS at a coating level of 5 % (•) and 10 % (○)

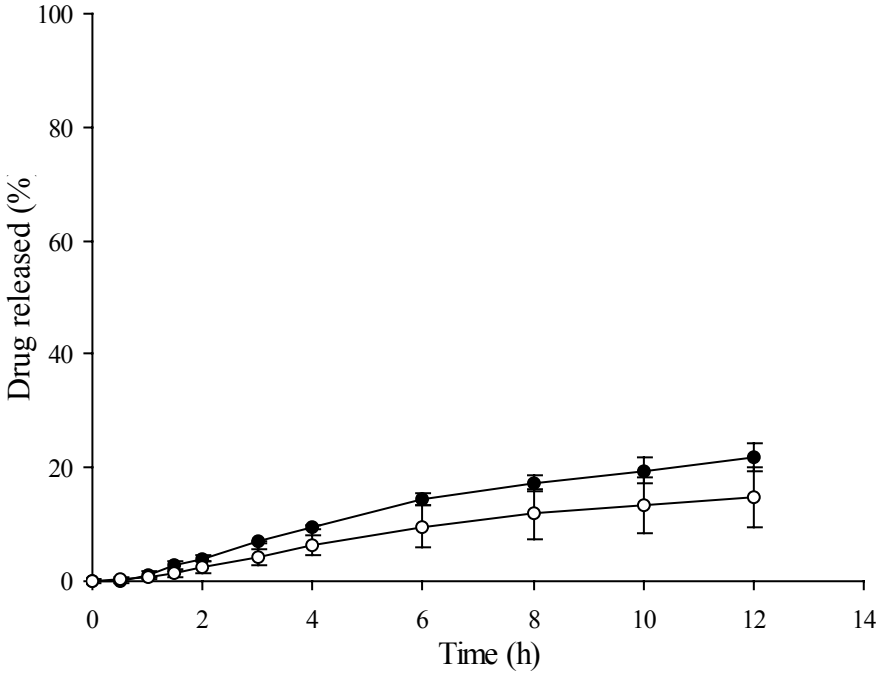



Figure 45. Dissolution of theophylline from pellets coated with Eudragit NE 30D containing 5% Span 60 at a coating level of 8 % (•) and 10 % (○)

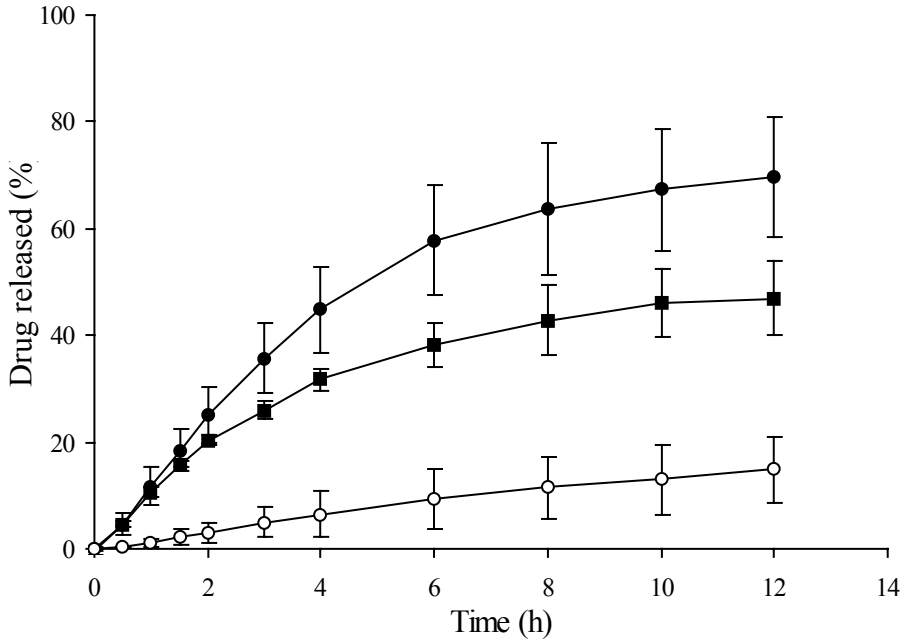



Figure 46. Dissolution of theophylline from pellets coated with Eudragit NE 30D containing 5 % Span 40 at a coating level of 5 % (●), 6 % (■), and 10 % (○)

the amount of the coating and the change of the polymer ratio in the mixture (158). However, the mixture of these two copolymers is often used for formulations of various controlled release drug delivery systems (3). Figure 47 exhibits the release profiles of theophylline from the pellets coated with the Eudragit RS30D/RL30D containing 5% GMS and 20% TEC at a constant coating level of 10% (based on pellet weight). The ratio of the polymers was varied. One can note that as the proportion of the Eudragit RS 30D increases, the release rate decreases. The drug release is 100% after 2 hours when the pellets were coated with the 1:1 ratio of RS30D/RL30D, whereas the release is only 60% after 6 hours when 9:1 ratio of the blend was used. The results were consistent with the theory and the previous studies (107,155). Since Eudragit RS 30D is less water permeable and swellable than Eudragit RL 30D, the increase of the Eudragit RS proportion, therefore, results in the decrease of the diffusion rate of the drug molecules through the polymer membrane. The agglomeration tendency of the pellets during the coating was also observed. No agglomeration was found and the pellets could freely flow in the chamber no matter GMS, Span 60 or Span 40 was used in the formulations.

The final stage of the film formation process is known as “further gradual coalescence” (FGC) and can proceed for a long time after coating (159,160). The time necessary to form a stable film without further aging effects on the drug release rates is quite variable and depends, for each system, on formulation factors, technical parameters selected for the coating process and finally, on the storage conditions of the finished products (161). During the storage period, the film coat properties such as the permeability to drugs continue to change. Much contradictory information on the effect of storage on the release pattern of drugs exists in the literature (162) with reports of an increase (163,164), a decrease (157,163,165,166) or no significant change (167) in drug release rate, from sustained-release pellets coated with aqueous polymer dispersions. Therefore, to complete film formation, the coated products are usually heated at temperatures higher than the $T_g$ of the membrane material (166,168). This process is called “curing” (post-coating conditioning). For the soft polymer such as Eudragit NE 30D, the curing temperature at 40$^{o}$C for 24 hours is enough for the complete film formation (157). Nevertheless, in case of the polymer with high $T_g$ such as Eudragit RS 30D or RL 30D, a higher curing temperature, such as 60 $^{o}$C for 24

hours, is recommended (161). The effect of the curing on the drug release of the pellets coated with the Eudragit RS30D/RL30D was also studied in this experiment. As shown in Figures 48 and 49, after the coated pellets were cured, the drug release rates decreased. These results indicate that "further gradual coalescence" occurred during the curing and the film formation was more complete, which resulted in a slower diffusion of the drug molecules through the polymer membranes.

Although there was no pellet sticking observed during the coating, after curing at 60 $^{o}$C for 24 hours, the pellet agglomeration was found in every Eudragit RS/RL 30D coating formulation. To solve this problem, the coated beads were thoroughly blended with 5 % talc (based on pellet weight) prior to curing. This easy step could prevent the pellet sticking during the curing effectively. The drug release profiles of the cured pellets coated with the Eudragit RS30D/RL30D (9:1) containing 5% GMS with and without talc blending are shown in Figure 50. The release rate from the cured beads without talc blending was faster, indicating that some portions of the films might be damaged during the separation of the agglomerated pellets into individual bead (6). When the beads were blended with talc before curing, talc behaved like an anti-tacking agent or a barrier that prevented the autohesion of the polymer films, therefore the films could maintain their integrity after the bead separation. Figures 51 and 52 exhibit the effects of the blending with talc prior to curing of the pellets coated with the Eudragit RS30D/RL30D (9:1) containing Span 60 and Span 40, respectively. The results were similar to those of the pellets coated with the polymer mixture containing GMS. When the coated beads were blended with talc prior to curing, the drug release rates significantly decreased. These results indicate that although these three surfactants can prevent the pellet sticking during the coating, in case of the curing at high temperature for a long period, however, the agglomeration of the coated substrates still possibly occur. This is due to the higher mobility of the polymer chains when temperature rises, resulting in the more intimate contact between the membrane surfaces, especially when a long period of the process is allowed.

The effects of the additives on the drug release were also investigated in this study. Figure 53 exhibits the dissolution of theophylline from the pellets coated with Eudragit RS30D/RL30D (9:1) containing 100% talc or 5% GMS, Span 60 or Span 40 at 10 % coating level. One can notice that the formulations containing either talc or

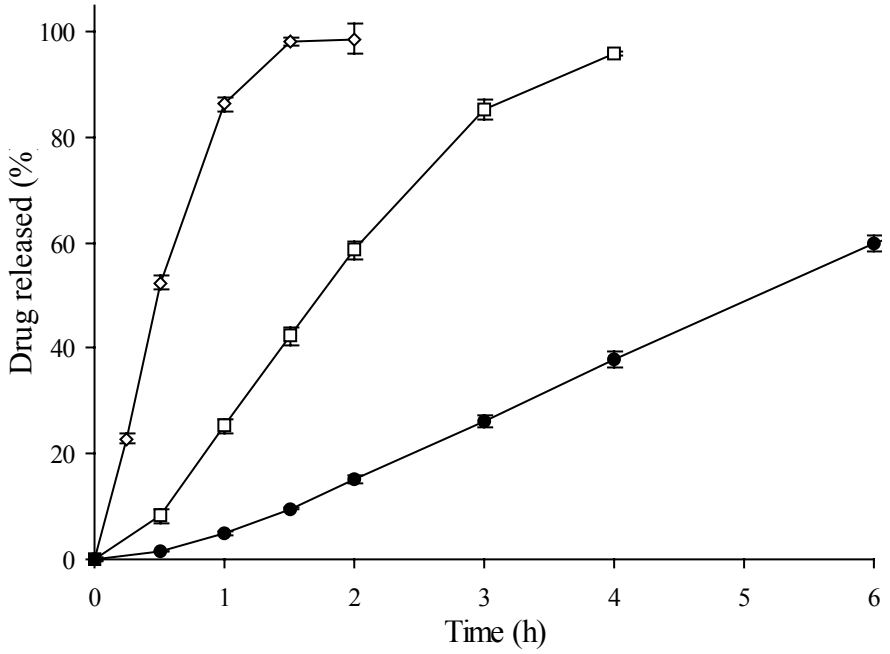



Figure 47. Dissolution of theophylline from pellets coated with Eudragit RS/RL30D containing 5 % GMS at 10 % coating level
The ratios of Eudragit RS30D/RL30D are 1:1 (◊), 8:2 (□), and 9:1 (•)

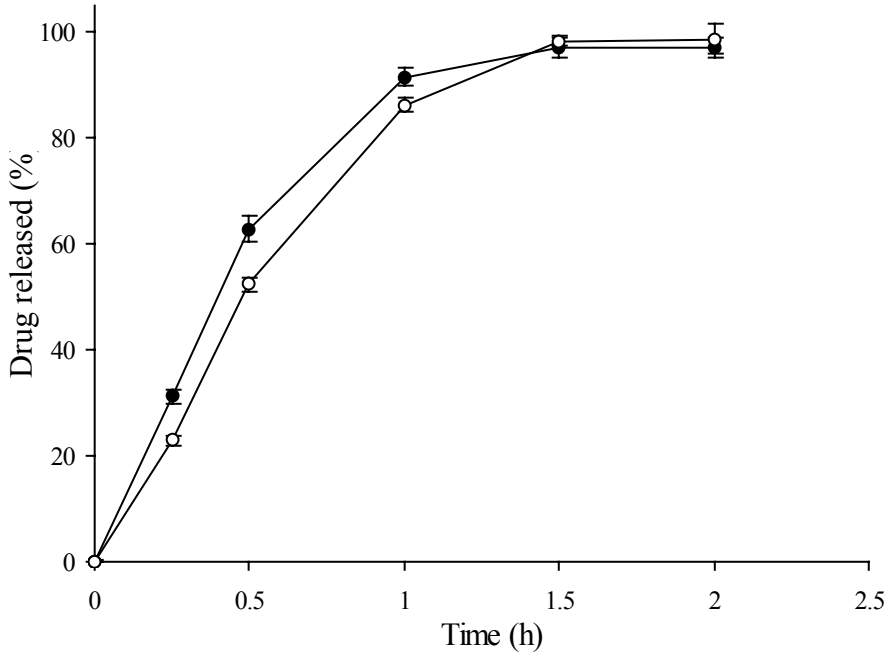



Figure 48. Dissolution of theophylline from pellets coated with Eudragit RS30D/RL 30D (1:1) containing 5 % GMS at 10 % coating level, without curing (●) and cured at 60°C, 24 h (○)

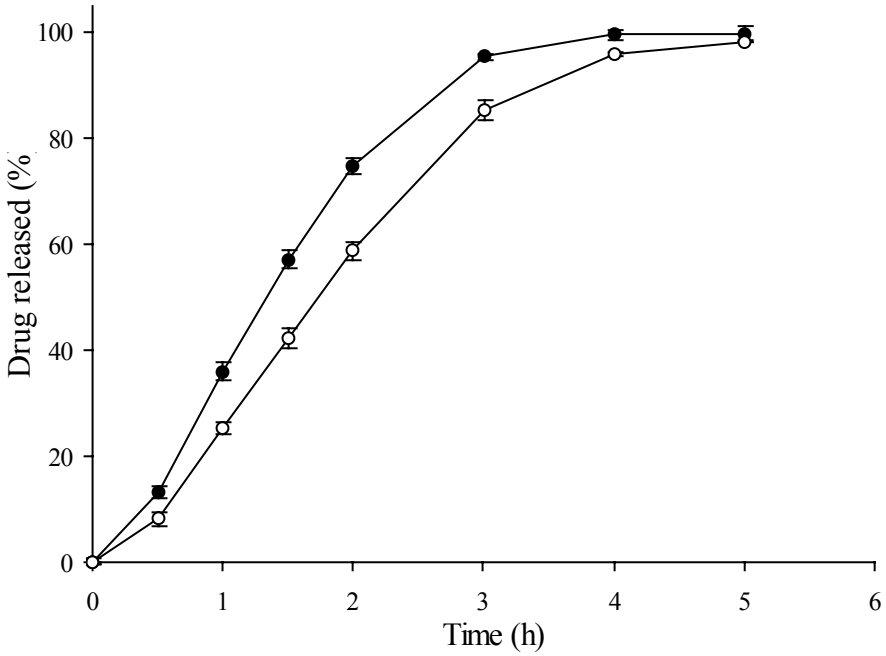



Figure 49. Dissolution of theophylline from pellets coated with Eudragit RS30D/RL 30D (8:2) containing 5 % GMS at 10 % coating level, without curing (●) and cured at 60$^{o}$C, 24 h (○)

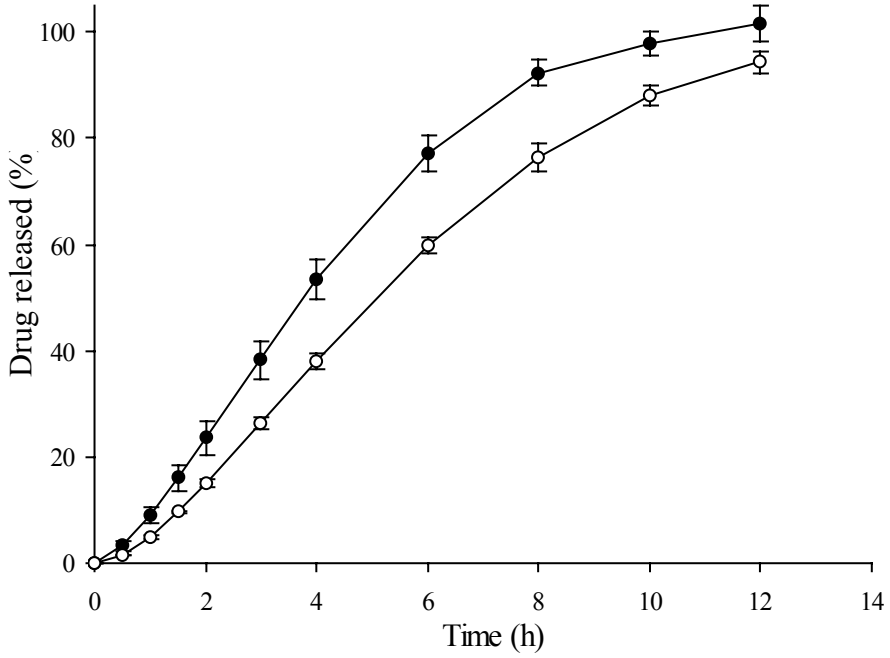



Figure 50. Dissolution of theophylline from pellets coated with Eudragit RS30D/RL 30D (9:1) containing 5 % GMS at 10 % coating level, with (○) and without (●) talc blending before curing

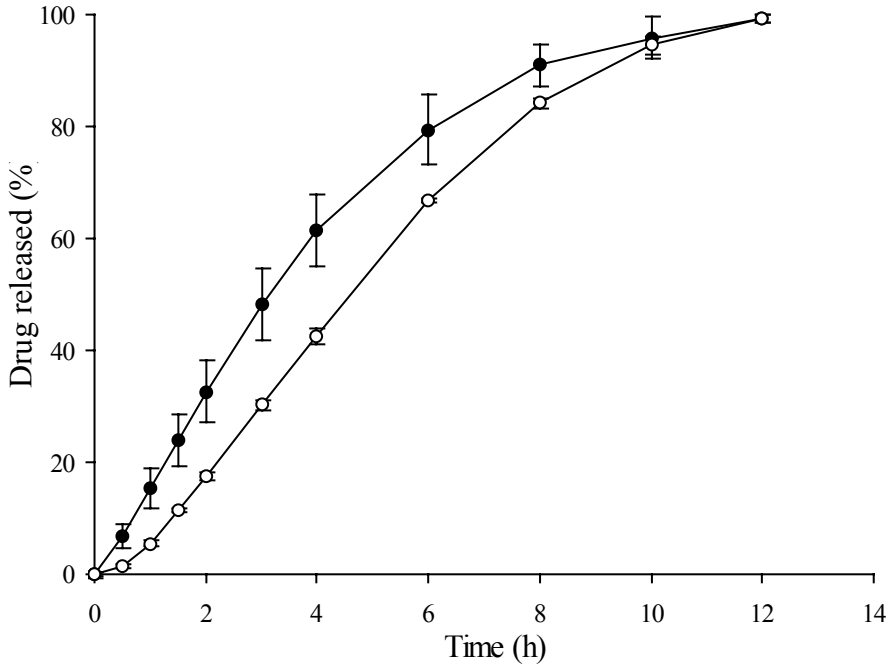



Figure 51. Dissolution of theophylline from pellets coated with Eudragit RS30D/RL 30D (9:1) containing 5 % Span 60 at 10 % coating level, with (○) and without (●) talc blending before curing

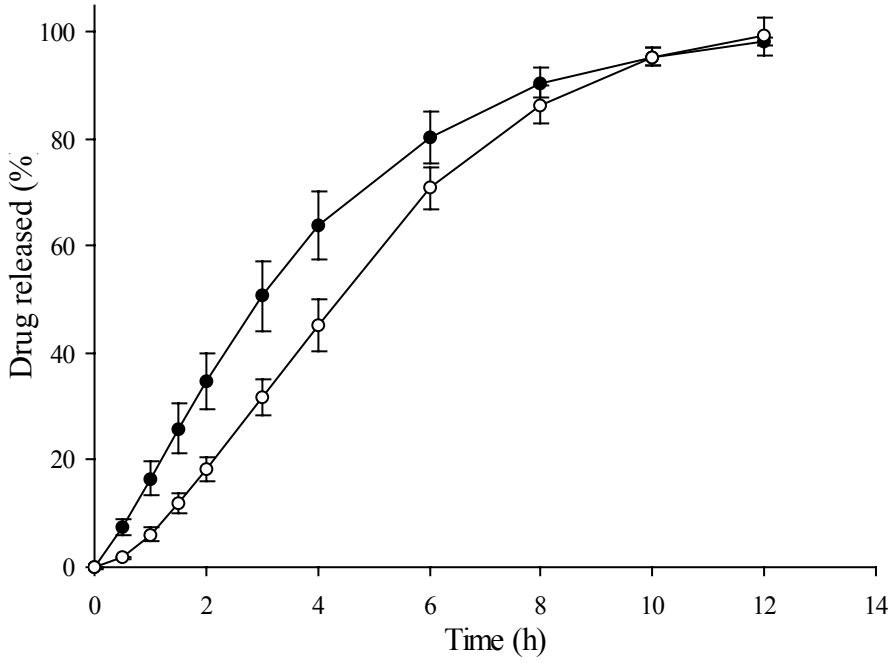



Figure 52. Dissolution of theophylline from pellets coated with Eudragit RS30D/RL 30D (9:1) containing 5 % Span 40 at 10 % coating level, with (○) and without (●) talc blending before curing

one of any surfactants gave no significant difference in the release rate. However, when comparing among the formulations containing the surfactants, the formulations containing Span 60 or Span 40 gave slightly faster release rate than that containing GMS. This is probably due to the fact that Span 60 and Span 40 are more hydrophilic than GMS (HLB of GMS, 3.8; Span 60, 4.7; Span 40, 6.7). Therefore, the films containing them are more water permeable than those containing GMS and thus, resulting in a higher diffusion rate of the drug molecules. Figures 54 and 55 show the drug releases from the pellets coated with the Eudragit NE 30D containing 5% GMS, Span 60 or Span 40 at the coating level of 5% and 10%, respectively. The results were similar to those obtained from the Eudragit RS/RL 30D formulations. The pellets coated with the polymer containing GMS show a slightly slower release rate than those coated with the polymer containing Span 60 or Span 40.

#### 4.1.5.2 Coating efficiency

After the pellets were coated and cured at optimal temperature for 24 hours, they were weighed and the coating efficiency of each batch was calculated. The values are shown in Table 14. The coating efficiency of all formulations is in an acceptable level. No significant difference in the coating efficiency among the formulations containing various surfactants was found. The coating efficiency of the formulation containing 100% talc was the lowest (74.6%). However, Maejima et al. (150) found that the coating efficiency could exceed 93 % when the theophylline pellets were coated with Eudragit RS30D/RL30D (95:5) containing 200% talc. Therefore the low coating efficiency of the formulation containing 100% talc in this experiment was possibly due to the process variables rather than the formulation variables.

#### 4.1.5.3 Stability study

The stability of the drug release from the substrates is necessary especially in the case of the controlled-release dosage forms. As the drug concentration level in the body at a specified period would change when the release rate of the drug molecules from the dosage form changes, and this would result in the change of the onset and duration of action of the medicaments. Therefore, after finishing the production, the dosage forms should be examined for their dissolution stability. For the polymeric film coated dosage forms prepared by aqueous coating system, the “further gradual coalescence” can proceed after the coating as mentioned above, and the curing step

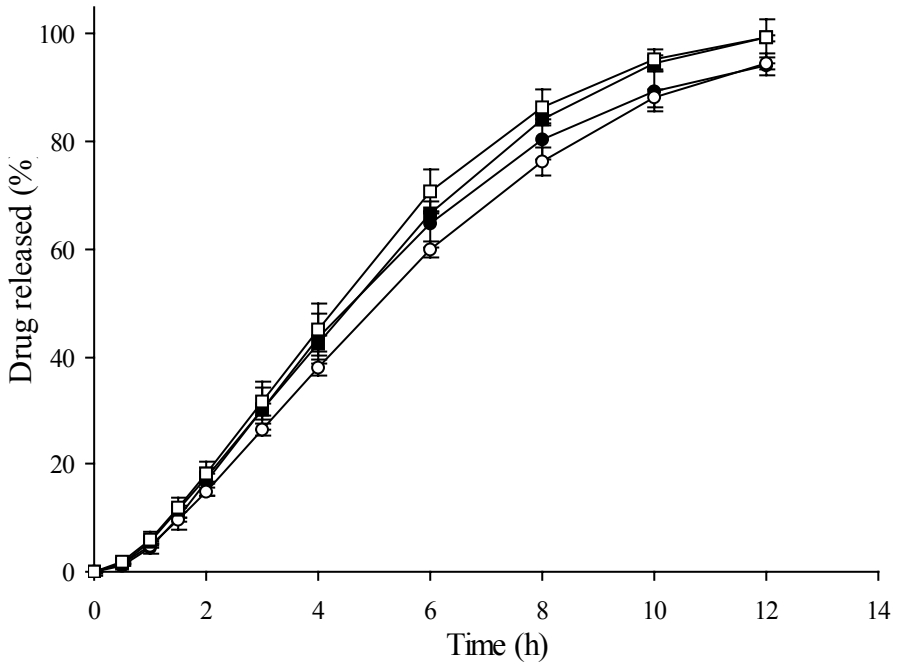



Figure 53. Dissolution of theophylline from pellets coated with Eudragit RS30D/RL 30D (9:1) containing additives: (●) 100% talc; (○) 5% GMS; (■) 5% Span 60; (□) 5% Span 40, at 10 % coating level

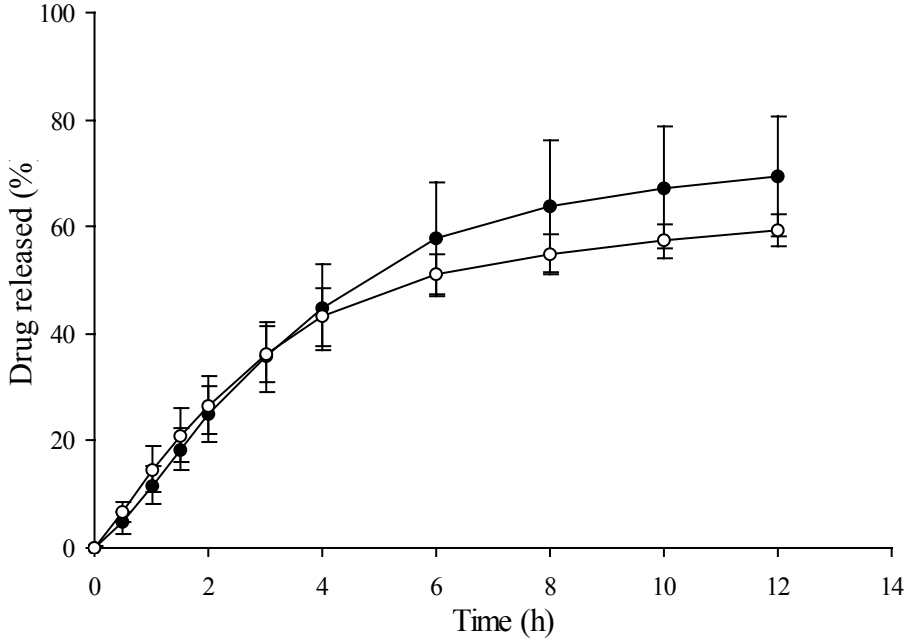



Figure 54. Dissolution of theophylline from pellets coated with Eudragit NE 30D containing: (○) 5 % GMS, (●) 5 % Span 40, at 5 % coating level

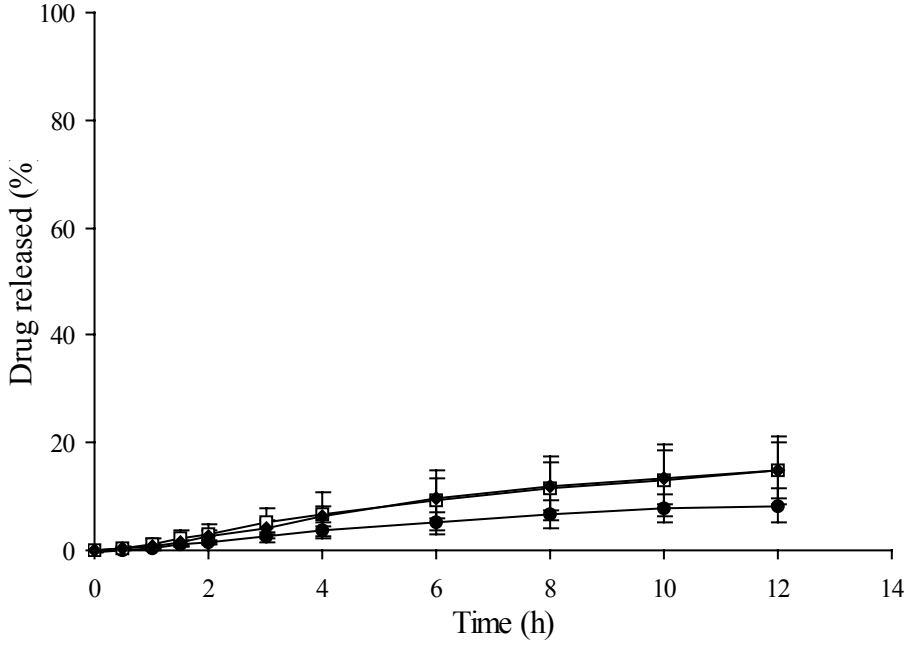



Figure 55. Dissolution of theophylline from pellets coated with Eudragit NE 30D containing: (●) 5 % GMS; (♦) 5 % Span 60; (□) 5 % Span 40, at 10 % coating level

Table 14. Efficiency of the coating of the pellets with the polymers containing 5 % surfactant or 100% talc

| Polymers | Anti-tack | Coating level (%) | Efficiency (%) |
|---|---|---|---|
| Eudragit NE 30D | GMS | 5 | 95.7 |
| | | 10 | 93.3 |
| | Span 60 | 8 | 80.8 |
| | | 10 | 78.6 |
| | Span 40 | 5 | 94.0 |
| | | 6 | 93.2 |
| | | 10 | 90.1 |
| Eudragit RS/RL30D | Talc | 10 | 74.6 |
| (9:1) | GMS | 10 | 88.7 |
| | Span 60 | 10 | 83.3 |
| | Span 40 | 10 | 87.9 |

would accelerate this phenomenon. If the polymer coalescence is complete, the drug release rate will be constant over the duration of the storage, and this means the curing condition is optimal. In this experiment, the stability of the drug release was also examined after the coated samples were stored for a period of time at various conditions. Figure 56 demonstrates the dissolution stability of the pellets coated with the Eudragit NE 30D containing 5% GMS at 10% coating level. The results showed that the drug release profiles are unchanged after the pellets were kept at room temperature for 10 months or at 40 $^{o}$C for 6 months. Nevertheless, the storage at 40$^{o}$ C, 75% relative humidity caused a significant change in the drug release. A possible explanation is that at a high humidity condition, the water molecules in the atmosphere could penetrate into the films and behaved like a plasticizer by lowering the $T_g$ of the polymer and increasing the chain mobility (169). Therefore the polymer chains could diffuse across the film surfaces easier and the film defect might occur after the pellets were separated into individual beads. This led to a higher diffusion rate of the drug molecules through the membranes.

The stability of the drug release from the pellets coated with Eudragit NE 30D containing 5% Span 40 was also examined and the results are shown in Figure 57. The results were similar to those obtained from the pellets coated with the polymer containing GMS. The drug release rate was unchanged after the storage at 40 $^{o}$C for 6 months or at room temperature for 10 months. This indicates that when considering the effects on the dissolution stability, there is no difference between the use of GMS and Span 40 as an anti-tacking agent in the coating formulations. In addition, the results from the study also suggest that these coated dosage forms should not be stored in a condition with high humidity for a long period of time.

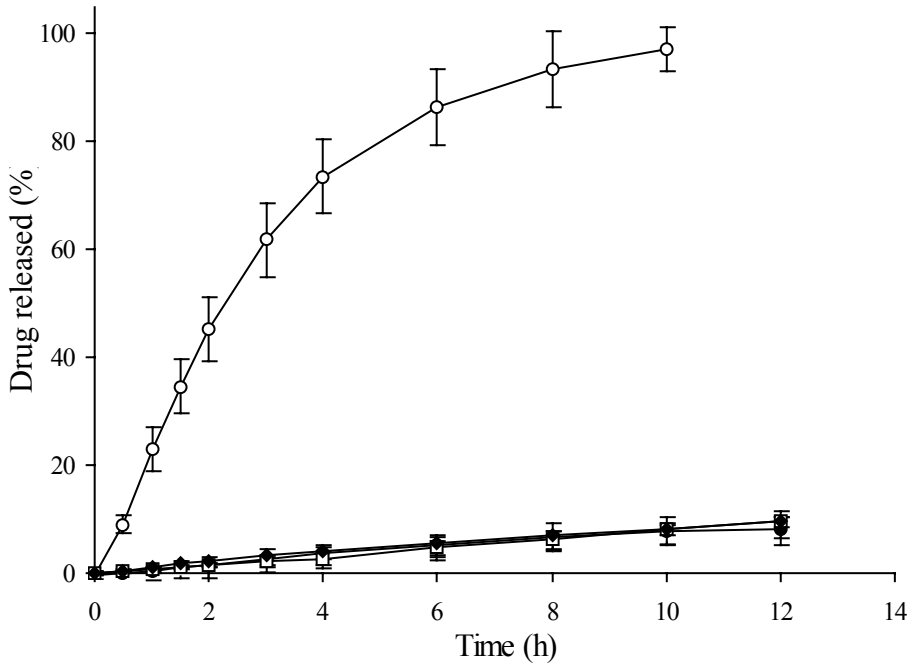



Figure 56. Dissolution stability of pellets coated with Eudragit NE 30D containing 5% GMS at 10% coating level, (●) initial; (♦) room temperature, 10 months; (□) 40 °C, 6 months; (○) 40 °C, 75% R.H., 6 months

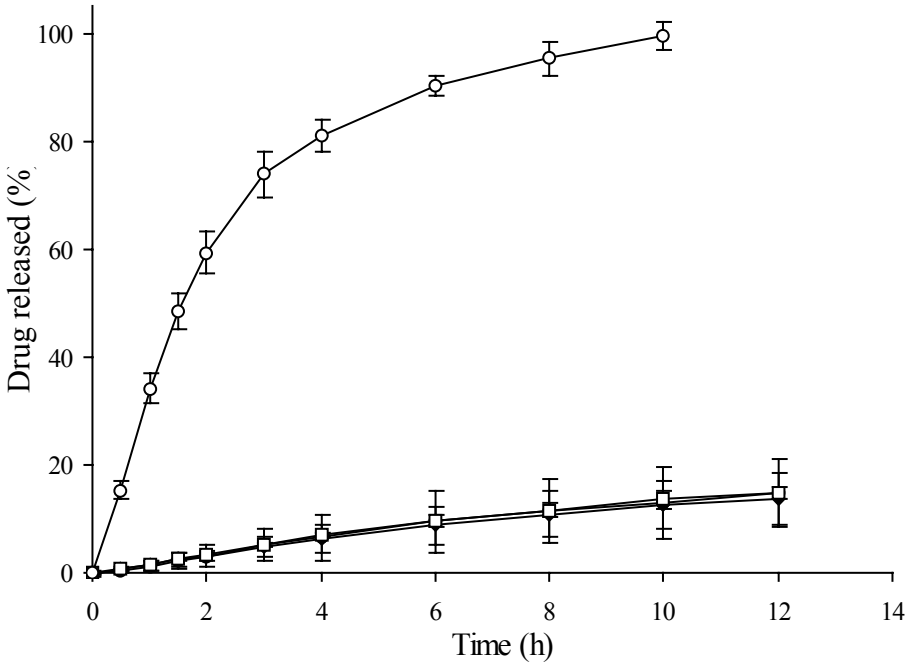



Figure 57. Dissolution stability of pellets coated with Eudragit NE 30D containing 5% Span 40 at 10% coating level, (●) initial; (♦) room temperature, 10 months; (□) 40 $^{o}$C, 6 months; (○) 40 $^{o}$C, 75% R.H., 6 months

## 4.2 Synthesis and evaluation of new acrylic copolymers

### 4.2.1 Characterization of polymerization reaction

In this study, a variety of latices were synthesized by varying the monomer ratios, whereas other ingredients and the conditions of the reaction were kept constant. The results are shown in Table 15. Every formulation had the percentage yield more than 85%, except the formulation of MA-EA (2:1). The loss of the product yield was mostly due to the formation of a solid residue during the reaction. It was noticed that these residues were the aggregates of the polymer films formed at the surface of the dispersions during the synthesis. It was possible that they were the polymers derived from the polymerization of the monomers outside the micelles since MA is soluble in water. It could be noticed that as the proportion of MA in the recipe increased, the size of the residue also increased and the percentage yield was less. The content of the dry solid substance and the percentage conversion of monomer to polymer were also calculated gravimetrically for each recipe. The solid content was found to be nearly 30% which was the theoretical value for all formulations, and the percentage conversion was more than 90%. As the percentage conversion was calculated on the basis of the solid content, therefore, the formulation with low solid content also showed low percentage conversion. Although the polymerization reaction might not be absolutely complete, it was observed that all the products obtained from the reactions did not give a pungent smell of the monomers.

### 4.2.2 Properties of the synthesized latices

The synthesized latices were characterized and the results are exhibited in Table 16. The particle size is one of the most important characterictics of the latex and is in the range of 10 to 1000 nm. When the particle size is between this range, the thermal convection and the Brownian movement of the particles are so high that the sedimentation velocity of the particles is overcompensated and no sedimentation occurs over a very long period of time (4). The particle sizes of the latices synthesized in this experiment were between 83-240 nm. It can be noticed that as the ratio of MA to EA increased, the particle size also increased. The largest particles belong to the formulation of MA-EA (2:1). The appearance of the latices was also consistent with the particle size. Since the latex gives a light-scattering effect resulting in a milky appearance. As the particle size is larger, the latex looks more turbid. Among the

Table 15. Results from the synthesis of the latices

| Latex | % Yield | % Solid | % Conversion |
|---|---|---|---|
| MA-EA (1:2) | 94.9 | 29.2 | 97.3 |
| MA-EA (2:3) | 93.8 | 30.0 | 100 |
| MA-EA (1:1) | 92.4 | 29.1 | 96.9 |
| MA-EA (3:2) | 88.6 | 29.0 | 96.7 |
| MA-EA (2:1) | 61.1 | 27.2 | 90.6 |
| MA-HEM-EA (4:1:5) | 88.0 | 29.3 | 97.7 |
| MA-HEM-EA (4:2:4) | 88.2 | 29.8 | 99.3 |
| MA-HEM-EA (5:1:4) | 85.3 | 28.1 | 93.7 |

Table 16. Properties of the synthesized latices

| Latex | Particle size (nm) (mean (S.D.),n = 3) | Viscosity (cp) | pH | MFT ($^{o}$C) |
|---|---|---|---|---|
| MA-EA (1:2) | 83.3 (1.7) | 10.8 | 2.3 | 6 |
| MA-EA (2:3) | 99.0 (0.6) | 9.9 | 2.4 | 16 |
| MA-EA (1:1) | 111.7 (0.6) | 8.7 | 2.4 | 27 |
| MA-EA (3:2) | 170.0 (3.6) | 8.4 | 2.5 | 33 |
| MA-EA (2:1) | 240.3 (3.1) | 8.1 | 2.7 | 37 |
| MA-HEM-EA (4:1:5) | 163.7 (0.6) | 8.4 | 2.5 | 15 |
| MA-HEM-EA (4:2:4) | 178.0 (1.0) | 8.1 | 2.6 | 18 |
| MA-HEM-EA (5:1:4) | 174.7 (1.5) | 8.1 | 2.5 | 22 |

synthesized latices, MA-EA (2:1) showed highest turbidity. After these latices were kept at room temperature for 3 months, sedimentation occurred to those with particle sizes larger than 160 nm. However, this did not happen to MA-EA (1:2), MA-EA (2:3) and MA-EA (1:1) latices. These latices did not sediment even after 6 months.

Latices are also characterized by low viscosity even when they have a high solid content. The viscosity of all latices in this experiment was low and showed no significant difference among various formulations. The pH was in the range of 2.3-2.7. The acidity of the latices was likely due to ionization of carboxylic groups in the molecules.

The measured MFT at 27 $^{o}$C of MA-EA (1:1) latex in this experiment was in good agreement with that of the commercial latex (Eudragit® L 30D-55) reported in the previous study (4). One can notice that as the ratio of MA to EA increased, the MFT of the latex also increased. The results correspond with the fact that the polymer derived from EA is softer than that derived from MA. EA can function as an internal plasticizer in the MA-EA copolymer structure. Thus, increasing the proportion of EA in the copolymer resulted in the decrease of the MFT. Change of MA:EA ratio from 1:1 to 2:3 could reduce the MFT from 27 to 16 $^{o}$C, which was low enough to promote film formation at the coating temperature. For the series of MA-HEM-EA, a partial substitution of MA by HEM decreased the MFT, whereas the MFT increased as EA was partially substituted by HEM. This is because the $T_g$ of PHEM (55 $^{o}$C) is between the $T_g$s of PMA (228 $^{o}$C) and PEA (-24 $^{o}$C).

### 4.2.3 Properties of the cast films

#### 4.2.3.1 Spectroscopic analyses

The structures of the copolymers synthesized in this experiment were analyzed by FTIR spectroscopy. The spectra of the copolymers in the series of MA-EA are shown in Figures 58-62. These spectra exhibit the characteristic absorbance of carboxylic acid compounds. The strong peaks at about 1735 and 1700 cm$^{-1}$ were assigned to the C=O stretching vibration of carboxylic ester and the dimers of carboxylic acids, respectively. The peaks at 1262, 1179 and 1158 cm$^{-1}$ were attributed to the C-O stretching band for carboxylic ester and acid (170). The $CH_3$, $CH_2$ bending vibrations can be observed at 1476, 1450 and 1385 cm$^{-1}$ (171). A very broad band detected between 3600-3000 cm$^{-1}$ was attributed to the presence of OH groups. The band shows

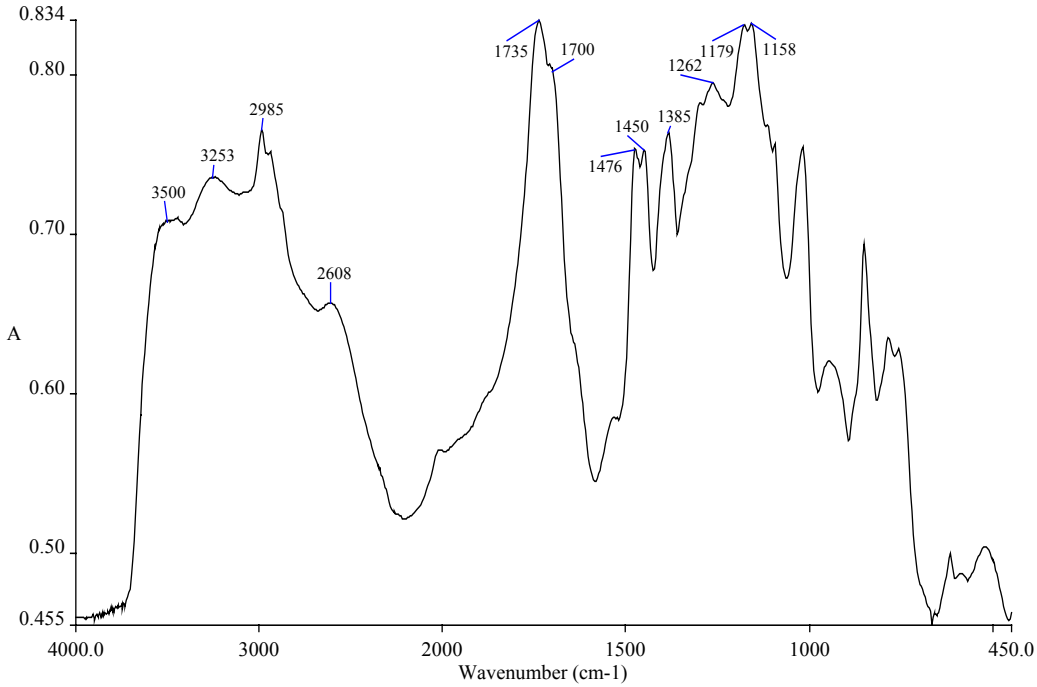



Figure 58. IR spectrum of MA-EA (1:2) copolymer

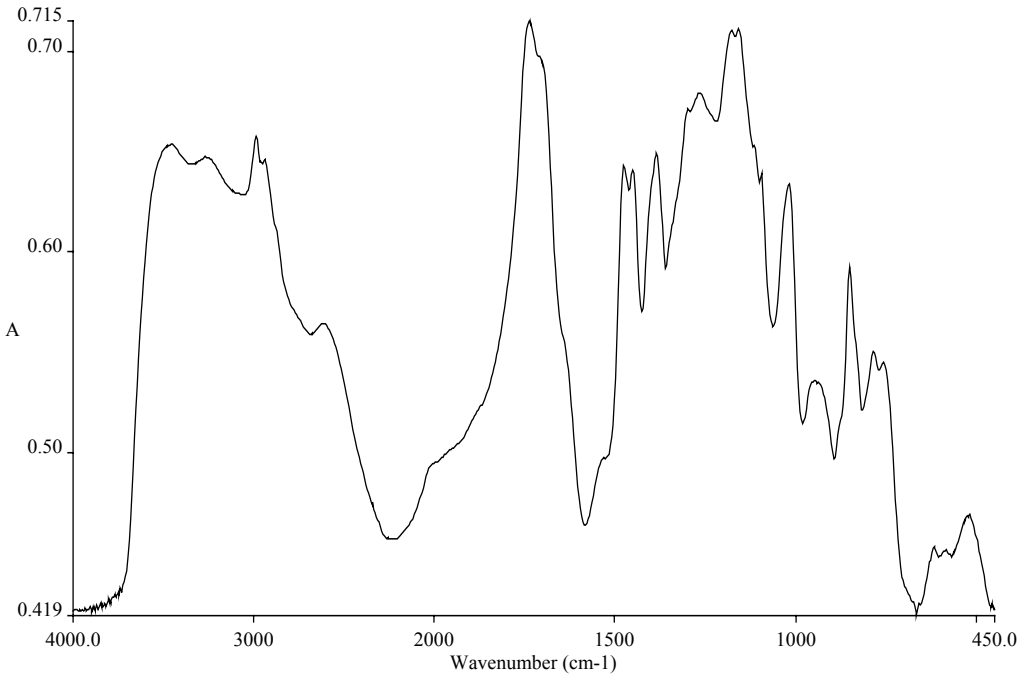



Figure 59. IR spectrum of MA-EA (2:3) copolymer

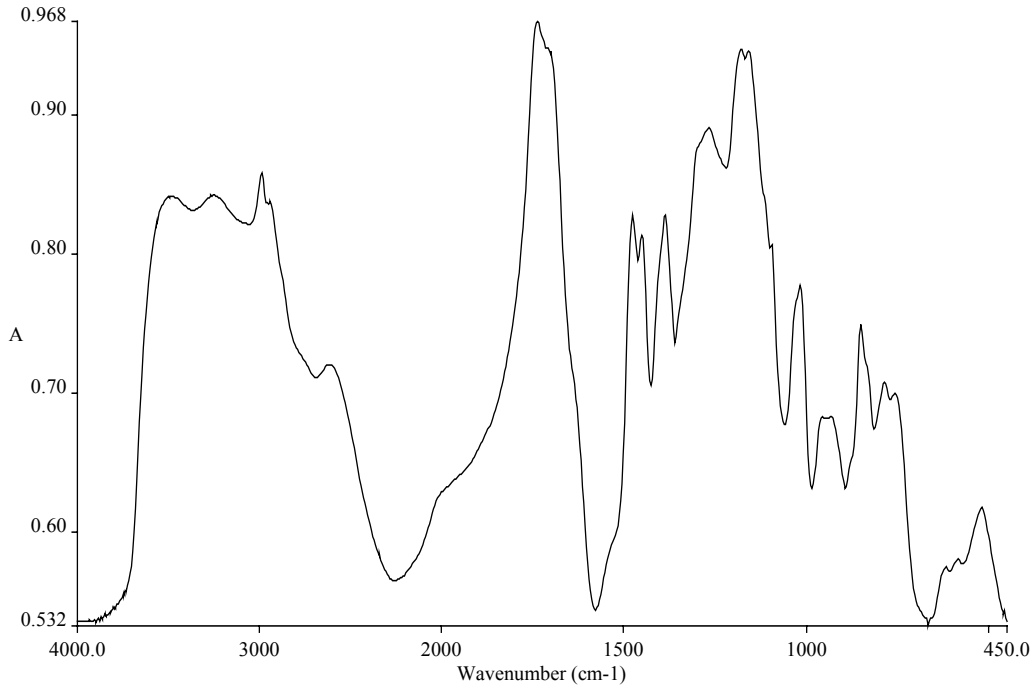



Figure 60. IR spectrum of MA-EA (1:1) copolymer

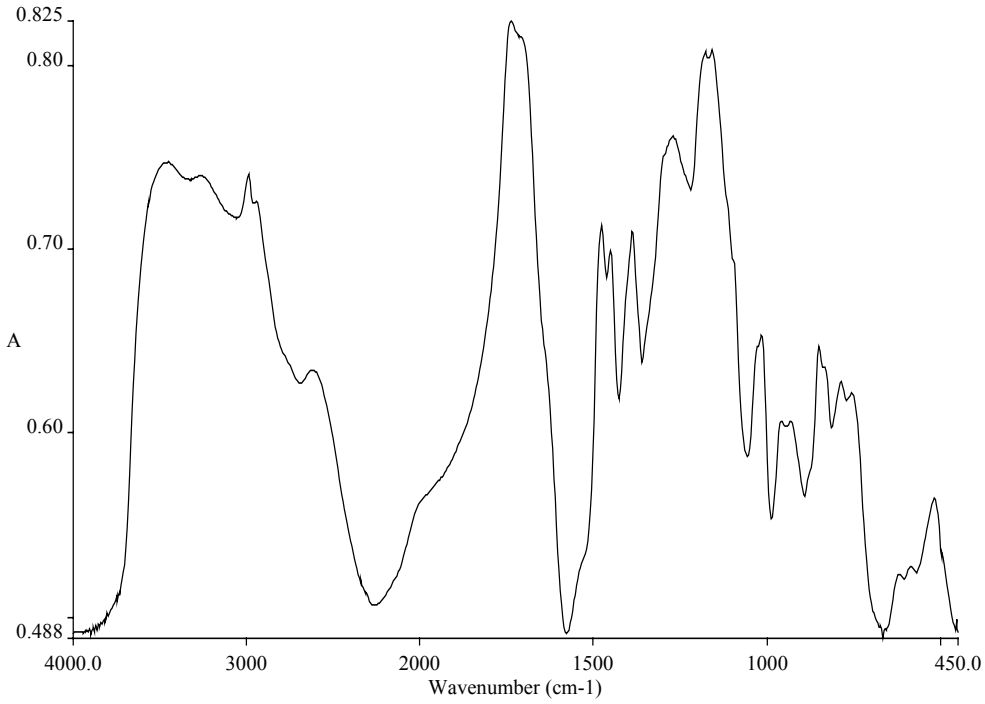



Figure 61. IR spectrum of MA-EA (3:2) copolymer

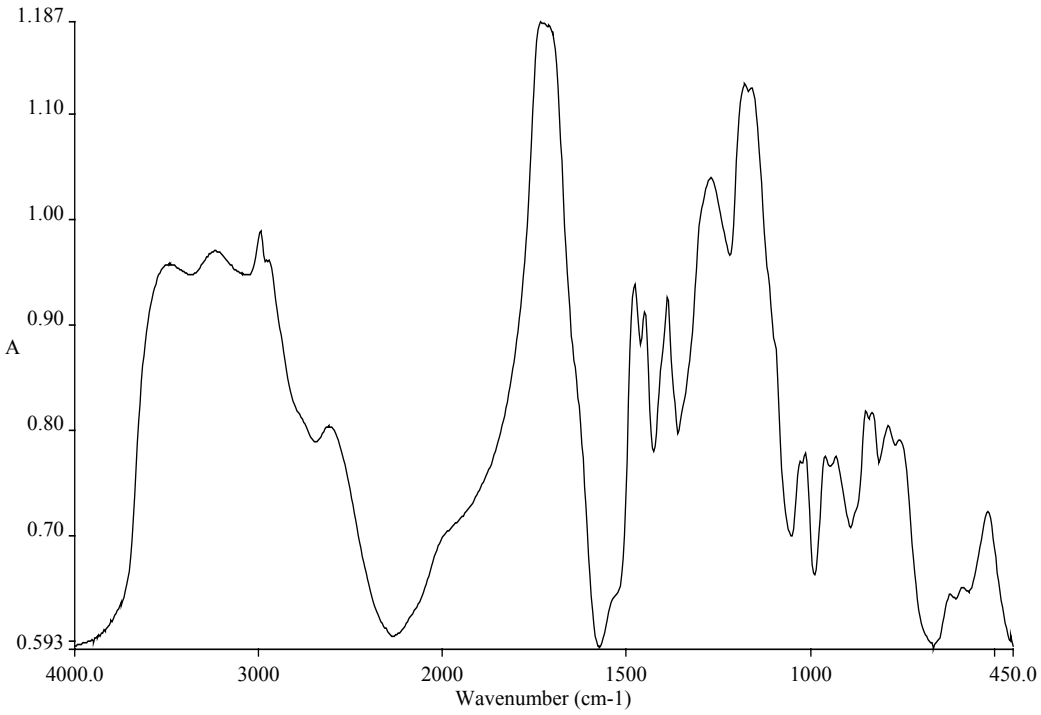



Figure 62. IR spectrum of MA-EA (2:1) copolymer

two maxima above 3000 $cm^{-1}$. The maximum around 3500 $cm^{-1}$ was usually ascribed to the free O-H stretching, while the maximum near 3250 $cm^{-1}$ was assigned to the self-associated carboxylic groups (172). The overtone and combinations bands were also observed in all spectra as a broad band centered at around 2600 $cm^{-1}$ (173).

The film obtained from the commercial MA-EA (1:1) copolymer, Eudragit L30D-55, was also analyzed and the spectrum is shown in Figure 63. When comparing the spectrum of the Eudragit L30D-55 with that of the synthesized MA-EA (1:1) copolymer as shown in Figure 64, it can be noticed that they are very similar to each other. The spectra of the synthesized copolymers were also compared as shown in Figure 65. One can notice that as the ratio of MA/EA increased, the peak at 1700 $cm^{-1}$ which was attributed to the C=O stretching band of carboxylic acid was stronger, compared with the C=O peak of ester at 1735 $cm^{-1}$. Moreover, the peak at 1016 $cm^{-1}$, which might be attributed to the asymmetric stretching band of C-O-C (170), was stronger as the ratio of MA/EA decreased. Although the exact co-monomer ratio in the polymer structure could not be elicited by FTIR technique, the results from the study indicated that the ratio of MA/EA in the polymer structure increased as this ratio in the recipe increased.

The spectra of the copolymers in the series of MA-HEM-EA are shown in Figures 66-68, and they are compared with one another in Figure 69. It can be seen that their spectra are very similar, especially around the fingerprint region. These spectra indicate the structure of carboxylic acid compounds the same as those obtained from the MA-EA copolymers. However, one can notice that among these three copolymers, the broad band of O-H stretching with the maximum at 3468 $cm^{-1}$ of the MA-HEM-EA (4:2:4) copolymer is strongest. This can be explained by the higher proportion of hydroxyethylmethacrylate in the structure, compared with the other two copolymers.

#### 4.2.3.2 Glass transition temperature

In this study, the $T_g$s of the cast films obtained from the latices were measured using differential scanning calorimetry (DSC). DSC measures the quantity of energy absorbed or given off by a sample as its temperature changes at a programmed rate.

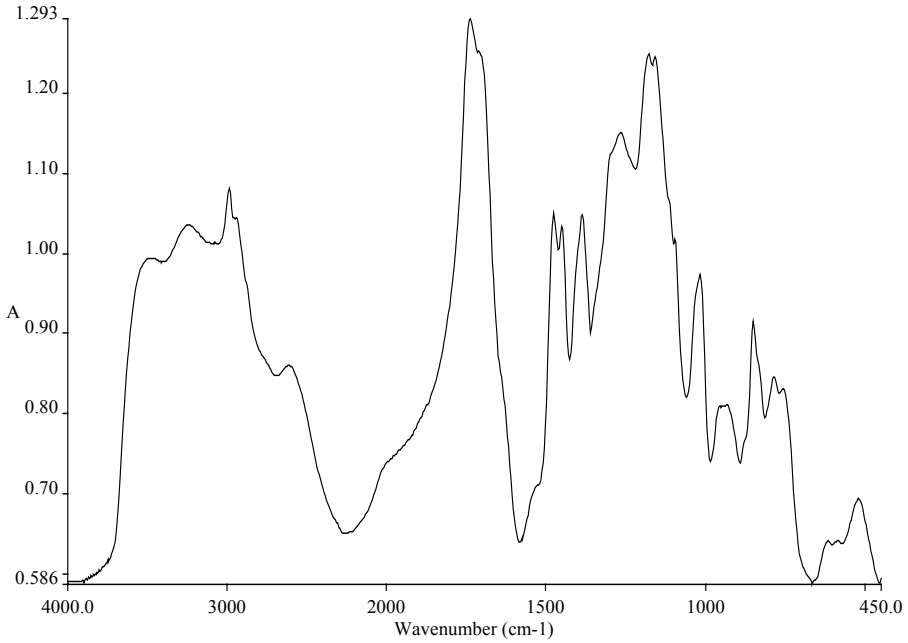



Figure 63. IR spectrum of Eudragit L30D-55

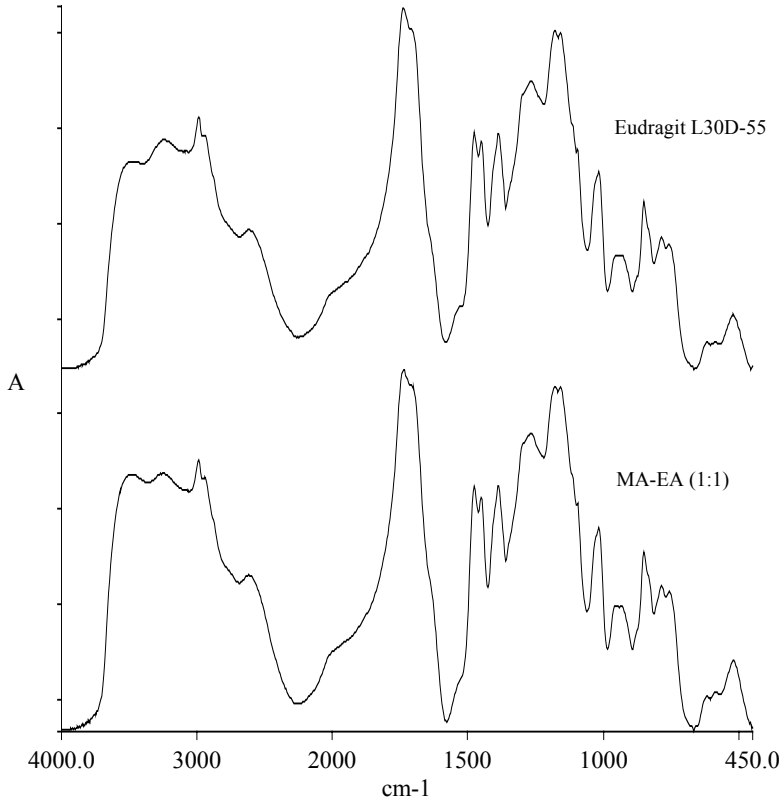



Figure 64. IR spectra of Eudragit L30D-55 vs MA-EA (1:1) copolymer

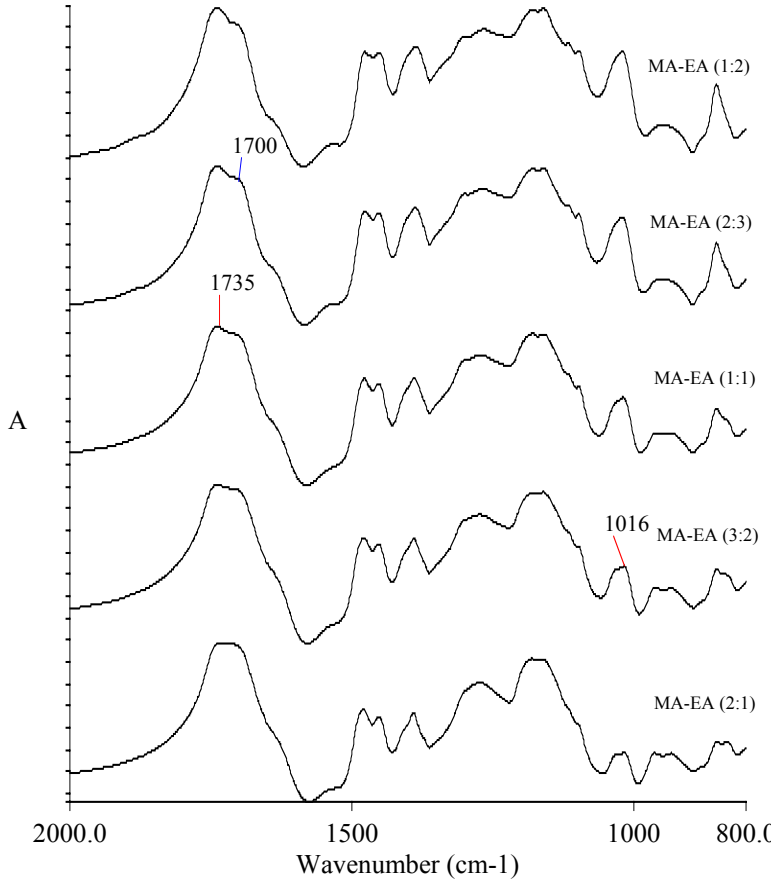



Figure 65. IR spectra of copolymers in the series of MA-EA

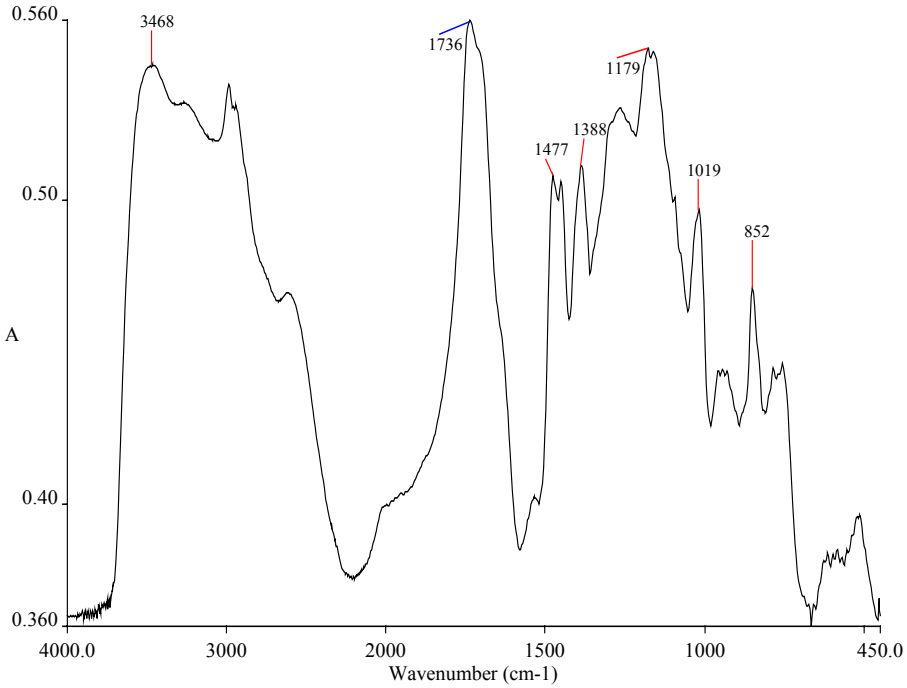



Figure 66. IR spectrum of MA-HEM-EA (4:1:5)

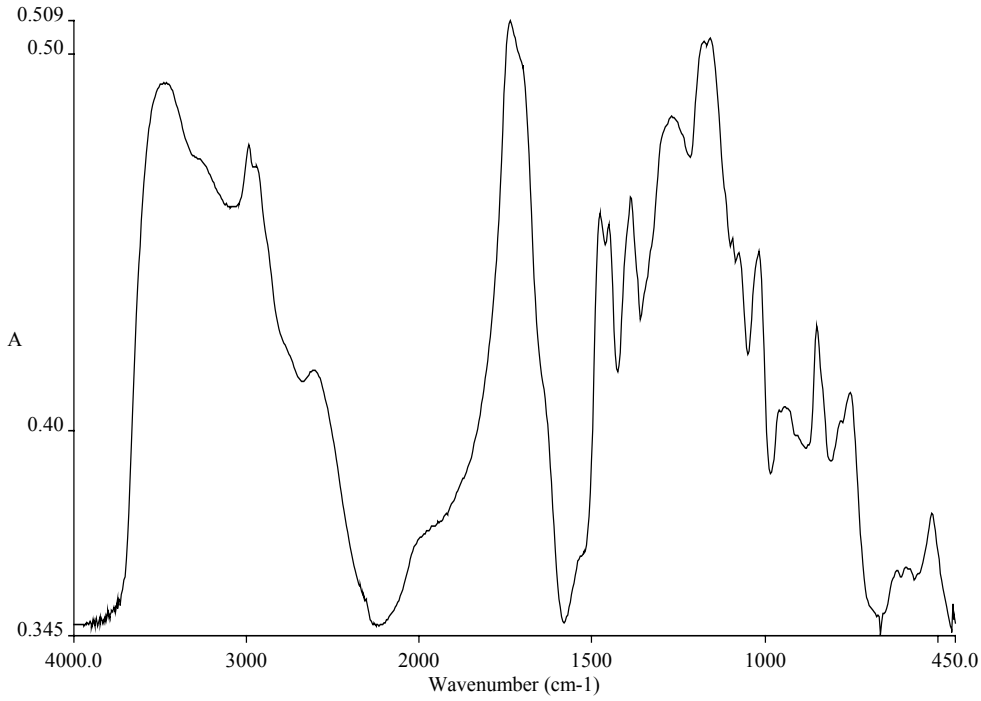



Figure 67. IR spectrum of MA-HEM-EA (4:2:4)

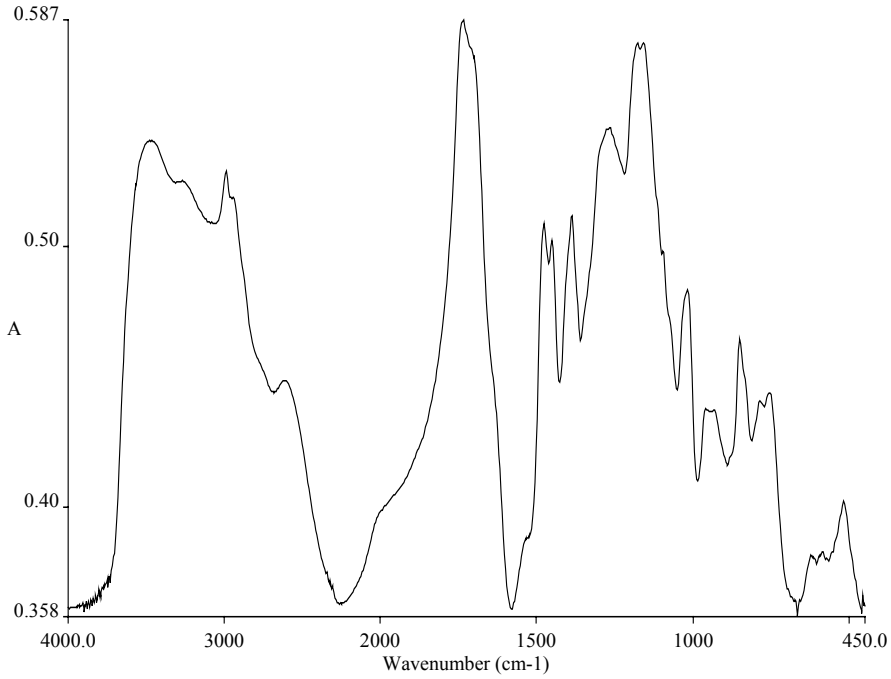



Figure 68. IR spectrum of MA-HEM-EA (5:1:4)

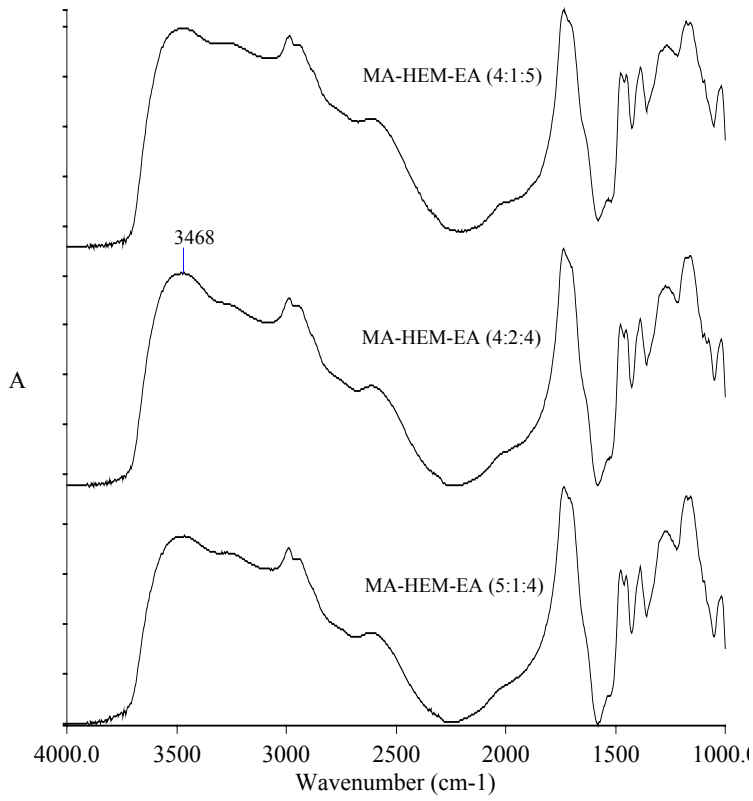



Figure 69. IR spectra of the copolymers in the series of MA-HEM-EA

The measured $T_g$s of the cast films are shown in Table 17. The $T_g$s of the films derived from all latices in this experiment were higher than room temperature (30 $^oC$), indicating that the films were in glassy state. The results also indicated that MA increased the $T_g$s of the copolymers while EA reduced these values. Change in $T_g$s was in the same direction as change in MFTs. This also confirmed the plasticizing function of EA in the molecular structure. Theoretically, $T_g$ of a random copolymer varies between the $T_g$s of the homopolymers and is frequently the weight-average of the $T_g$s of the homopolymers on a weight fraction basis (174). The theoretical $T_g$s were also calculated and shown in Table 17 ($T_g$ of PMA, 228; PEA, -24; PHEM, 55 $^oC$). The measured $T_g$s were in good agreement with the theoretical $T_g$s.

The addition of 10% (w/w) triethyl citrate (TEC) into MA-EA (1:1) reduced the $T_g$ from 105.9 to 72.9 $^oC$. The $T_g$ of this plasticized copolymer was close to that of MA-EA (2:3).

#### 4.2.3.3 Mechanical properties

Tensile modulus, tensile strength and elongation at break of the cast films were measured and the results are displayed in Table 18. The mechanical properties were correspondent with the $T_g$s. As all these polymer films were in a glassy state, they were hard and brittle. This could be observed from their moduli and elongation at break. MA in the structure increased the film hardness as well as the $T_g$. In the case of MA-EA (3:2) and MA-EA (2:1), the films were very brittle and their mechanical properties could not be measured by a tensile tester. The addition of 10% TEC into the MA-EA (1:1) film could slightly increase the flexibility. Generally, brittleness is a drawback of a polymeric film former as a brittle film can crack during the coating. However, for the manufacturing process that does not involve a high mechanical stress during and after the coating, a low flexible film should be acceptable, unless it is too brittle. On the contrary, the advantage of a low flexible film is its low tackiness. The agglomeration is rarely found for the substrates coated with a low flexible film.

Table 17. Glass transition temperatures of the films from synthesized latices

| Film | $T_g$ ($^oC$) (measured) | $T_g$ ($^oC$) (theoretical) |
|---|---|---|
| MA-EA (1:2) | 52.9 | 59.7 |
| MA-EA (2:3) | 69.7 | 76.8 |
| MA-EA (1:1) | 105.9 | 102.0 |
| MA-EA (3:2) | 129.0 | 127.2 |
| MA-EA (2:1) | 135.3 | 143.6 |
| MA-HEM-EA (4:1:5) | 89.4 | 84.7 |
| MA-HEM-EA (4:2:4) | 94.3 | 92.6 |
| MA-HEM-EA (5:1:4) | 109.9 | 109.9 |
| MA-EA (1:1)+TEC10% | 72.9 | - |

Table 18. Mechanical properties of the films from synthesized latices (n =5)

| Latex | Tensile modulus MPa, Mean (S.D.) | Tensile strength MPa, Mean (S.D.) | Elongation at break (%) |
|---|---|---|---|
| MA:EA (1:2) | 233 (9) | 30.3 (1.8) | 14.1 (3.5) |
| MA:EA (2:3) | 321 (60) | 29.5 (5.9) | 11.0 (3.7) |
| MA:EA (1:1) | 342 (7) | 26.4 (5.6) | 9.8 (3.7) |
| MA:EA (3:2) | * | * | * |
| MA:EA (2:1) | * | * | * |
| MA:HEM:EA (4:1:5) | 348 (27) | 36.0 (7.9) | 12.1 (4.1) |
| MA:HEM:EA (4:2:4) | 315 (49) | 38.1 (12.6) | 12.5 (3.1) |
| MA:HEM:EA (5:1:4) | 353 (22) | 38.8 (17.6) | 12.6 (5.9) |
| MA:EA (1:1)+TEC10% | 299 (28) | 35.6 (2.6) | 12.4 (1.5) |

* Could not be measured, as the films were too brittle

#### 4.2.3.4 Dissolution rate of the films

The film dissolution rates in buffer solution of various pH are displayed in Table 19. The relationship among film dissolution rate, type of polymer and pH were revealed as three-dimensional graph and presented in Figure 70. For the series of MA-EA, it can be noticed that as the pH increased, the rates of film dissolution also increased. The higher pH promoted more ionization of the carboxylic groups, which led to the higher dissolution of the polymers. However, when some portions of EA or MA in the structures were replaced by HEM, the film dissolution was less pH dependent. The films from the series of MA-HEM-EA showed low dissolution rates even at pH 6.8. HEM is a water-soluble monomer and was introduced in this experiment to study its effect on the dissolution of the copolymers. The results revealed that HEM in the structure did not promote the dissolution of the films. A possible explanation is that there might be more intermolecular hydrogen bonding due to the OH groups of HEM in the structure, resulting in the retardation of the dissolution of the films. These results indicated that the MA-HEM-EA copolymers were not appropriate for using as enteric film formers.

The results also showed that MA-EA (1:1) copolymer started to dissolve apparently at pH 5.5. This agreed with the property of the commercial MA-EA (1:1) copolymers. MA-EA (3:2) and MA-EA (2:1) could dissolve at pH 5.0, whereas MA-EA (2:3) and MA-EA (1:2) started to dissolve at pH 6.0 and 6.8, respectively. However, at pH 6.8, the dissolution rate of MA-EA (2:3) was not significantly different from those of the copolymers with higher MA content, whereas MA-EA (1:2) was less soluble and showed no sign of dissolving at pH 6.0. Considering both MFT and dissolution rate, the results therefore indicated that MA-EA (2:3) was the most appropriate to be tested as a plasticizer-free enteric film former.

### 4.2.4 Properties of the paracetamol cores

In this study, paracetamol was selected as the active substance in the core tablets because no pH-dependent interactions with the film former were expected from it. In addition, its high solubility in water allowed a pronounced escape from the cores if the film leaked during the test for resistance to gastric juice. The properties of the cores were investigated and summarized in Table 20. There was no significant difference between the disintegration time in 0.1 N HCl and that in the buffer solution of pH 6.8.

Table 19. Dissolution rates of films in buffer solutions at various pH (n = 3)

| Polymer | Dissolution rate (μg/cm$^2$.min) | | | |
|---|---|---|---|---|
| | pH | | | |
| | 5.0 | 5.5 | 6.0 | 6.8 |
| MA-EA (1:2) | 4.2 (1.0) | 7.0 (1.6) | 7.1 (0.9) | 51.7 (7.3) |
| MA-EA (2:3) | 6.7 (0.2) | 4.4 (0.7) | 25.4 (1.2) | 147.6 (29.0) |
| MA-EA (1:1) | 7.7 (2.0) | 78.0 (19.5) | 97.1 (6.7) | 142.7 (0.9) |
| MA-EA (3:2) | 28.4 (0.6) | 77.4 (16.2) | 65.7 (5.5) | 182.4 (2.8) |
| MA-EA (2:1) | 35.5 (5.4) | 79.8 (1.3) | 89.3 (7.7) | 157.2 (3.5) |
| MA-HEM-EA (4:1:5) | 1.9 (0.5) | 5.0 (0.3) | 36.3 (3.8) | 28.7 (1.7) |
| MA-HEM-EA (4:2:4) | 0.2 (0.3) | 8.4 (0.1) | 20.7 (0.8) | 18.3 (1.3) |
| MA-HEM-EA (5:1:4) | 2.4 (1.1) | 23.2 (2.8) | 31.5 (4.8) | 24.0 (0.8) |

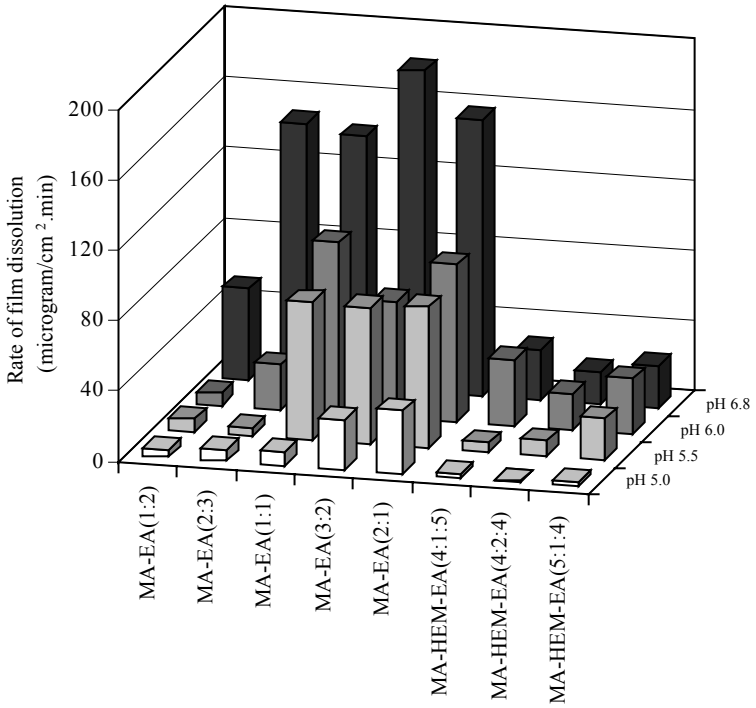



Figure 70. Dissolution rates of films in buffer solutions at various pH

Table 20. Properties of paracetamol cores

| Properties | Mean (S.D.) |
|---|---|
| Weight/tab (mg), n = 20 | 402.4 (6.4) |
| Hardness (N), n = 20 | 84.5 (21.5) |
| Thickness (mm), n = 20 | 6.12 (0.06) |
| Disintegration in 0.1 N HCl (sec), n = 6 | 31 (2) |
| Disintegration in buffer pH6.8 (sec), n = 6 | 36 (2) |
| Content of paracetamol (%), n = 20 | 95.18 |

The cores disintegrated very fast in both liquids. The fast disintegration of the cores allowed the disintegration of the coated tablets to be dependent mostly on the dissolution of the film. This was good for the evaluation of the film property.

The content of paracetamol in the core tablets was determined using UV spectrophotometry. The absorbances of various concentrations of the drug solution at wavelength 243 nm in 0.1 N HCl and in buffer solution of pH 6.8 are shown in Tables 21 and 22, respectively. The absorbances were plotted against the concentrations as shown in Figures 71 and 72. The relationships were linear with good correlation coefficients. The slope and y-intercept were calculated by linear regression analysis. The paracetmol content in the tablets calculated from spectrophotometric measurement was 95.18 %.

### 4.2.5 Evaluation of the coating

As the properties of the cast films indicated that the MA-EA (2:3) copolymer was most appropriate to be tested as a plasticizer-free enteric film former. To prove the efficiency as well as the reproducibility, three batches of this polymer with identical formulation were used to coat on the same batch of the paracetamol cores under the same process parameters, compared with the formulation of MA-EA (1:1) incorporated with 10% TEC. Beside these two formulations, the coating formulation of MA-HEM-EA (4:1:5) was also applied on the paracetamol cores in order to reexamine the properties of the film. The coating process could be completed without any problems for every coating. After finishing, the products were weighed and the coating efficiencies were calculated. The results are summarized in Table 23. The efficiency for each coating was higher than 80% which was regarded as an acceptable level. No agglomeration of the coated tablets was observed both during and after the coating. This was due to the low tack of the film itself and also the contribution of talc in the formulation.

### 4.2.6 Properties of the coated tablets

#### 4.2.6.1 Enteric property

The resistance to gastric juice of the coated products was determined from the weight increase after immersing in 0.1 N HCl for 2 hours under the disintegration test. For the tablets coated with the formulation of MA-EA (2:3), at the beginning the cores were coated at a polymer level of 4 mg/cm$^2$, however after a few minutes one of six

Table 21. UV absorbance of paracetamol in 0.1 N HCl at 243 nm

| Standard concentration (μg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 1.98 | 0.1289 |
| 4.94 | 0.3266 |
| 9.88 | 0.6470 |
| 15.82 | 1.0291 |
| 19.77 | 1.3055 |

Table 22. UV absorbance of paracetamol in pH 6.8 phosphate buffer at 243 nm

| Standard concentration (μg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2.04 | 0.1385 |
| 6.12 | 0.3943 |
| 10.20 | 0.6595 |
| 16.32 | 1.0418 |
| 20.40 | 1.3522 |

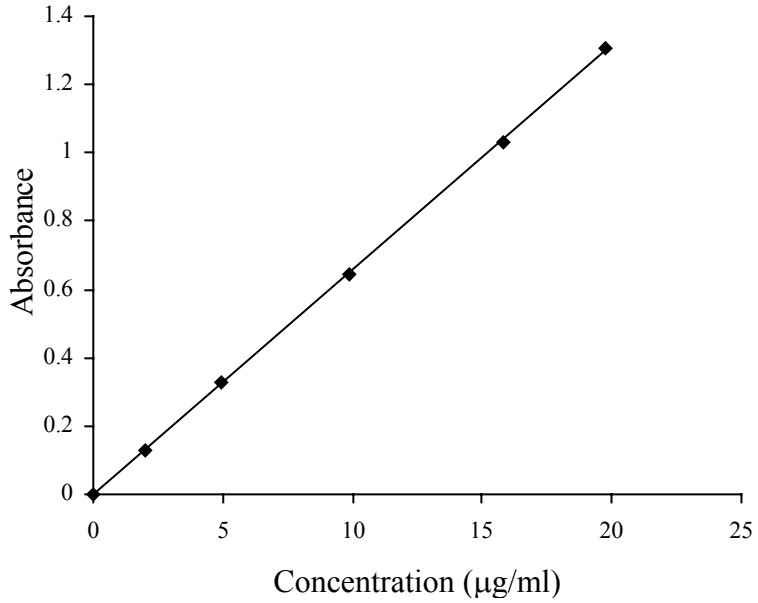



Figure 71. Standard curve of paracetamol in 0.1 N HCl at 243 nm

($y = 0.0657\ x - 0.0008$, $r^2 = 0.9999$)

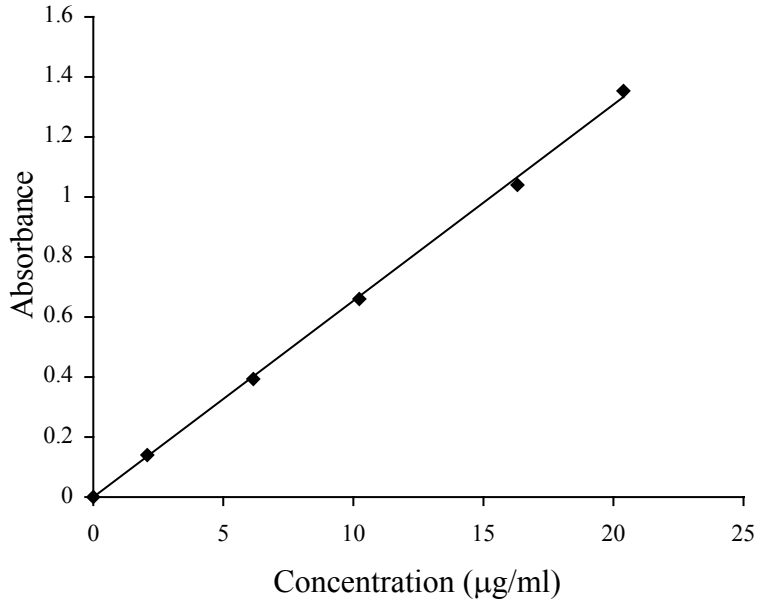



Figure 72. Standard curve of paracetamol in phosphate buffer at 243 nm

($y = 0.0654\ x - 0.0025$, $r^2 = 0.9992$)

Table 23. Efficiency of the coating of the paracetamol cores with the synthesized copolymers

| Polymer | Efficiency (%) |
|---|---|
| MA-EA (2:3) | |
| Batch 1 | 90.8 |
| Batch 2 | 89.0 |
| Batch 3 | 96.5 |
| MA-EA (1:1) + TEC 10% | 84.4 |
| MA-HEM-EA (4:1:5) | 89.5 |

tablets disintegrated. The cores were then coated at a level of 6 mg/cm$^2$ which the tablet disintegration was not observed and the tablet weight increase was very low, as shown in Table 24. In this experiment, coating of the cores with MA-EA (1:1) was also performed and the result was as expected. The coated tablets disintegrated immediately after immersing in 0.1 N HCl. This indicated that the MFT at 27 $^{o}$C of this copolymer was not low enough to promote film formation at the coating temperature of 30-35 $^{o}$C. This also agreed with the practical application of the commercial MA-EA (1:1) latices that at least 10% plasticizer (based on polymer weight) is required in the coating formulation. The weight increases of the tablets coated with MA-EA (1:1) + 10% TEC and MA-HEM-EA (4:1:5) are also shown in Table 24. The results show that the weight increase of the tablets coated with plasticized MA-EA (1:1) was slightly higher than that of the tablets coated with MA-EA (2:3), whereas the weight increase of the tablets coated with MA-HEM-EA (4:1:5) was highest. This indicated that among these three polymer, MA-EA (2:3) gave the least permeable film. It was possibly because this copolymer has less hydrophilic MA portion than MA-EA (1:1) and MA-HEM-EA (4:1:5). The water soluble TEC might also contribute to the permeability of the plasticized MA-EA (1:1) films.

The disintegration of the coated cores in buffer solution at pH 6.8 is summarized in Table 25. As the cores used in this study could disintegrate completely within one minute, therefore the time required for the disintegration was almost due to the dissolution of the films. The disintegration time of the tablets coated with MA-EA (2:3) was approximately 15 min. This indicated that there should not be a problem in producing enteric-coated tablets from rapid disintegrating cores by using MA-EA (2:3) as a film former. The results obtained also proved the reproducibility of the coating process. The disintegration time of the tablets coated with MA-EA (2:3) and of those coated with plasticized MA-EA (1:1) was comparable, indicating that both films had nearly equal dissolution rate. Considering the tablets coated with MA-HEM-EA (4:1:5), their disintegration was the slowest. This was consistent with the dissolution of the films studied in the previous section. The results indicated that the polymers in the series of MA-HEM-EA were less appropriate to be enteric-film formers, compared with MA-EA (2:3).

Table 24. Weight increase after resistance test in 0.1 N HCl of the coated tablets with a coating level of 6 mg/cm$^2$ (n=6)

| Polymer | Weight increase (%) | |
|---|---|---|
| | After 1 h | After 2 h |
| MA-EA (2:3) | | |
| Batch 1 | 3.58 (0.20) | 5.97 (0.33) |
| Batch 2 | 1.35 (0.08) | 2.34 (0.16) |
| Batch 3 | 1.75 (0.05) | 3.09 (0.13) |
| MA-EA (1:1) + TEC 10% | 4.55 (0.26) | 7.81 (0.40) |
| MA-HEM-EA (4:1:5) | 4.83 (0.26) | 8.90 (0.79) |

Table 25. Disintegration time in phosphate buffer of the coated tablets with a coating level of 6 mg/cm$^2$ (n=6)

| Polymer | Disintegration time (min) |
|---|---|
| MA-EA (2:3) | |
| Batch 1 | 13.76 (1.27) |
| Batch 2 | 15.36 (1.32) |
| Batch 3 | 13.55 (0.87) |
| MA-EA (1:1) + TEC 10% | 15.08 (1.34) |
| MA-HEM-EA (4:1:5) | 19.17 (3.53) |

#### 4.2.6.2 Drug dissolution

Figures 73, 74 and 75 displayed the drug releases of the paracetamol tablets coated with MA-EA (2:3) for the first, second and third batch, respectively. It can be said that there was nearly no drug release in the gastric state. This suggested the very high efficiency of the films in protecting the dissolution of the active substance as the films could maintain their integrity in 0.1 N HCl. In the buffer state, no release was found within the first 10 minutes, as the films were not completely dissolved in this period. Some of the six tablets started to release the drug within 20 minutes. This was corresponding to their disintegration time. The drug was nearly completely released from every tablet within 30 minutes. Thus the requirement to the pharmacopeia was met. The drug release of the tablets coated with MA-EA (1:1) plasticized with 10% TEC is shown in Figure 76. The release profile was similar to those of the tablets coated with MA-EA (2:3). There was nearly no release within 10 minutes in the buffer. A pronounced release occurred after 20 minutes. The drug release was complete within 40 minutes. In the case of the tablets coated with MA-HEM-EA (4:1:5), the release rate is displayed in Figure 77. It can be noticed that the tablets started to release the drug apparently after 30 minutes in the buffer and the release amount was still less than 80% after 50 minutes. Therefore, it did not meet the requirement of the pharmacopeia. This was because the film dissolution was too slow. All the results obtained from the experiments indicated that the MA-EA (2:3) copolymer could be used as a film former for the enteric-coating of the tablets without the need of plasticizer.

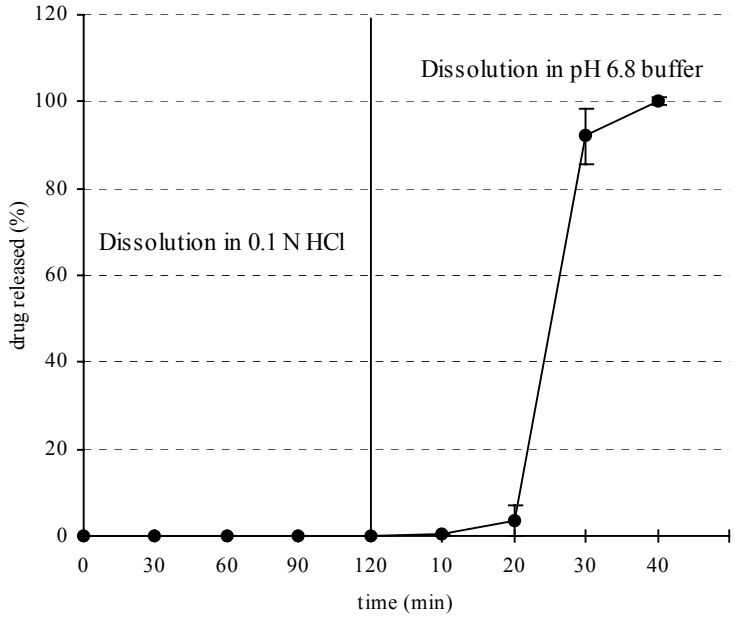



Figure 73. Dissolution rate of the coated tablets with a coating level of 6 mg/cm$^2$ in 0.1 N HCl and pH 6.8 phosphate buffer, coated with MA-EA (2:3), batch 1

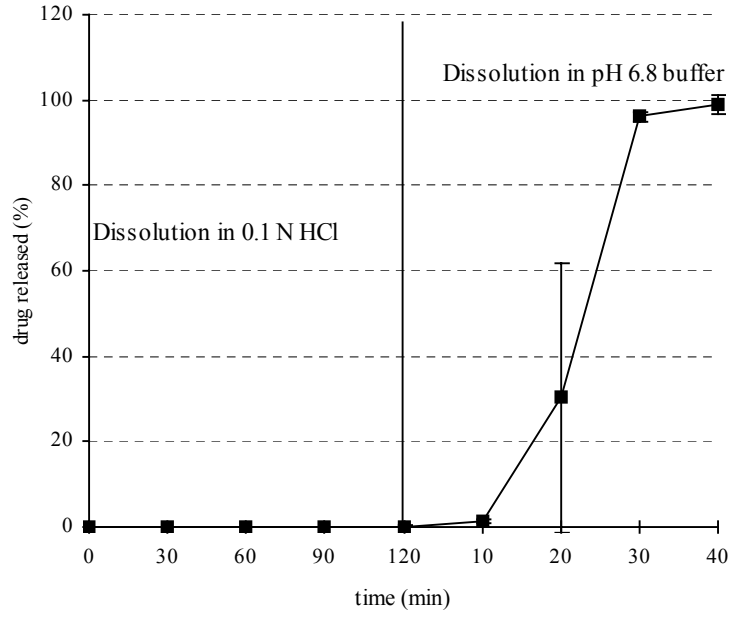



Figure 74. Dissolution rate of the coated tablets with a coating level of 6 mg/cm$^2$ in 0.1 N HCl and pH 6.8 phosphate buffer, coated with MA-EA (2:3), batch 2

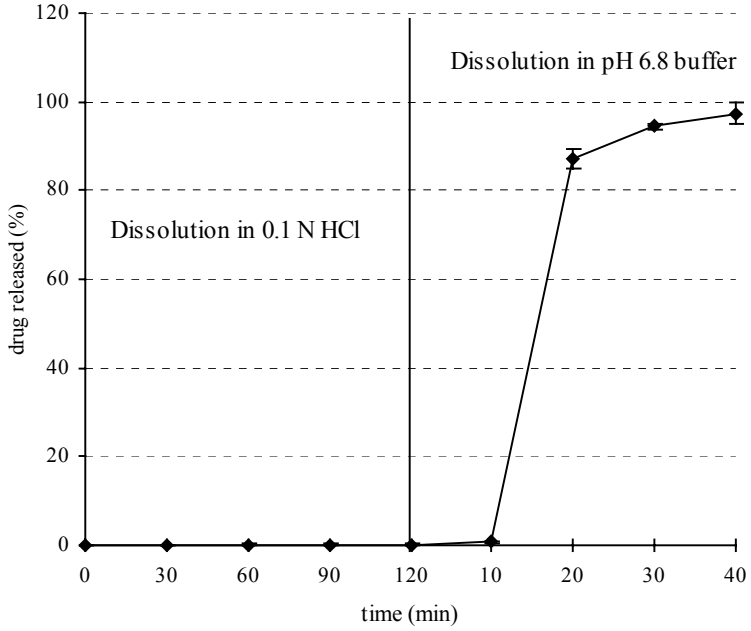



Figure 75. Dissolution rate of the coated tablets with a coating level of 6 mg/cm$^2$ in 0.1 N HCl and pH 6.8 phosphate buffer, coated with MA-EA (2:3), batch 3

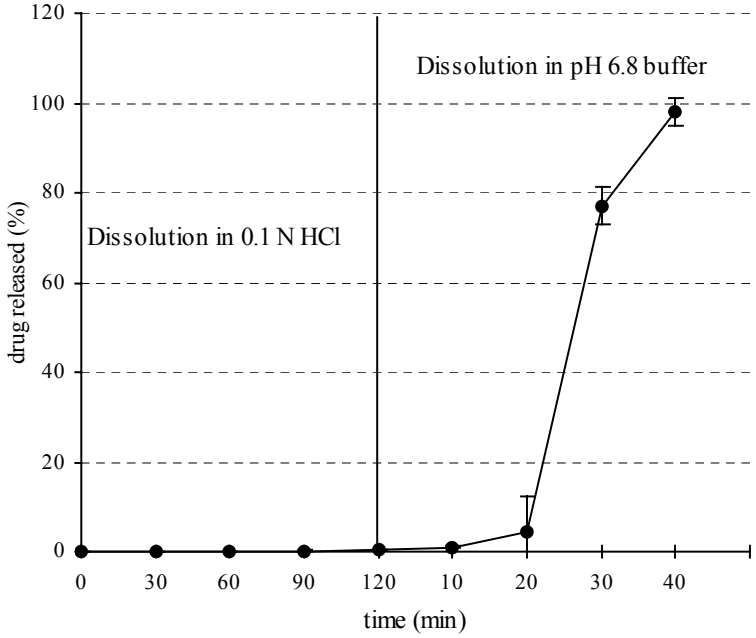



Figure 76. Dissolution rate of the coated tablets with a coating level of 6 mg/cm$^2$ in 0.1 N HCl and pH 6.8 phosphate buffer, coated with MA-EA (1:1) + TEC 10%

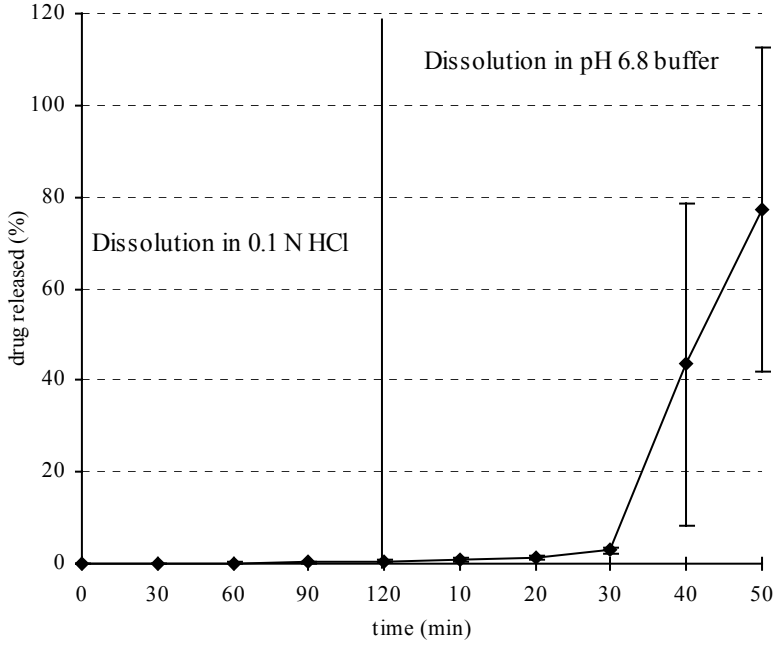



Figure 77. Dissolution rate of the coated tablets with a coating level of 6 mg/cm$^2$ in 0.1 N HCl and pH 6.8 phosphate buffer, coated with MA-HEM-EA (4:1:5)

# CHAPTER 5
# CONCLUSION

## 5.1 Investigation of the anti-tacking property of selected surfactants

The ability of certain nonionic surfactants in a group of sorbitan ester in reducing the tackiness of the films obtained from aqueous acrylic polymer dispersions (Eudragit®) were investigated, compared with those of talc and glyceryl monostearate (GMS). The results could be concluded as the followings:

1. The results from the peel tests revealed that GMS, Span 60 and Span 40 could significantly reduce the tackiness of both Eudragit NE 30D and Eudragit RS 30D films. On the contrary, Span 80 and Span 20 could only reduce the tackiness of the Eudragit NE 30D films, but were ineffective for the Eudragit RS 30D film.

2. The ability to reduce the film tackiness of these surfactants is related to the distribution of small-size particles throughout the film mass, resulting in a notable decrease of the polymer content at the film surface. The incorporated surfactants could also change the modulus of the films, nevertheless change in the film hardness is not involved in the anti-tacking mechanism.

3. The use of only 5 %w/w GMS, Span 60 or Span 40 in the coating formulations was enough to prevent pellet agglomeration during the coating without adverse effects on film flexibility. However, when the curing at an elevated temperature for a long time is needed, approximately 5 %w/w talc should be blended with the coated pellets prior to curing to prevent the pellet sticking.

4. The pellets coated with Eudragit RS 30D/RL 30D (9:1 w/w) did not exhibit any difference in the drug release profile when either 100 %w/w talc or 5 %w/w GMS was used in the coating formulation. While the formulations containing either Span 60 or Span 40 gave a slightly faster release rate.

5. The drug dissolution was proved to be stable, at least for 10 months at room temperature or 6 months at 40 $^{o}$C. However, the storage in the condition with high humidity should be avoided as the drug release could change.

## 5.2 Synthesis and evaluation of new acrylic copolymers

The objective of the study was to find new copolymers, which could form enteric films in the aqueous coating process without the use of external plasticizers. A variety of copolymer latices with variable monomer ratios were synthesized. Methacrylic acid (MA)-ethyl acrylate (EA) copolymer with a ratio of 1:1 was used as a prototype. The results could be concluded as the followings:

1. The acrylic polymer latices with 30% solid content were successfully synthesized by emulsion polymerization using semi-batch technique. The polymerization was complete within 6 hours of the reaction.

2. All synthesized latices had low viscosity and the pH in the range of acid. The MFT was lowered as the ratio of MA to EA decreased.

3. The films derived from all latices had the $T_g$s above room temperature, indicating that they were in a glassy state. All of them were hard and brittle. MA in the structure increased the film hardness as well as the $T_g$.

4. The MA-EA (2:3) copolymer with the MFT of 16 $^{o}$C could form a film at the coating temperature and the film started to dissolve in buffer solution at pH 6.0. However at pH 6.8 the dissolution of the MA-EA (2:3) film was not far different from that of the film derived from MA-EA (1:1).

5. With the coating level of 6 mg/cm$^2$, the tablets coated with MA-EA (2:3) were very resistant to gastric fluid and the drug release in pH 6.8 buffer conformed to the requirement of the pharmacopeia. The drug release profile was similar to that of the tablets coated with plasticized MA-EA (1:1). No tablet agglomeration was observed because the film tackiness was low. In conclusion, the latex of MA-EA at the ratio of 2:3 could be used as an enteric coating polymer without the plasticizer in the coating formulation.

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# APPENDIX

# APPENDIX A
# PEEL FORCE DATA

Table 26. Individual peel force of the Eudragit NE 30D films containing additives

| Additives | %w/w | Peel force (N) | | | | |
|---|---|---|---|---|---|---|
| | | Sample | | | | |
| | | 1 | 2 | 3 | 4 | 5 |
| No | 0 | 10.9 | 10.7 | 11.5 | 10.6 | 11.7 |
| Talc | 5 | 11.6 | 11.1 | 10.3 | 11.4 | 11.2 |
| | 10 | 9.9 | 9.7 | 10.0 | 10.3 | 9.8 |
| | 15 | 12.2 | 12.0 | 12.1 | 11.2 | 9.8 |
| | 50 | 12.4 | 11.9 | 9.5 | 7.8 | 12.4 |
| | 100 | 4.5 | 4.8 | 6.3 | 5.7 | 3.2 |
| GMS | 5 | 7.2 | 5.4 | 6.9 | 6.4 | 6.4 |
| | 10 | 2.3 | 2.2 | 3.1 | 3.7 | 2.6 |
| | 15 | 0.7 | 0.2 | 0.6 | 0.4 | 0.8 |
| Span 80 | 5 | 3.2 | 2.8 | 3.7 | 3.4 | 3.5 |
| | 10 | 2.9 | 1.9 | 1.5 | 1.6 | 2.4 |
| | 15 | 2.6 | 2.0 | 2.4 | 2.4 | 2.5 |
| Span 60 | 5 | 6.7 | 7.6 | 7.4 | 6.5 | 6.5 |
| | 10 | 3.4 | 4.0 | 4.4 | 5.3 | 3.8 |
| | 15 | 2.9 | 4.0 | 2.9 | 2.9 | 3.1 |
| Span 40 | 5 | 5.7 | 5.5 | 6.7 | 7.2 | 6.8 |
| | 10 | 5.2 | 5.2 | 4.8 | 5.1 | 5.2 |
| | 15 | 1.5 | 1.4 | 1.5 | 1.8 | 1.7 |
| Span 20 | 5 | 2.7 | 3.1 | 2.2 | 3.2 | 3.4 |
| | 10 | 2.4 | 2.3 | 2.4 | 2.6 | 2.0 |
| | 15 | 3.2 | 2.0 | 3.3 | 3.0 | 2.7 |

Table 27. Individual peel force of the Eudragit RS 30D films containing additives

| Additives | %w/w | Peel force (N) | | | | |
|---|---|---|---|---|---|---|
| | | Sample | | | | |
| | | 1 | 2 | 3 | 4 | 5 |
| No | 0 | 5.5 | 4.9 | 5.9 | 5.2 | 5.9 |
| GMS | 5 | 0.9 | 0.9 | 0.8 | 0.9 | 1.0 |
| | 10 | 0.7 | 0.5 | 0.6 | 0.6 | 0.7 |
| Span 80 | 5 | 5.6 | 4.9 | 5.4 | 5.0 | 4.4 |
| | 10 | 8.5 | 8.2 | 8.3 | 7.6 | 8.0 |
| Span 60 | 5 | 2.6 | 2.1 | 2.3 | 2.2 | 2.8 |
| | 10 | 1.4 | 1.4 | 1.9 | 1.7 | 1.9 |
| Span 40 | 5 | 3.6 | 3.0 | 4.3 | 4.4 | 3.7 |
| | 10 | 2.4 | 2.1 | 2.0 | 1.6 | 1.9 |
| Span 20 | 5 | 4.9 | 5.2 | 5.5 | 5.1 | 5.4 |
| | 10 | 9.4 | 8.8 | 9.6 | 8.7 | 8.0 |

# APPENDIX B

# MECHANICAL PROPERTY DATA

Table 28. Storage modulus of Eudragit NE 30D films containing additives

| Strain (%) | Storage modulus (MPa) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No additive | GMS (%) | | Span 80 (%) | | Span 60 (%) | | Span 40 (%) | | Span 20 (%) | |
| | | 5 | 15 | 5 | 15 | 5 | 15 | 5 | 15 | 5 | 15 |
| 0.10 | 42.90 | 51.59 | 93.00 | 21.82 | 8.82 | 45.98 | 52.88 | 33.51 | 38.20 | 13.67 | 5.81 |
| 0.16 | 43.58 | 51.86 | 94.69 | 21.82 | 8.90 | 46.12 | 52.98 | 33.74 | 38.00 | 13.79 | 5.82 |
| 0.25 | 43.60 | 51.42 | 94.39 | 21.62 | 9.11 | 45.78 | 52.42 | 33.86 | 38.02 | 13.77 | 5.91 |
| 0.40 | 43.23 | 50.42 | 91.19 | 21.58 | 9.29 | 44.58 | 51.85 | 33.34 | 37.36 | 13.71 | 6.05 |
| 0.64 | 41.42 | 47.34 | 69.80 | 21.19 | 9.14 | 41.97 | 49.15 | 31.95 | 35.46 | 13.43 | 6.05 |
| 1.02 | 36.58 | 36.77 | 48.35 | 18.01 | 8.78 | 33.20 | 36.95 | 27.15 | 27.83 | 12.25 | 5.96 |
| 1.60 | 24.46 | 25.79 | 32.01 | 13.66 | 7.45 | 22.31 | 25.29 | 18.95 | 19.58 | 9.87 | 5.56 |
| 2.53 | 15.94 | 17.18 | 20.84 | 9.65 | 5.62 | 14.34 | 16.78 | 12.64 | 13.18 | 7.26 | 4.53 |
| 4.00 | 10.09 | 11.04 | 12.73 | 6.59 | 4.00 | 8.42 | 10.94 | 8.23 | 8.68 | 5.09 | 3.34 |
| 6.33 | 5.77 | 6.39 | 7.90 | 4.47 | 2.78 | 5.08 | 6.45 | 5.70 | 5.04 | 3.50 | 2.37 |

Table 29. Storage modulus of Eudragit RS 30D films containing additives

| Strain (%) | Storage modulus (MPa) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No additive | GMS (%) | | Span 80 (%) | | Span 60 (%) | | Span 40 (%) | | Span 20 (%) | |
| | | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 | 5 | 10 |
| 0.10 | 70.76 | 68.38 | 56.62 | 79.84 | 42.63 | 75.01 | 51.54 | 69.68 | 45.28 | 55.49 | 17.46 |
| 0.14 | 70.33 | 67.68 | 55.05 | 81.34 | 42.57 | 74.87 | 52.18 | 70.15 | 46.53 | 55.28 | 17.76 |
| 0.25 | 69.62 | 60.86 | 51.18 | 73.00 | 33.02 | 73.82 | 50.42 | 66.29 | 46.29 | 47.55 | 13.90 |
| 0.40 | 55.83 | 43.98 | 38.34 | 50.75 | 22.37 | 54.13 | 38.69 | 46.65 | 34.07 | 32.94 | 9.32 |
| 0.64 | 38.40 | 29.55 | 25.98 | 33.45 | 14.38 | 36.28 | 26.64 | 30.65 | 22.55 | 21.39 | 5.93 |
| 1.01 | 25.37 | 19.25 | 17.06 | 21.36 | 9.19 | 23.43 | 17.50 | 19.58 | 14.57 | 13.66 | 3.67 |
| 1.59 | 16.35 | 12.46 | 11.12 | 13.78 | 5.86 | 13.91 | 11.48 | 12.63 | 9.37 | 8.69 | 2.26 |
| 2.52 | 10.58 | 7.35 | 7.28 | 7.90 | 3.79 | 8.48 | 6.76 | 7.31 | 5.34 | 5.58 | 1.41 |
| 3.99 | 6.95 | 4.57 | 4.18 | 4.89 | 2.11 | 5.04 | 4.27 | 4.24 | 3.23 | 3.13 | 0.92 |

Table 30. Individual elongation at break of the Eudragit NE 30D films containing additives

| Additives | %w/w | Elongation at break (%) | | | | |
|---|---|---|---|---|---|---|
| | | Sample | | | | |
| | | 1 | 2 | 3 | 4 | 5 |
| No | 0 | 659 | 652 | 639 | 564 | 588 |
| Talc | 5 | 550 | 498 | 483 | 541 | 510 |
| | 10 | 693 | 604 | 593 | 527 | 483 |
| | 15 | 395 | 384 | 399 | 426 | 390 |
| | 50 | 294 | 236 | 254 | 275 | 208 |
| | 100 | 38 | 37 | 50 | 37 | 34 |
| GMS | 5 | 692 | 704 | 714 | 672 | 578 |
| | 10 | 672 | 665 | 691 | 567 | 663 |
| | 15 | 672 | 715 | 592 | 595 | 574 |
| Span 80 | 5 | 816 | 895 | 861 | 933 | 914 |
| | 10 | 891 | 1032 | 966 | 971 | 936 |
| | 15 | 953 | 925 | 1040 | 943 | 999 |
| Span 60 | 5 | 582 | 598 | 538 | 581 | 467 |
| | 10 | 515 | 480 | 498 | 580 | 546 |
| | 15 | 534 | 573 | 537 | 568 | 528 |
| Span 40 | 5 | 543 | 568 | 549 | 575 | 592 |
| | 10 | 621 | 668 | 669 | 606 | 585 |
| | 15 | 596 | 593 | 671 | 645 | 631 |
| Span 20 | 5 | 707 | 699 | 772 | 644 | 709 |
| | 10 | 879 | 873 | 927 | 908 | 851 |
| | 15 | 1050 | 1045 | 1136 | 1093 | 1138 |

Table 31. Individual elongation at break of the Eudragit RS 30D films containing additives

| Additives | %w/w | Elongation at break (%) | | | | |
|---|---|---|---|---|---|---|
| | | Sample | | | | |
| | | 1 | 2 | 3 | 4 | 5 |
| No | 0 | 170 | 125 | 135 | 138 | 137 |
| GMS | 5 | 134 | 168 | 155 | 145 | 142 |
| | 10 | 181 | 149 | 140 | 146 | 146 |
| Span 80 | 5 | 170 | 174 | 174 | 167 | 141 |
| | 10 | 176 | 190 | 177 | 194 | 206 |
| Span 60 | 5 | 124 | 144 | 129 | 121 | 126 |
| | 10 | 111 | 152 | 156 | 178 | 170 |
| Span 40 | 5 | 188 | 153 | 154 | 155 | 174 |
| | 10 | 238 | 227 | 218 | 220 | 222 |
| Span 20 | 5 | 199 | 202 | 189 | 209 | 187 |
| | 10 | 253 | 217 | 254 | 228 | 235 |

Table 32. Individual tensile modulus of films from synthesized copolymers

| Polymer | Tensile modulus (MPa) | | | | |
|---|---|---|---|---|---|
| | Sample | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| MA-EA (1:2) | 228 | 240 | 223 | 243 | - |
| MA-EA (2:3) | 382 | 238 | 327 | 337 | - |
| MA-EA (1:1) | 395 | 315 | 314 | 203 | 236 |
| MA-HEM-EA (4:1:5) | 337 | 361 | 305 | 368 | 370 |
| MA-HEM-EA (4:2:4) | 304 | 337 | 270 | 388 | 275 |
| MA-HEM-EA (5:1:4) | 379 | 333 | 367 | 328 | 356 |
| MA-EA (1:1)+TEC10% | 269 | 329 | 318 | 269 | 311 |

Table 33. Individual tensile strength of films from synthesized copolymers

| Polymer | Tensile strength (MPa) | | | | |
|---|---|---|---|---|---|
| | Sample | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| MA-EA (1:2) | 31.9 | 29.6 | 28.1 | 31.7 | - |
| MA-EA (2:3) | 25.8 | 29.2 | 25.1 | 38.0 | - |
| MA-EA (1:1) | 21.8 | 32.7 | 24.7 | 10.4 | - |
| MA-HEM-EA (4:1:5) | 28.5 | 36.7 | 46.2 | 40.7 | 27.6 |
| MA-HEM-EA (4:2:4) | 49.2 | 27.9 | 48.8 | 26.5 | - |
| MA-HEM-EA (5:1:4) | 42.8 | 45.8 | 19.7 | 23.2 | 62.5 |
| MA-EA (1:1)+TEC10% | 35.2 | 39.9 | 34.4 | 32.9 | 35.6 |

Table 34. Individual elongation at break of films from synthesized copolymers

| Polymer | Elongation at break (%) | | | | |
|---|---|---|---|---|---|
| | Sample | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| MA-EA (1:2) | 17.1 | 9.0 | 14.5 | 15.9 | - |
| MA-EA (2:3) | 7.8 | 14.3 | 7.9 | 14.1 | - |
| MA-EA (1:1) | 5.5 | 11.7 | 12.1 | 12.1 | 4.4 |
| MA-HEM-EA (4:1:5) | 9.2 | 11.7 | 18.8 | 12.7 | 8.4 |
| MA-HEM-EA (4:2:4) | 16.3 | 9.7 | 13.7 | 10.2 | - |
| MA-HEM-EA (5:1:4) | 13.4 | 15.8 | 5.9 | 7.8 | 20.2 |
| MA-EA (1:1)+TEC10% | 13.1 | 12.3 | 10.2 | 12.1 | 14.3 |

# APPENDIX C
# DRUG RELEASE DATA

Table 35. Individual drug release of the theophylline core pellets (n = 3)

| Time (min) | Drug released (%) | | |
|---|---|---|---|
| | Sample | | |
| | 1 | 2 | 3 |
| 0 | 0.1 | -0.2 | 0 |
| 10 | 60.8 | 63.6 | 59.2 |
| 20 | 87.4 | 88.1 | 89.1 |
| 30 | 97.8 | 99.2 | 97.4 |
| 40 | 97.9 | 97.2 | 102.7 |
| 50 | 98.2 | 100.8 | 99.1 |
| 60 | 102.6 | 102.4 | 103.2 |

Table 36. Individual drug release of pellets coated with Eudragit NE 30D containing 5% GMS at a coating level of 5 % and 10 % (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | Coating level (%) | | | | | |
| | 5 | | | 10 | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0.1 | 0.1 | 0 | -0.3 | -0.4 | -0.1 |
| 0.5 | 6 | 8.9 | 5.2 | -0.2 | 0.2 | 0.3 |
| 1 | 15.4 | 18.5 | 10.1 | -0.1 | 0.3 | 1.1 |
| 1.5 | 22.8 | 25 | 15.3 | 1.1 | 0.9 | 1.3 |
| 2 | 28.8 | 30.4 | 20.4 | 1.4 | 1 | 1.8 |
| 3 | 38.8 | 39.3 | 30.1 | 2.4 | 1.6 | 3.3 |
| 4 | 45.9 | 46.7 | 36.9 | 3.8 | 2.4 | 5 |
| 5 | 49.7 | 49.4 | 42.2 | 4.9 | 2 | 6.3 |
| 6 | 53.4 | 52.9 | 46.5 | 5.7 | 2.8 | 6.6 |
| 7 | 54.7 | 55 | 48.8 | 6.8 | 3.6 | 8.1 |
| 8 | 57.1 | 56.8 | 50.9 | 7.8 | 3.6 | 8.4 |
| 9 | 57.5 | 58.5 | 52.1 | 8.4 | 4 | 9 |
| 10 | 58.5 | 59.7 | 53.7 | 9.1 | 4.7 | 9.4 |
| 11 | 59.7 | 61.3 | 55.4 | 9.7 | 5.4 | 9.7 |
| 12 | 60.9 | 61.5 | 56 | 10.3 | 4.7 | 9.9 |

Table 37. Individual drug release of pellets coated with Eudragit NE 30D containing 5% Span 60 at a coating level of 8 % and 10 % (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | Coating level (%) | | | | | |
| | 8 | | | 10 | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0.3 | 0.1 | -0.2 | 0 | 0 | 0.2 |
| 0.5 | -0.4 | -0.1 | 0.4 | 0.3 | 0.5 | 0.7 |
| 1 | 0.7 | 1 | 1.8 | 0.5 | 0.8 | 0.8 |
| 1.5 | 2 | 2.4 | 3.7 | 0.6 | 1.7 | 1.7 |
| 2 | 3.6 | 3.8 | 4.7 | 1.3 | 3.2 | 3 |
| 3 | 6.6 | 6.9 | 7.2 | 3.1 | 5.7 | 3.9 |
| 4 | 9 | 9.7 | 9.7 | 5.2 | 8.5 | 5.3 |
| 5 | 11.2 | 12.2 | 11.7 | 6.8 | 11.5 | 6 |
| 6 | 15 | 14.9 | 13.2 | 8.1 | 13.9 | 6.9 |
| 7 | 16.4 | 16.5 | 14.6 | 9.7 | 15.8 | 7.4 |
| 8 | 16.9 | 19 | 16.1 | 10.6 | 16.8 | 8.2 |
| 9 | 18.3 | 20.1 | 16.3 | 11.1 | 17.9 | 8.3 |
| 10 | 19.7 | 21.8 | 17.1 | 12 | 19 | 9.3 |
| 11 | 20.4 | 22.7 | 18.7 | 12.9 | 19.3 | 9.9 |
| 12 | 21.8 | 24.3 | 19.4 | 13.5 | 20.7 | 10.4 |

Table 38. Individual drug release of pellets coated with Eudragit NE 30D containing 5% Span 40 at a coating level of 5 %, 6 % and 10 % (n = 3)

| Time (h) | Drug released (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Coating level (%) | | | | | | | | |
| | 5 | | | 6 | | | 10 | | |
| | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0.3 | 0 | 0.2 | -0.1 | -1.2 | -0.3 | 0 | -0.4 | -0.1 |
| 0.5 | 6.9 | 3.6 | 3.5 | 4.8 | 5.3 | 3.9 | 0.4 | 0.5 | 0.5 |
| 1 | 15.7 | 10.2 | 9.3 | 10.5 | 11.5 | 9.8 | 0.3 | 2 | 1.3 |
| 1.5 | 22.7 | 17.9 | 14.8 | 15.6 | 16.6 | 15.5 | 0.9 | 3.7 | 2.3 |
| 2 | 30.5 | 24.3 | 20.2 | 20.3 | 21.3 | 19.3 | 1.2 | 5.1 | 2.8 |
| 3 | 42.1 | 36.1 | 29.1 | 28 | 25.2 | 24.8 | 2.6 | 8.3 | 4.2 |
| 4 | 52.5 | 45.5 | 36.5 | 34.1 | 29.9 | 31.1 | 3 | 11.2 | 5.4 |
| 5 | 60.7 | 53.9 | 42.3 | 38.5 | 30.7 | 34.9 | 4 | 13.6 | 6.2 |
| 6 | 66.5 | 60.6 | 46.3 | 42.3 | 34 | 38.6 | 4.9 | 15.7 | 7.7 |
| 7 | 72.2 | 63.3 | 49.8 | 44.8 | 35.2 | 40.6 | 5.2 | 17.5 | 9 |
| 8 | 73.9 | 67.3 | 49.8 | 49.3 | 36.3 | 42.7 | 6.8 | 18.1 | 9.7 |
| 9 | 75.3 | 68.8 | 53.1 | 49.9 | 38.8 | 43.5 | 6.7 | 19.7 | 10 |
| 10 | 76.7 | 70.8 | 54.5 | 52.3 | 39.6 | 46 | 7.8 | 20.4 | 10.8 |
| 11 | 77.2 | 73.2 | 56.2 | 54.1 | 40.4 | 45.9 | 8 | 21.3 | 11.4 |
| 12 | 78.7 | 72.9 | 57.1 | 54.7 | 41.1 | 45.1 | 9.7 | 21.9 | 12.8 |

Table 39. Individual drug release of pellets coated with Eudragit RS30D/RL30D containing 5% GMS at 10 % coating level (n = 3)

| Time (h) | Drug released (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Ratio of RS30D/RL30D | | | | | | | | |
| | 1:1 | | | 8:2 | | | 9:1 | | |
| | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0 | 0.4 | -0.1 | -0.1 | 0.1 | -0.2 | -0.1 | -0.1 | 0.1 |
| 0.25 | 23.4 | 21.9 | 23.4 | - | - | - | - | - | - |
| 0.5 | 52.3 | 51.2 | 53.7 | 9.7 | 7.4 | 7.4 | 1.6 | 1.6 | 1.5 |
| 1 | 87.4 | 84.9 | 86.5 | 26.8 | 24.5 | 24.7 | 4.3 | 5.0 | 5.1 |
| 1.5 | 98.7 | 98.5 | 97.2 | 44.2 | 40.66 | 42 | 9.4 | 9.6 | 9.9 |
| 2 | 97.2 | 96.9 | 102.0 | 59.9 | 56.8 | 59.5 | 14.2 | 15.3 | 15.6 |
| 3 | 98.5 | 96.1 | 94.7 | 87 | 83.3 | 86 | 25.1 | 26.4 | 27.3 |
| 4 | 98.5 | 97.9 | 99.2 | 96.3 | 95.5 | 96.2 | 36.4 | 38.3 | 39.3 |
| 5 | - | - | - | 98.2 | 98.4 | 98.3 | 48.1 | 50.5 | 50.5 |
| 6 | - | - | - | - | - | - | 58.3 | 59.9 | 61.3 |
| 7 | - | - | - | - | - | - | 68.4 | 68.0 | 69.9 |
| 8 | - | - | - | - | - | - | 76.3 | 73.9 | 79.0 |
| 9 | - | - | - | - | - | - | 84.4 | 82.2 | 84.4 |
| 10 | - | - | - | - | - | - | 87.0 | 87.1 | 90.2 |
| 11 | - | - | - | - | - | - | 91.0 | 90.7 | 89.3 |
| 12 | - | - | - | - | - | - | 93.1 | 93.3 | 96.8 |

Table 40. Individual drug release of pellets coated with Eudragit RS30D/RL30D (1:1) containing 5% GMS at 10 % coating level, without curing and cured at 60$^{o}$C, 24 h (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | Uncured | | | Cured | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0 | 0.1 | 0.1 | 0 | 0.4 | -0.1 |
| 0.25 | 32.8 | 30.5 | 30.3 | 23.4 | 21.9 | 23.4 |
| 0.5 | 65.8 | 61.0 | 61.8 | 52.3 | 51.2 | 53.7 |
| 1 | 93.5 | 90.3 | 90.8 | 87.4 | 84.9 | 86.5 |
| 1.5 | 97.5 | 95.2 | 99.0 | 98.7 | 98.5 | 97.2 |
| 2 | 99.3 | 96.7 | 95.4 | 97.2 | 96.9 | 102.0 |
| 3 | 97.9 | 100.6 | 96.2 | 98.5 | 96.1 | 94.7 |
| 4 | 98.5 | 98.8 | 96.9 | 98.5 | 97.9 | 99.2 |

Table 41. Individual drug release of pellets coated with Eudragit RS30D/RL30D (8:2) containing 5% GMS at 10 % coating level, without curing and cured at 60$^{o}$C, 24 h (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | Uncured | | | Cured | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0.5 | -0.5 | 0.5 | -0.1 | 0.1 | -0.2 |
| 0.5 | 14 | 14.1 | 12.1 | 9.7 | 7.4 | 7.4 |
| 1 | 37.1 | 36.7 | 34 | 26.8 | 24.5 | 24.7 |
| 1.5 | 58.6 | 57.6 | 55.4 | 44.2 | 40.66 | 42 |
| 2 | 76.4 | 73.9 | 73.8 | 59.9 | 56.8 | 59.5 |
| 3 | 96 | 94.6 | 95.6 | 87 | 83.3 | 86 |
| 4 | 99 | 100.7 | 99 | 96.3 | 95.5 | 96.2 |
| 5 | 99.5 | 101.3 | 98.2 | 98.2 | 98.4 | 98.3 |

Table 42. Individual drug release of pellets coated with Eudragit RS30D/RL30D (9:1) containing 5% GMS at 10 % coating level, with and without talc blending prior to curing (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | No blend | | | Blend | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | -0.1 | 0 | -0.1 | -0.1 | -0.1 | 0.1 |
| 0.5 | 4.4 | 2.7 | 2.6 | 1.6 | 1.6 | 1.5 |
| 1 | 10.9 | 8.4 | 8.2 | 4.3 | 5.0 | 5.1 |
| 1.5 | 18.6 | 14.3 | 15.1 | 9.4 | 9.6 | 9.9 |
| 2 | 27 | 21.1 | 22.5 | 14.2 | 15.3 | 15.6 |
| 3 | 42.1 | 35.2 | 37.5 | 25.1 | 26.4 | 27.3 |
| 4 | 57.8 | 50.2 | 52.4 | 36.4 | 38.3 | 39.3 |
| 5 | 69.3 | 62.1 | 65 | 48.1 | 50.5 | 50.5 |
| 6 | 80.8 | 74.3 | 76.3 | 58.3 | 59.9 | 61.3 |
| 7 | 88 | 83.8 | 85.1 | 68.4 | 68.0 | 69.9 |
| 8 | 91.7 | 90.3 | 95 | 76.3 | 73.9 | 79.0 |
| 9 | 99.5 | 94.3 | 95.5 | 84.4 | 82.2 | 84.4 |
| 10 | 98.7 | 95.3 | 99.3 | 87.0 | 87.1 | 90.2 |
| 11 | 99.6 | 99.5 | 101.4 | 91.0 | 90.7 | 89.3 |
| 12 | 103.5 | 97.7 | 103.8 | 93.1 | 93.3 | 96.8 |

Table 43. Individual drug release of pellets coated with Eudragit RS30D/RL30D (9:1) containing 5% Span 60 at 10 % coating level, with and without talc blending prior to curing (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | No blend | | | Blend | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | -0.1 | -0.3 | 0.3 | -0.2 | 0.4 | -0.6 |
| 0.5 | 7.7 | 4.4 | 8.4 | 1.7 | 1.7 | 1.0 |
| 1 | 16.7 | 11.2 | 18.1 | 5.5 | 5.9 | 5.1 |
| 1.5 | 26.1 | 18.7 | 27.2 | 11.9 | 11.1 | 11.4 |
| 2 | 35.3 | 26.2 | 36.5 | 18.1 | 16.8 | 17.5 |
| 3 | 51.4 | 40.8 | 52.4 | 31.4 | 29.6 | 29.6 |
| 4 | 64 | 54.1 | 66 | 43.9 | 40.9 | 42.6 |
| 5 | 75.6 | 63.7 | 76.5 | 57.7 | 53.8 | 54.9 |
| 6 | 82.3 | 72.4 | 83.6 | 67.0 | 66.5 | 67.0 |
| 7 | 90.3 | 79 | 89.2 | 78.6 | 76.4 | 75.2 |
| 8 | 93.2 | 86.6 | 93 | 84.4 | 83.2 | 84.9 |
| 9 | 97.8 | 89.3 | 95.5 | 91.2 | 93.7 | 92.9 |
| 10 | 99.4 | 91.9 | 95.9 | 94.5 | 96.2 | 93.0 |
| 11 | 100.9 | 95.6 | 96.8 | 99.2 | 100.0 | 100.0 |
| 12 | 98.8 | 99.2 | 100.1 | 100.0 | 99.0 | 98.8 |

Table 44. Individual drug release of pellets coated with Eudragit RS30D/RL30D (9:1) containing 5% Span 40 at 10 % coating level, with and without talc blending prior to curing (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | No blend | | | Blend | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | -0.1 | 0 | -0.2 | 0.2 | -0.2 | -0.3 |
| 0.5 | 9.2 | 5.9 | 7.4 | 2.0 | 1.7 | 1.4 |
| 1 | 19.7 | 13.3 | 16.5 | 7.0 | 6.7 | 4.6 |
| 1.5 | 30.6 | 21.6 | 25.7 | 12.8 | 13.2 | 9.8 |
| 2 | 40 | 29.4 | 35 | 19.5 | 19.7 | 15.9 |
| 3 | 57.3 | 44.4 | 50.2 | 33.7 | 33.9 | 27.7 |
| 4 | 70.7 | 58.4 | 62.5 | 47.8 | 48.0 | 39.6 |
| 5 | 78 | 68.4 | 73.4 | 60.1 | 60.7 | 52.0 |
| 6 | 85.5 | 75.8 | 80.1 | 73.2 | 72.9 | 66.4 |
| 7 | 89.1 | 81.5 | 86 | 83.2 | 82.4 | 75.4 |
| 8 | 93.5 | 87.8 | 90.2 | 87.6 | 89.2 | 82.7 |
| 9 | 97.7 | 90.4 | 93.6 | 94.1 | 94.6 | 87.2 |
| 10 | 95.1 | 93.8 | 97.3 | 95.1 | 97.3 | 93.8 |
| 11 | 96 | 95.6 | 97.1 | 95.0 | 97.8 | 97.7 |
| 12 | 98.3 | 99.1 | 97.6 | 101.0 | 101.7 | 95.1 |

Table 45. Individual drug release of pellets coated with Eudragit RS30D/RL30D (9:1) containing additives at 10 % coating level (n = 3)

| Time (h) | Drug released (%) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Additives | | | | | | | | | | | |
| | 100% talc | | | 5% GMS | | | 5% Span 60 | | | 5% Span 40 | | |
| | 1 | 2 | 2 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0 | -0.1 | 0 | -0.1 | -0.1 | 0.1 | -0.2 | 0.4 | -0.6 | 0.2 | -0.2 | -0.3 |
| 0.5 | 1.5 | 1.2 | 1.1 | 1.6 | 1.6 | 1.5 | 1.7 | 1.7 | 1.0 | 2.0 | 1.7 | 1.4 |
| 1 | 5.6 | 3.3 | 4.3 | 4.3 | 5.0 | 5.1 | 5.5 | 5.9 | 5.1 | 7.0 | 6.7 | 4.6 |
| 1.5 | 12.3 | 7.9 | 10.0 | 9.4 | 9.6 | 9.9 | 11.9 | 11.1 | 11.4 | 12.8 | 13.2 | 9.8 |
| 2 | 19.5 | 14.2 | 16.4 | 14.2 | 15.3 | 15.6 | 18.1 | 16.8 | 17.5 | 19.5 | 19.7 | 15.9 |
| 3 | 34.3 | 26.7 | 29.9 | 25.1 | 26.4 | 27.3 | 31.4 | 29.6 | 29.6 | 33.7 | 33.9 | 27.7 |
| 4 | 48.3 | 39.1 | 42.7 | 36.4 | 38.3 | 39.3 | 43.9 | 40.9 | 42.6 | 47.8 | 48.0 | 39.6 |
| 5 | 59.9 | 50.5 | 54.7 | 48.1 | 50.5 | 50.5 | 57.7 | 53.8 | 54.9 | 60.1 | 60.7 | 52.0 |
| 6 | 69.5 | 61.1 | 63.6 | 58.3 | 59.9 | 61.3 | 67.0 | 66.5 | 67.0 | 73.2 | 72.9 | 66.4 |
| 7 | 79.4 | 69.4 | 73.0 | 68.4 | 68.0 | 69.9 | 78.6 | 76.4 | 75.2 | 83.2 | 82.4 | 75.4 |
| 8 | 84.3 | 76.6 | 80.3 | 76.3 | 73.9 | 79.0 | 84.4 | 83.2 | 84.9 | 87.6 | 89.2 | 82.7 |
| 9 | 89.0 | 82.9 | 84.9 | 84.4 | 82.2 | 84.4 | 91.2 | 93.7 | 92.9 | 94.1 | 94.6 | 87.2 |
| 10 | 93.5 | 88.0 | 86.7 | 87.0 | 87.1 | 90.2 | 94.5 | 96.2 | 93.0 | 95.1 | 97.3 | 93.8 |
| 11 | 94.6 | 90.3 | 90.1 | 91.0 | 90.7 | 89.3 | 99.2 | 100 | 100 | 95.0 | 97.8 | 97.7 |
| 12 | 94.0 | 93.4 | 94.7 | 93.1 | 93.3 | 96.8 | 100 | 99.0 | 98.8 | 101 | 101 | 95.1 |

Table 46. Individual drug release of pellets coated with Eudragit NE 30D containing 5 % GMS or 5 % Span 40, at 5 % coating level (n = 3)

| Time (h) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|
| | GMS | | | Span 40 | | |
| | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0.1 | 0.1 | 0 | 0.3 | 0 | 0.2 |
| 0.5 | 6 | 8.9 | 5.2 | 6.9 | 3.6 | 3.5 |
| 1 | 15.4 | 18.5 | 10.1 | 15.7 | 10.2 | 9.3 |
| 1.5 | 22.8 | 25 | 15.3 | 22.7 | 17.9 | 14.8 |
| 2 | 28.8 | 30.4 | 20.4 | 30.5 | 24.3 | 20.2 |
| 3 | 38.8 | 39.3 | 30.1 | 42.1 | 36.1 | 29.1 |
| 4 | 45.9 | 46.7 | 36.9 | 52.5 | 45.5 | 36.5 |
| 5 | 49.7 | 49.4 | 42.2 | 60.7 | 53.9 | 42.3 |
| 6 | 53.4 | 52.9 | 46.5 | 66.5 | 60.6 | 46.3 |
| 7 | 54.7 | 55 | 48.8 | 72.2 | 63.3 | 49.8 |
| 8 | 57.1 | 56.8 | 50.9 | 73.9 | 67.3 | 49.8 |
| 9 | 57.5 | 58.5 | 52.1 | 75.3 | 68.8 | 53.1 |
| 10 | 58.5 | 59.7 | 53.7 | 76.7 | 70.8 | 54.5 |
| 11 | 59.7 | 61.3 | 55.4 | 77.2 | 73.2 | 56.2 |
| 12 | 60.9 | 61.5 | 56 | 78.7 | 72.9 | 57.1 |

Table 47. Individual drug release of pellets coated with Eudragit NE 30D containing 5 % GMS, Span 60, Span 40 at 10 % coating level (n = 3)

| Time (h) | Drug released (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Additives | | | | | | | | |
| | GMS | | | Span 60 | | | Span 40 | | |
| | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | -0.3 | -0.4 | -0.1 | 0 | 0 | 0.2 | 0 | -0.4 | -0.1 |
| 0.5 | -0.2 | 0.2 | 0.3 | 0.3 | 0.5 | 0.7 | 0.4 | 0.5 | 0.5 |
| 1 | -0.1 | 0.3 | 1.1 | 0.5 | 0.8 | 0.8 | 0.3 | 2 | 1.3 |
| 1.5 | 1.1 | 0.9 | 1.3 | 0.6 | 1.7 | 1.7 | 0.9 | 3.7 | 2.3 |
| 2 | 1.4 | 1 | 1.8 | 1.3 | 3.2 | 3 | 1.2 | 5.1 | 2.8 |
| 3 | 2.4 | 1.6 | 3.3 | 3.1 | 5.7 | 3.9 | 2.6 | 8.3 | 4.2 |
| 4 | 3.8 | 2.4 | 5 | 5.2 | 8.5 | 5.3 | 3 | 11.2 | 5.4 |
| 5 | 4.9 | 2 | 6.3 | 6.8 | 11.5 | 6 | 4 | 13.6 | 6.2 |
| 6 | 5.7 | 2.8 | 6.6 | 8.1 | 13.9 | 6.9 | 4.9 | 15.7 | 7.7 |
| 7 | 6.8 | 3.6 | 8.1 | 9.7 | 15.8 | 7.4 | 5.2 | 17.5 | 9 |
| 8 | 7.8 | 3.6 | 8.4 | 10.6 | 16.8 | 8.2 | 6.8 | 18.1 | 9.7 |
| 9 | 8.4 | 4 | 9 | 11.1 | 17.9 | 8.3 | 6.7 | 19.7 | 10 |
| 10 | 9.1 | 4.7 | 9.4 | 12 | 19 | 9.3 | 7.8 | 20.4 | 10.8 |
| 11 | 9.7 | 5.4 | 9.7 | 12.9 | 19.3 | 9.9 | 8 | 21.3 | 11.4 |
| 12 | 10.3 | 4.7 | 9.9 | 13.5 | 20.7 | 10.4 | 9.7 | 21.9 | 12.8 |

Table 48. Individual drug release of pellets coated with Eudragit NE 30D containing 5 % GMS at 10 % coating level kept at various storage conditions (n = 3)

| Time (h) | Drug released (%) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Storage condition | | | | | | | | | | | |
| | Initial | | | R.T., 10 mths | | | 40°C, 6 mths | | | 40°C,75%RH, 6 mths | | |
| | 1 | 2 | 2 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | -0.3 | -0.4 | -0.1 | -0.1 | 0.3 | 0.3 | -0.1 | 0.3 | -0.2 | -0.1 | -0.5 | -1 |
| 0.5 | -0.2 | 0.2 | 0.3 | 0.5 | 0.4 | 0.3 | 0.4 | 0.7 | 0.4 | 7.2 | 10.3 | 9.7 |
| 1 | -0.1 | 0.3 | 1.1 | 1 | 1.1 | 1.1 | 0.4 | 0.7 | 0.6 | 18.4 | 25.7 | 25.2 |
| 1.5 | 1.1 | 0.9 | 1.3 | 1.4 | 1.7 | 2.1 | 0.7 | 0.9 | 1.2 | 28.8 | 37.4 | 37.8 |
| 2 | 1.4 | 1 | 1.8 | 1.7 | 2.2 | 3 | 1 | 1.5 | 1.6 | 38.4 | 48.7 | 48.6 |
| 3 | 2.4 | 1.6 | 3.3 | 3.2 | 2.6 | 4.4 | 1.8 | 1.4 | 3 | 53.9 | 65.2 | 66.3 |
| 4 | 3.8 | 2.4 | 5 | 3.9 | 3.5 | 5.1 | 2.5 | 1.6 | 4.1 | 65.7 | 76.9 | 78 |
| 5 | 4.9 | 2 | 6.3 | 5.3 | 4.6 | 6.2 | 3.5 | 2.5 | 5.2 | 72.6 | 84.5 | 84.4 |
| 6 | 5.7 | 2.8 | 6.6 | 5.3 | 5.1 | 6.7 | 4.9 | 3.2 | 5.9 | 78.3 | 89.7 | 91.1 |
| 7 | 6.8 | 3.6 | 8.1 | 6.3 | 5.8 | 7.6 | 5.4 | 4.2 | 6.7 | 83.3 | 92.7 | 91.6 |
| 8 | 7.8 | 3.6 | 8.4 | 7.4 | 6.6 | 7.7 | 5.7 | 4.9 | 8 | 85.2 | 98.3 | 96.8 |
| 9 | 8.4 | 4 | 9 | 7.7 | 7 | 8.3 | 6.7 | 5.9 | 9.1 | 90.4 | 96.6 | 99.8 |
| 10 | 9.1 | 4.7 | 9.4 | 8.5 | 7.7 | 8.8 | 8 | 7 | 9.2 | 92.7 | 99.1 | 100 |
| 11 | 9.7 | 5.4 | 9.7 | 9.7 | 8.5 | 9 | 8.3 | 7.6 | 10.2 | | | |
| 12 | 10.3 | 4.7 | 9.9 | 10.2 | 8.9 | 10 | 9.2 | 8.8 | 10.6 | | | |

Table 49. Individual drug release of pellets coated with Eudragit NE 30D containing 5% Span 40 at 10 % coating level kept at various storage conditions (n = 3)

| Time (h) | Drug released (%) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Storage condition | | | | | | | | | | | |
| | Initial | | | R.T., 10 mths | | | 40°C, 6 mths | | | 40°C,75%RH, 6 mths | | |
| | 1 | 2 | 2 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 0 | 0 | -0.4 | -0.1 | -0.9 | -0.2 | -0.3 | 0.2 | 0 | -0.4 | 0 | -0.2 | 0 |
| 0.5 | 0.4 | 0.5 | 0.5 | -0.2 | 0.9 | 1 | 0.6 | 0.7 | 0.5 | 15.5 | 16.7 | 13.5 |
| 1 | 0.3 | 2 | 1.3 | 0.6 | 2.3 | 1.3 | 1.4 | 1.8 | 1.5 | 32.9 | 37.2 | 32.4 |
| 1.5 | 0.9 | 3.7 | 2.3 | 0.9 | 3.3 | 3.2 | 2.2 | 2.8 | 2.4 | 46 | 52.2 | 47.1 |
| 2 | 1.2 | 5.1 | 2.8 | 1.9 | 3.8 | 3.6 | 3.4 | 3.7 | 3.2 | 55.9 | 63.7 | 58.4 |
| 3 | 2.6 | 8.3 | 4.2 | 2.7 | 5.5 | 6.2 | 5.2 | 5.7 | 4.9 | 69.9 | 78.4 | 73.1 |
| 4 | 3 | 11.2 | 5.4 | 3.5 | 7.3 | 8.1 | 7 | 7.2 | 6.5 | 77.9 | 83.9 | 81.1 |
| 5 | 4 | 13.6 | 6.2 | 5.1 | 8.5 | 9.5 | 8.8 | 8.4 | 7.2 | 83.2 | 90.4 | 87.9 |
| 6 | 4.9 | 15.7 | 7.7 | 4.8 | 9.9 | 11.7 | 10.3 | 9.9 | 8.2 | 88.1 | 91.4 | 91.3 |
| 7 | 5.2 | 17.5 | 9 | 5.4 | 11 | 13.1 | 11.5 | 10.6 | 9.3 | 87.9 | 96.7 | 97.2 |
| 8 | 6.8 | 18.1 | 9.7 | 6 | 12.3 | 14.4 | 12.8 | 11.6 | 10.5 | 92.5 | 98.6 | 94.6 |
| 9 | 6.7 | 19.7 | 10 | 6.7 | 13.1 | 15.1 | 13.4 | 12.7 | 11.2 | 94.2 | 98.5 | 97 |
| 10 | 7.8 | 20.4 | 10.8 | 7.6 | 14.3 | 15.9 | 14.9 | 13.8 | 11.9 | 96.8 | 101 | 99.7 |
| 11 | 8 | 21.3 | 11.4 | 7.7 | 15.1 | 16.5 | 15.2 | 13.8 | 12.6 | | | |
| 12 | 9.7 | 21.9 | 12.8 | 8.3 | 15.7 | 17.4 | 16 | 14.1 | 13.9 | | | |

Table 50. Individual drug release of paracetamol tablets coated with MA-EA (2:3) batch 1, at a polymer level of 6 mg/cm$^2$ (n = 6)

| Stage | Time (min) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| Acid | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 30 | 0.2 | 0.2 | 0 | 0 | 0 | 0.1 |
| | 60 | 0.1 | 0.2 | 0.1 | 0 | 0 | 0 |
| | 90 | 0.1 | 0.1 | 0.2 | 0.1 | 0 | 0 |
| | 120 | 0.1 | 0.1 | 0.2 | 0.2 | 0.2 | 0 |
| Buffer | 10 | 0.2 | 0.2 | 0.7 | 0.5 | 0.5 | 0.4 |
| | 20 | 2.4 | 2.1 | 10.7 | 2.2 | 2.4 | 1.8 |
| | 30 | 97.3 | 92.8 | 97.5 | 82.8 | 96.9 | 85.8 |
| | 40 | 100.5 | 98.8 | 99.7 | 100.1 | 100.8 | 100.7 |

Table 51. Individual drug release of paracetamol tablets coated with MA-EA (2:3) batch 2, at a polymer level of 6 mg/cm$^2$ (n = 6)

| Stage | Time (min) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| Acid | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 30 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 60 | 0 | 0.2 | 0 | 0 | 0.2 | 0 |
| | 90 | 0.2 | 0 | 0.2 | 0.2 | 0.2 | 0 |
| | 120 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0 |
| Buffer | 10 | 0.6 | 1.4 | 1.7 | 1.6 | 1.6 | 1.1 |
| | 20 | 2.5 | 1.2 | 55.2 | 1.3 | 60.9 | 61.4 |
| | 30 | 94.6 | 96.7 | 96.2 | 96.1 | 95.8 | 98.0 |
| | 40 | 100.5 | 102.6 | 98.7 | 97.7 | 97.5 | 97.0 |

Table 52. Individual drug release of paracetamol tablets coated with MA-EA (2:3) batch 3, at a polymer level of 6 mg/cm$^2$ (n = 6)

| Stage | Time (min) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| Acid | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 30 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 60 | 0 | 0 | 0 | 0.4 | 0 | 0.4 |
| | 90 | 0 | 0 | 0.4 | 0 | 0 | 0.4 |
| | 120 | 0 | 0 | 0.4 | 0.4 | 0 | 0 |
| Buffer | 10 | 0.7 | 0.6 | 0.8 | 1.0 | 0.5 | 0.4 |
| | 20 | 87.7 | 88.8 | 83.2 | 89.0 | 86.5 | 87.3 |
| | 30 | 94.8 | 94.6 | 93.8 | 95.1 | 93.9 | 94.1 |
| | 40 | 98.7 | 94.8 | 98.2 | 100.8 | 96.7 | 94.9 |

Table 53. Individual drug release of paracetamol tablets coated with MA-EA (1:1) + TEC 10%, at a polymer level of 6 mg/cm$^2$ (n = 6)

| Stage | Time (min) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| Acid | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 30 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 60 | 0 | 0.1 | 0 | 0.2 | 0 | 0 |
| | 90 | 0.2 | 0.2 | 0.1 | 0.4 | 0.3 | 0.2 |
| | 120 | 0.4 | 0.4 | 0.3 | 0.5 | 0.5 | 0.5 |
| Buffer | 10 | 0.7 | 0.8 | 0.7 | 1.1 | 1.2 | 0.9 |
| | 20 | 1.3 | 1.1 | 20.2 | 1.5 | 1.4 | 1.5 |
| | 30 | 77.1 | 84.4 | 76.6 | 71.8 | 75.1 | 77.6 |
| | 40 | 101.0 | 101.2 | 99.6 | 94.9 | 93.9 | 98.7 |

Table 54. Individual drug release of paracetamol tablets coated with MA-HEM-EA (4:1:5), at a polymer level of 6 mg/cm$^2$ (n = 6)

| Stage | Time (min) | Drug released (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Sample | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 6 |
| Acid | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 30 | 0 | 0 | 0 | 0 | 0 | 0.1 |
| | 60 | 0.1 | 0.4 | 0.1 | 0 | 0.1 | 0.2 |
| | 90 | 0.2 | 0.3 | 0.4 | 0.2 | 0.3 | 0.2 |
| | 120 | 0.4 | 0.7 | 0.5 | 0.8 | 0.5 | 0.3 |
| Buffer | 10 | 0.6 | 0.8 | 0.7 | 1.2 | 1 | 0.4 |
| | 20 | 1.1 | 1.6 | 1.2 | 2.1 | 1.7 | 0.8 |
| | 30 | 2.7 | 3.4 | 2.7 | 4.0 | 3.1 | 2.1 |
| | 40 | 5.5 | 93.6 | 38.6 | 50.0 | 68.3 | 4.8 |
| | 50 | 95.3 | 93.2 | 95.2 | 73.2 | 99.3 | 7.3 |

# APPENDIX D

## DSC thermograms of synthesized copolymers

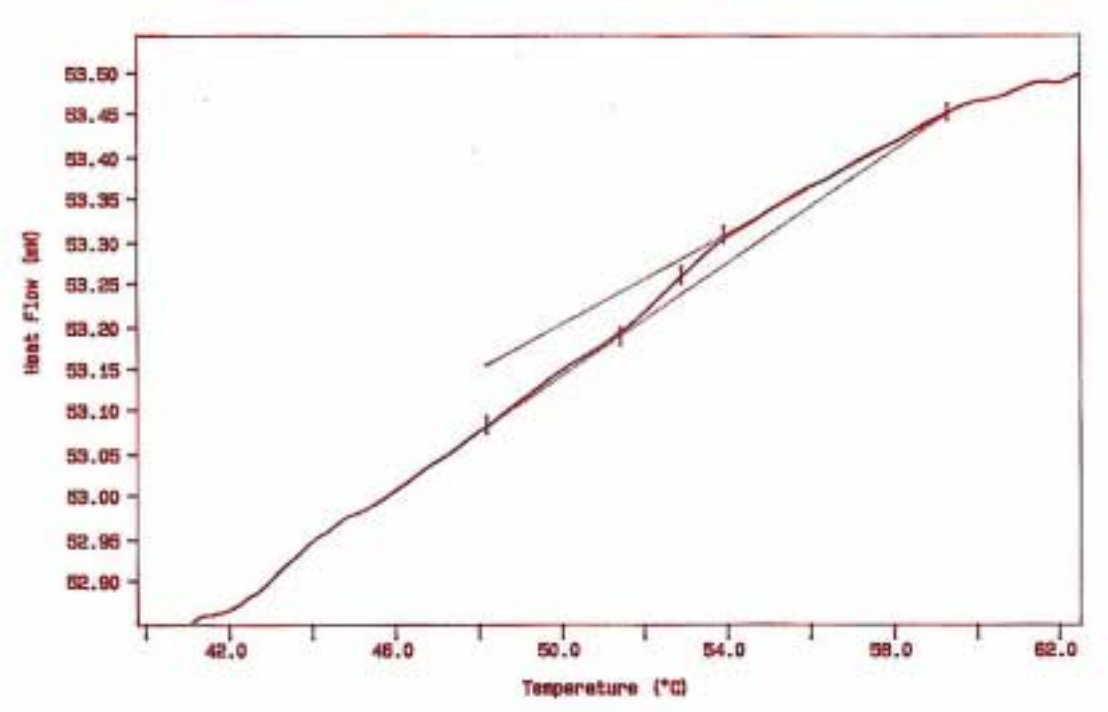



Figure 78. DSC thermogram of MA-EA (1:2) film

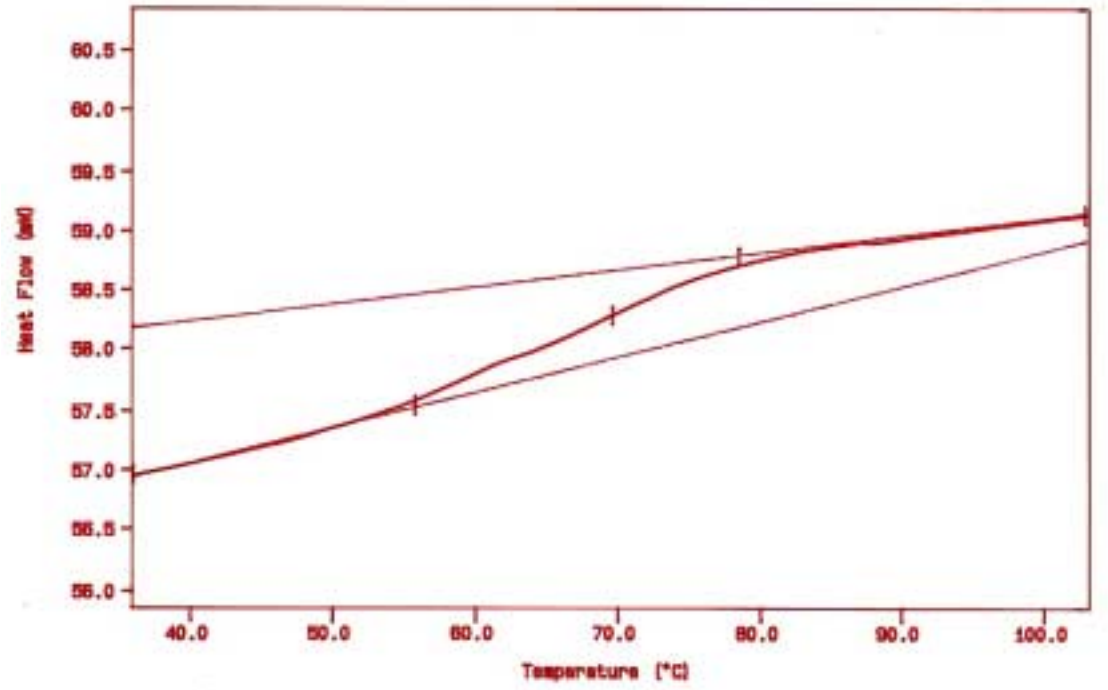



Figure 79. DSC thermogram of MA-EA (2:3) film

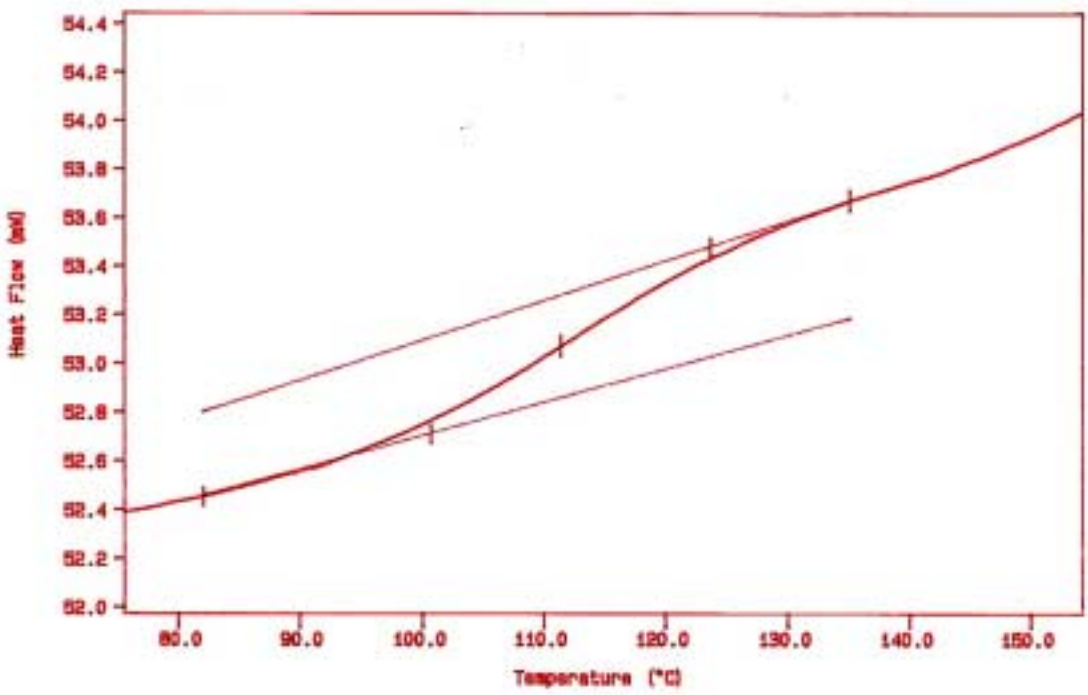



Figure 80. DSC thermogram of MA-EA (1:1) film

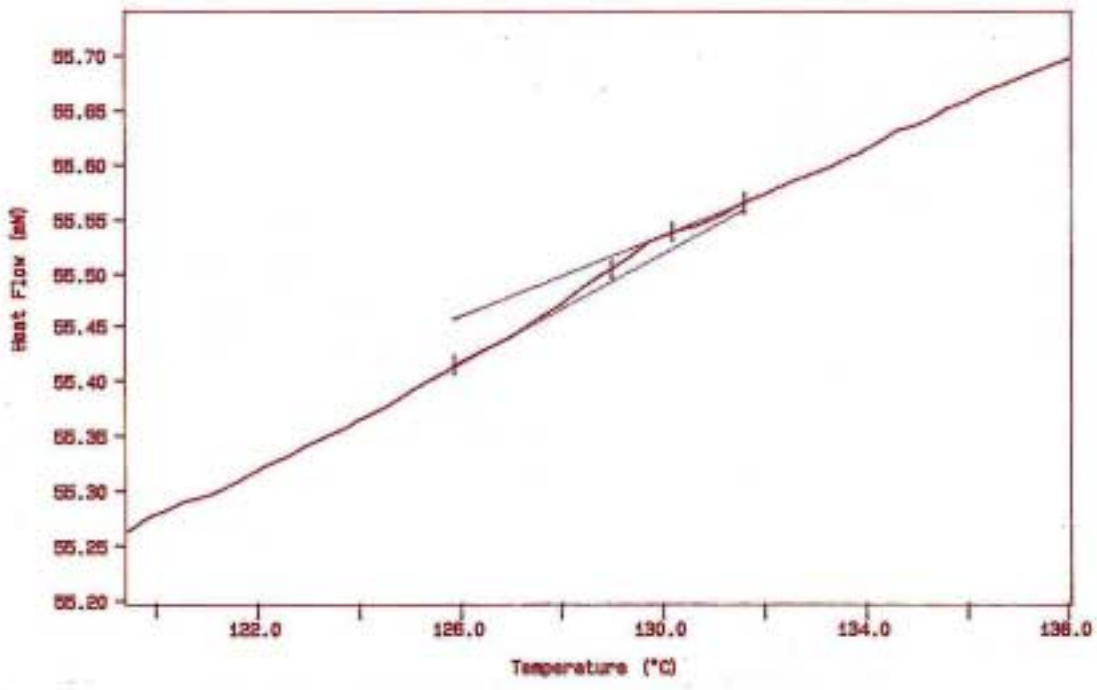



Figure 81. DSC thermogram of MA-EA (3:2) film

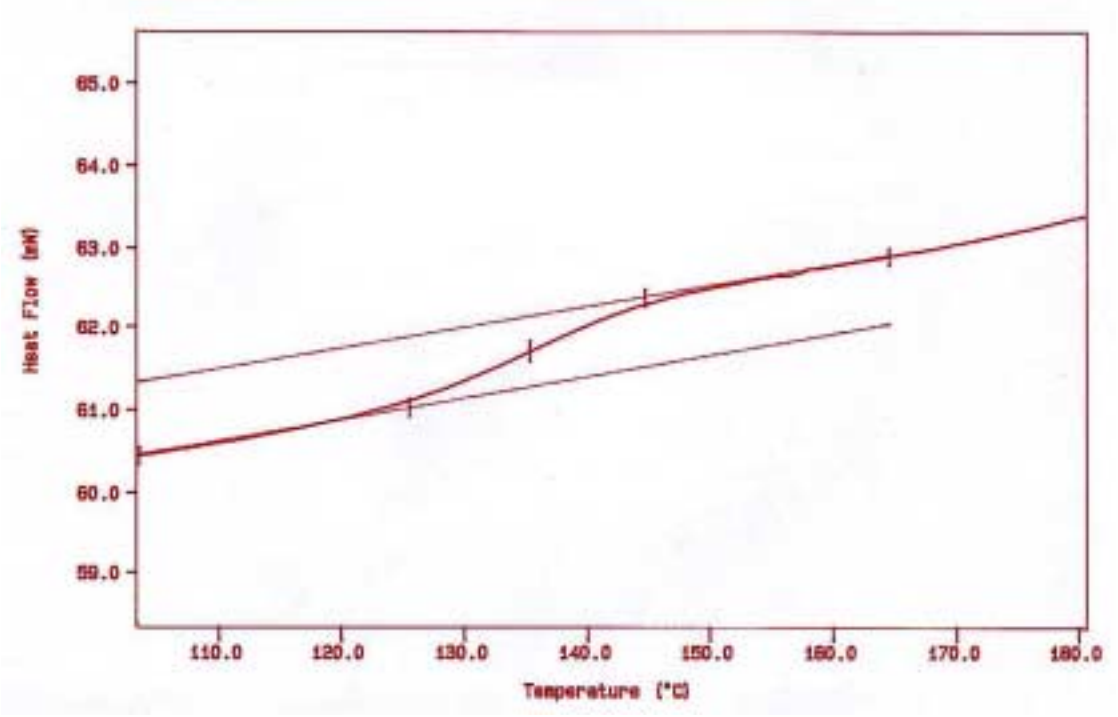



Figure 82. DSC thermogram of MA-EA (2:1) film

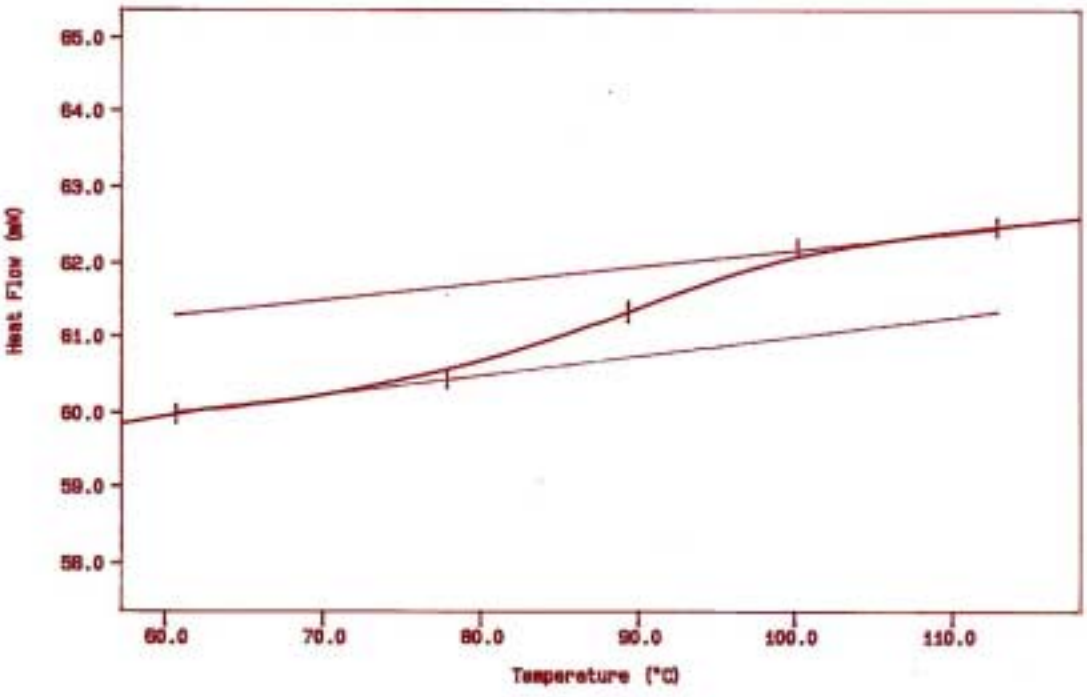



Figure 83. DSC thermogram of MA-HEM-EA (4:1:5) film

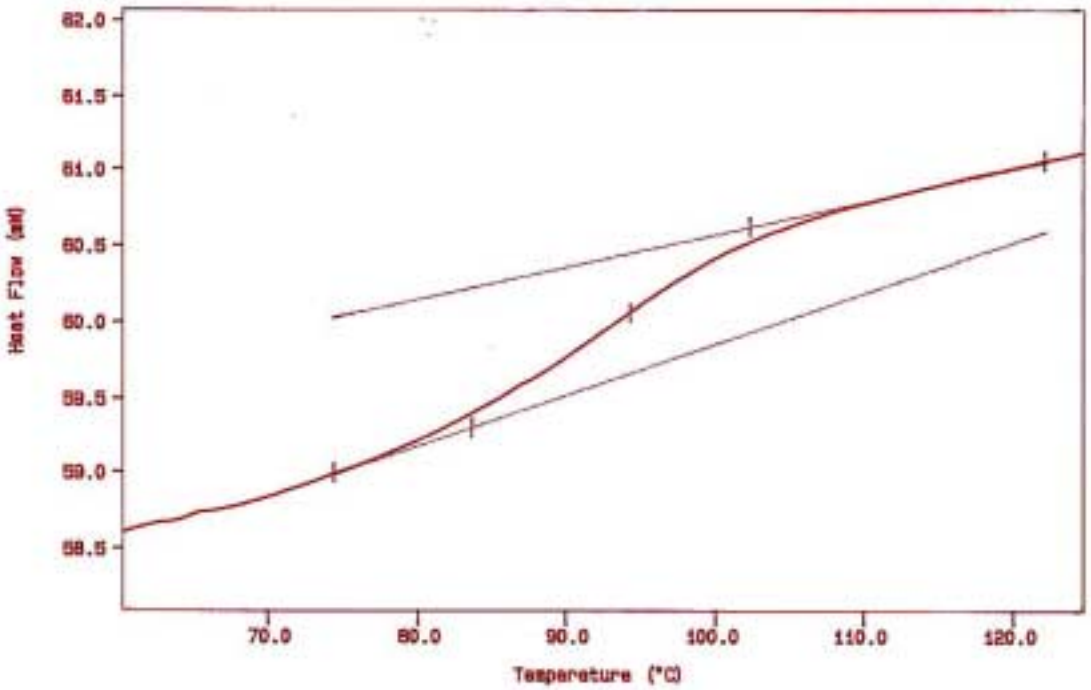



Figure 84. DSC thermogram of MA-HEM-EA (4:2:4) film

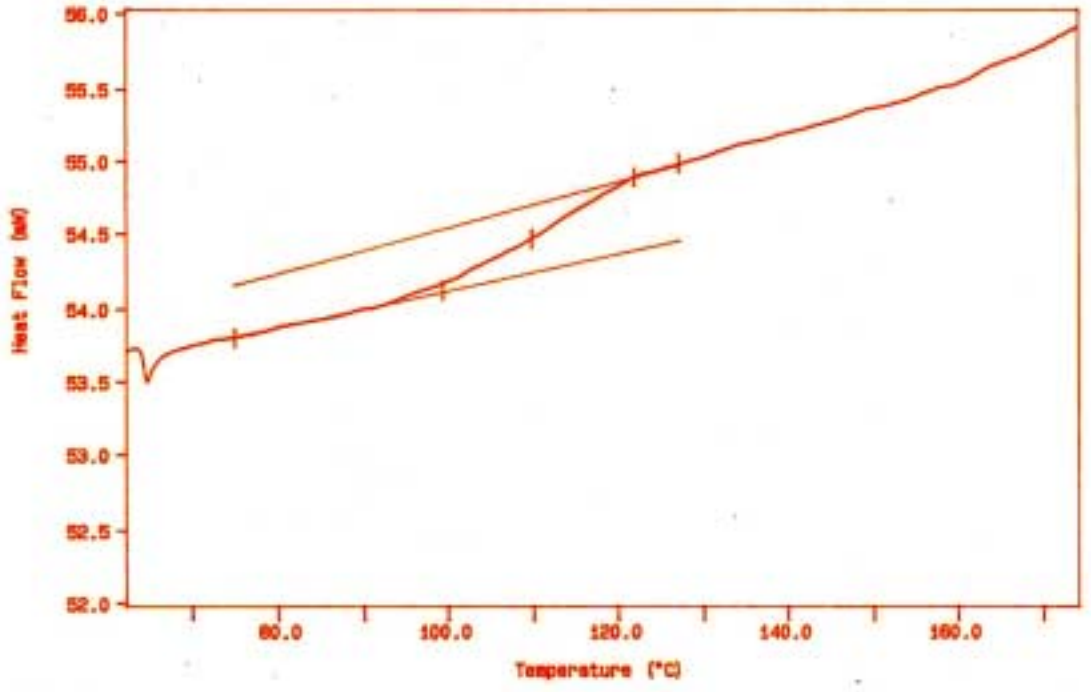



Figure 85. DSC thermogram of MA-HEM-EA (5:1:4) film

# APPENDIX E
# FILM DISSOLUTION RATES

Table 55. Dissolution rates of individual film in pH 5.0 buffer solution

| Polymer | Dissolution rate (μg/cm$^2$.min) | | |
|---|---|---|---|
| | Sample | | |
| | 1 | 2 | 3 |
| MA-EA (1:2) | 3.35 | 4.05 | 5.30 |
| MA-EA (2:3) | 6.85 | 6.45 | 6.65 |
| MA-EA (1:1) | 5.95 | 7.10 | 9.90 |
| MA-EA (3:2) | 28.8 | 28.0 | - |
| MA-EA (2:1) | 40.1 | 29.6 | 36.9 |
| MA-HEM-EA (4:1:5) | 2.40 | 1.45 | 1.85 |
| MA-HEM-EA (4:2:4) | 0 | 0 | 0.50 |
| MA-HEM-EA (5:1:4) | 2.50 | 1.35 | 3.45 |

Table 56. Dissolution rates of individual film in pH 5.5 buffer solution

| Polymer | Dissolution rate ($\mu g/cm^2.min$) | | |
|---|---|---|---|
| | Sample | | |
| | 1 | 2 | 3 |
| MA-EA (1:2) | 8.25 | 5.20 | 7.40 |
| MA-EA (2:3) | 3.75 | 4.45 | 5.10 |
| MA-EA (1:1) | 83.8 | 93.9 | 56.3 |
| MA-EA (3:2) | 58.9 | 84.1 | 89.3 |
| MA-EA (2:1) | 78.4 | 79.9 | 81.0 |
| MA-HEM-EA (4:1:5) | 5.10 | 5.21 | 4.69 |
| MA-HEM-EA (4:2:4) | 8.44 | 8.33 | 8.44 |
| MA-HEM-EA (5:1:4) | 23.5 | 20.2 | 25.7 |

Table 57. Dissolution rates of individual film in pH 6.0 buffer solution

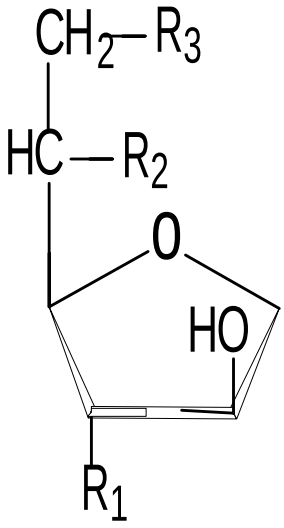
| Polymer | Dissolution rate ($\mu g/cm^2.min$) | | |
|---|---|---|---|
| | Sample | | |
| | 1 | 2 | 3 |
| MA-EA (1:2) | 7.0 | 8.10 | 6.25 |
| MA-EA (2:3) | 26.2 | 23.9 | 25.9 |
| MA-EA (1:1) | 91.1 | 95.4 | 104.6 |
| MA-EA (3:2) | 62.1 | 63.1 | 72.0 |
| MA-EA (2:1) | 83.8 | 94.8 | - |
| MA-HEM-EA (4:1:5) | 34.9 | 33.7 | 40.3 |
| MA-HEM-EA (4:2:4) | 21.0 | 20.1 | 21.3 |
| MA-HEM-EA (5:1:4) | 28.8 | 37.1 | 28.7 |

Table 58. Dissolution rates of individual film in pH 6.8 buffer solution

| Polymer | Dissolution rate ($\mu g/cm^2.min$) | | |
|---|---|---|---|
| | Sample | | |
| | 1 | 2 | 3 |
| MA-EA (1:2) | 499.1 | 60.0 | 46.2 |
| MA-EA (2:3) | 177.3 | 119.4 | 146.0 |
| MA-EA (1:1) | 143.5 | 142.9 | 141.7 |
| MA-EA (3:2) | 184.8 | 183.0 | 179.3 |
| MA-EA (2:1) | 160.5 | 157.4 | 153.6 |
| MA-HEM-EA (4:1:5) | 30.1 | 29.2 | 26.8 |
| MA-HEM-EA (4:2:4) | 18.8 | 16.9 | 19.4 |
| MA-HEM-EA (5:1:4) | 23.5 | 24.9 | 23.4 |

# APPENDIX F

# STRUCTURAL FORMULAS OF SORBITAN ESTERS




$R_1 = R_2 = OH$, $R_3 = R$ for sorbitan monoesters

$R_1 = OH$, $R_2 = R_3 = R$ for sorbitan diesters

$R_1 = R_2 = R_3 = R$ for sorbitan triesters,

Where R = $(C_{17}H_{35})COO$ for stearate,

$(C_{11}H_{23})COO$ for laurate,

$(C_{17}H_{33})COO$ for oleate,

$(C_{15}H_{31})COO$ for palmitate.

# APPENDIX G: STRUCTURAL FORMULAS OF EUDRAGITS

Amino alkyl methacrylate copolymer

**EUDRAGIT** **E 100 / E PO**

(R) = $-CO-OCH_2CH_2N(CH_3)_2$ (0.5 mol)

soluble in gastric fluid

Methacrylic acid copolymers

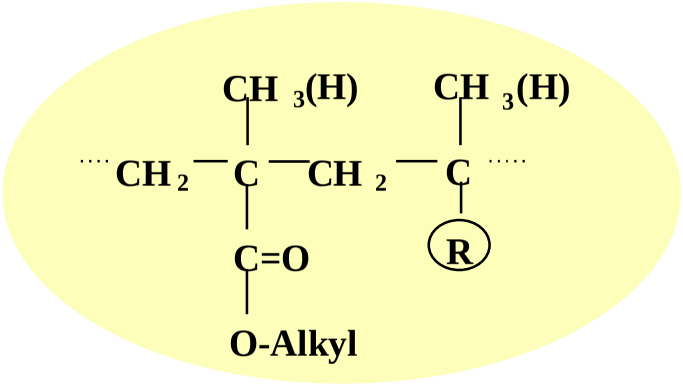
**EUDRAGIT** **S 100**

**L 100/L 100-55**

**EUDRAGIT** **L 30 D-55**

(R) = -COOH (0.3 - 0.5 mol)

resistance to gastric fluid
soluble in intestinal fluid




Amonio alkyl methacrylate copolymers

**EUDRAGIT** **RS 100 / RL 100**

**EUDRAGIT** **RS 30 D / RL 30 D**

(R) = $-CO-OCH_2CH_2N(CH_3)_3Cl$ (0.05-0.1 mol)

insoluble, permeable
independent from pH

Methacrylic ester copolymers

**EUDRAGIT** **NE 30 D**

(R) = $-CO-OCH_3$

insoluble, permeable
independent from pH

# BIOGRAPHY

| | |
|---|---|
| **NAME** | Mr.Sathaporn Nimkulrat |
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| **PLACE OF BIRTH** | Bangkok, Thailand |
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| **POSITION & OFFICE** | 1997 - present,<br>Faculty of Pharmacy,<br>Srinakharinwirot University,<br>Nakhonnayok, Thailand<br>Position: Lecturer |