VISCOSITY OF THE CONTINUOUS PHASE AND OTHER FACTORS IN THE OPTIMIZATION OF MATRIX MICROSPHERE FORMULATIONS PREPARED BY EMULSION-SOLVENT EVAPORATION

by

MERVIN LEE WILLIAMS, JR.

(Under the Direction of JAMES C. PRICE)

ABSTRACT

The objective of this study was to examine the effect of the continuous phase viscosity and other formulation factors on microsphere properties. Matrix microspheres were prepared using emulsion-solvent evaporation; anhydrous theophylline was incorporated as the model drug. The theoretical drug loading range was 33.3 % for most of the formulations. Eudragit® polymers (Eudragit® RL 100, Eudragit® RS 100), and ethylcellulose polymers (ETHOCEL® 100, ETHOCEL® 20) were used to prepare different concentrations of polymer in acetone. It was discovered that at Eudragit® polymer concentrations of 27 % in acetone, with light mineral oil as the external phase, produced larger particle sizes and wider range of particle sizes. Furthermore, the microspheres that were formulated did not have immediate release, especially at the larger particle sizes (the release was slower). This was in contrast to Eudragit® polymer concentrations of 27 % in acetone, that used heavy mineral oil as the external phase, where smaller particle sizes and immediate release was common. However, it was demonstrated that larger particle sizes could be attained in heavy mineral oil by increasing the polymer concentration and the polymer phase viscosity through the incorporation of two polymers

(Eudragit® RL 100/ ETHOCEL® 100) in acetone and mixing them at a substantially higher rpm. Furthermore, there was a considerable difference in microsphere size and the range of particle sizes between ETHOCEL® polymer concentrations using heavy mineral oil, and ETHOCEL® polymer concentrations using light mineral oil. Light mineral oil preparations had a tendency to favor larger particle sizes and a wider range of microsphere sizes. Calculated geometric mean diameters in light and heavy mineral oil indicated that average microsphere size was at least three times higher in light mineral oil preparations. In addition, the drug release rates from microspheres prepared with a higher molecular weight polymer of ETHOCEL® 100 were uncharacteristically faster than release from microspheres prepared from lower molecular weight ETHOCEL® 20. This was attributed to the presence of aggregates of small particles, hollow shell-like particles, and smaller particles that were attached to the larger particle sizes.

INDEX WORDS: controlled-release, microencapsulation, matrix microspheres, polymer solution phase viscosity, Eudragit® polymers, ETHOCEL® polymers, molecular weight, light mineral oil, heavy mineral oil, emulsion-solvent evaporation, particle size distribution

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DEDICATION

Dedicated to GOD, my mother, late father, and my entire family. I would especially like to dedicate this dissertation to the most important women in my life: Mrs. Daisy Stroud and Mrs. Melva Williams.

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TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

In comparison with other routes, oral administration has been determined to be the most acceptable to the patient, the least likely to cause harm, as well as being a natural and basic means of drug delivery (1)(2). The development of oral controlled-release formulations has been widespread due to the many advantages that they have over conventional dosage forms for many drugs. Some of these advantages are better patient compliance, reduction of side effects, a decrease in frequency of administration, and the optimization of drug concentration in plasma (3). For most drugs, an oral controlled-release dosage form should be capable of steady and adequate drug release over an extended period of time in order to maintain a stable plasma level (3). However, physiological factors within the gastrointestinal tract that can affect drug absorption, such as gastric emptying rate, intestinal motility, and gastrointestinal pH, as well as the physical-chemical properties of the drug, all contribute to the difficulty involved in formulating an ideal controlled-release dosage form (4)(5). Molecular size, aqueous solubility, and drug concentration are some of the physical-chemical characteristics that must be accounted for in order to formulate a drug delivery system that exhibits controlled-release behavior (5).

The gastrointestinal (GI) tract is a complicated system consisting of smooth muscle, connective tissue, and an inner epithelial layer. This complex tube has three important roles: food digestion, extraction of nutrients, and elimination of wastes. In terms of oral drug administration, one of the most essential processes within the GI tract system is absorption,

which is the uptake of ions and organic material from the intestinal lumen into the systemic circulation (6). The overall scheme of gastrointestinal absorption involves three general aspects: supply, removal, and uptake of drug (6). As the dosage form is given, a supply builds up and forms a drug solution next to the absorptive sites; a portion of this drug solution may be removed by chemical decomposition (hydrolysis), physical removal by gastric transit, and/or biochemical conversion, prior to any absorption ever occurring (6). The fraction of drug that is not removed is then absorbed into the epithelia of the intestinal wall structure (6). Since most of the absorption occurs in the upper region (duodenum & jejunum) of the small intestine (greatest amount of surface area), it would be beneficial to use a dosage form that will take full advantage of these absorptive sites without causing toxicity or any adverse effects (7). A controlled-release microparticulate formulation would be especially suitable for these circumstances. Microencapsulation has been acknowledged as an effective way to attain a controlled-release effect (8).

As stated earlier, the main objective of an oral controlled-release formulation is to deliver drug over a prolonged period of time that will enhance efficacy as well as reduce the amount of side effects (9). Although it has been proven that controlled release can be obtained through formulations such as matrix tablets, there are very good reasons for the development of microparticulate schemes such as polymeric microcapsules (10). One major incentive of polymeric microcapsules is that they allow for improved dispersion of the drug source in the gastrointestinal tract, thus decreasing localized high concentrations of drug (less irritation) (10).

There are two primary types of polymeric microcapsules: reservoir and matrix. Reservoir microspheres can be described as a drug core enclosed by a polymeric shell that restricts the rate of diffusion into the contiguous media; matrix microspheres contain drug that is

more or less evenly dispersed within a polymer environment (10). Both types of polymeric microcapsules have their advantages and disadvantages. The advantage of reservoir microcapsules is the probability of zero-order release for uniform microcapsule populations (10). The disadvantage is that they are fragile; this shortcoming is an important point, because one of the requisites for zero-order release is that the shell remains unbroken with no alterations as the drug is released into the surrounding medium (10). Matrix microcapsules, on the other hand, are rugged and durable; however, except for some particular situations, their release cannot be described as zero-order (10). Release from most spherical matrix microspheres is more accurately described by the Higuchi equation, for spherical matrices represented by the simplified form below (10):

$$1 + 2F - 3F^{2/3} = Kt \ldots\ldots \quad (1)$$

Where, F represents the fraction of drug remaining in relation to time, t. A graphical representation of drug release is typically done by plotting $1 + 2F - 3F^{2/3}$ (y-axis) versus t (x-axis).

There are numerous ways to prepare matrix microspheres. One particular procedure is the emulsion solvent evaporation method. The emulsion-solvent evaporation method allows for the formation of matrix microspheres through diffusion of polymer solvent from polymer solution globules into the external phase and eventual evaporation of solvent to leave polymer matrix spheres (9). In the early stages, an initial gel matrix is created consisting of suspended drug particles and the solvent/polymer phase; after complete evaporation of the solvent, firm matrix microcapsules are formed (10). Some advantages of using the emulsion solvent evaporation method over other microencapsulation processes are the following: 1) no change in pH is necessary, 2) the method can be performed at low or moderate temperatures, 3) the process

does not require catalysts or reactive agents to be present, and 4) it is highly versatile and can accommodate many different drugs through choice of solvents and external phase (11). Various types of drugs can be encapsulated within the matrix structure (12). Drugs such as succinylsulfathiazole (antimicrobial), indomethacin (anti-inflammatory for arthritis), and theophylline (bronchodilator for asthma), have all been utilized in matrix microsphere formulations. Specifically, previous studies using indomethacin and theophylline have shown that a controlled-release effect can be exhibited through matrix microsphere formulations of these active ingredients (3)(13).

The polymer phase of matrix microspheres is an essential factor in attaining a controlled release effect, as they usually function as a rate-controlling matrix (14). Drugs such as ibuprofen (anionic) and prazosin hydrochloride (cationic) have benefited from latex polymer coatings that aid in controlled delivery of the dosage form (15)(16). Other polymers such as Eudragits®, cellulose acetate butyrates, methylcellulose, and ethylcellulose have been frequently used in multiparticulate controlled-release formulations (3)(13)(17). Cellulose acetate butyrates, methylcellulose, and ethylcellulose are all pH independent polymers that typically remain chemically intact as they travel through the gut (18). In addition, cellulose acetate butyrates and ethylcellulose also remain physically intact throughout the human gut. Eudragits® on the other hand, are available as both pH dependent and pH independent polymers (Eudragit® RL 100 and Eudragit® RS 100 are examples). The pH dependent polymers are resistant to the low pH environment of the stomach, but dissolve at a higher pH (about 6), whereas the pH independent Eudragit® polymers will pass through both the stomach and intestines without dissolving (18). Biodegradable polymers have also been demonstrated in extensive research studies to aid in achieving a controlled-release effect, as well as a safe and biocompatible means for drug delivery

within the human gastrointestinal tract; poly(lactic acid), copoly(dl-lactic/glycolic)acid (PLGA), and other related polyesters are examples of polymers commonly used in biodegradable controlled-release microspheres (19)(20).

In addition to choosing ingredients that are suitable for a matrix microsphere formulation, there are several other issues of importance that must be considered, especially for the purpose of attaining an optimal controlled-release effect. Due to the numerous intricacies that are possible throughout the microencapsulation process, analysis and characterization of physical aspects that are significant to the release properties is very important during the development of a method for drug delivery (10). Physical factors that are typically characterized include surface area, porosity, density, true volume, microsphere size, particle size distribution, drug particle size, drug content, and how fast or slow the release of drug is into the surrounding media (dissolution) (10).

A particular challenge in the area of pharmaceutical research is achieving maximum therapy from an oral drug delivery system without compromising the safety of the patient. Since oral delivery is considered to be the most favorable and suitable route of drug administration (1), the development of optimal controlled-release dosage forms would be quite beneficial to the pharmaceutical industry. Optimization has often been approached by empirical changes in formulation and processing in order to achieve the desired result. However, it has been demonstrated that adjusting the viscosity of the polymer phase of CAB381-2 and CAB381-20 can predictably change the release rates of theophylline matrix microspheres, hence contributing to the optimization of a controlled-release formulation (21). On the other hand, the effect of the polymer solution phase viscosity of Eudragit® RL 100 and Eudragit® RS 100 on release rates of theophylline matrix microspheres prepared by the emulsion solvent evaporation method, has not

been adequately reported; the same can be said for ethylcellulose polymers ETHOCEL® 100 and ETHOCEL® 20. In addition to polymer solution phase viscosity, other factors of the microencapsulation process must be taken into consideration for the optimization of a matrix microsphere formulation. It is proposed that continuous (external) phase viscosity is also an important factor in the emulsion-solvent evaporation process for matrix microspheres. Furthermore, it is probable that the properties of the microspheres resulting from a particular emulsion-solvent evaporation process will depend to some extent on all of the following factors: continuous (external) phase viscosity, polymer phase viscosity, polymer type and molecular weight, surfactants used, as well as physical and mechanical aspects (agitation rate, temperature, and ventilation). Therefore, the goals of this study were the following:

1. To examine the effect of using a high viscosity external phase (heavy mineral oil) in comparison to a low viscosity external phase (light mineral oil) on matrix microsphere characteristics utilizing the emulsion solvent evaporation method.
2. To investigate the effect of the polymer solution phase apparent viscosity of Eudragit® RL 100 and Eudragit® RS 100, as well as ETHOCEL® 20 and ETHOCEL®100 (viscosity grade) on the drug release properties of theophylline matrix microspheres.
3. To evaluate the interaction between polymer molecular weight with the apparent viscosity of the polymer phase and drug release rates of matrix microspheres (since it affects both aspects).
4. To prepare matrix microspheres containing theophylline using a (1:1) mixture of two polymers (Eudragit® RL 100 and ETHOCEL® 100) in order to see how they interrelate and how they affect drug release rates as well as other microsphere properties.

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CHAPTER 2

LITERATURE REVIEW

As is the case with many oral dosage forms, the primary goal is to reach a constant plasma level that is therapeutically beneficial over a prolonged period of time without exhibiting any toxic effects (1,2). Moreover, an oral controlled-release drug delivery system that establishes a consistent blood or tissue level from drug release can essentially be a major step towards achieving a therapeutic benefit to the body (3). However, the physicochemical and biological properties of the drug, as well as factors within the gastrointestinal tract that influence drug release and absorption (gastric emptying, gastric pH, etc.), are limitations that contribute to the difficulty in formulating such an ideal controlled-release dosage form (1)(3). Despite these restrictions, oral delivery is still the most favorable and frequently used route of administration because it is the safest, most convenient, and natural means of drug delivery in comparison to other routes (parenteral, rectal, epicutaneous, etc.)(3-5). Therefore, the convenience and safety implications of oral administration alone are enough to justify the need for extensive research and development of oral controlled-release drug delivery systems.

The expression "controlled-release" can be used to depict any drug formulation that does not exhibit an immediate release pattern (6). Specifically, in addition to oral delivery, controlled-release has been shown in parenteral, topical, and ocular routes of drug administration (3)(7-9). Vyas et al. were successful in demonstrating controlled ocular delivery through the preparation of pseudolatex-based formulations containing pilocarpine (7). Historically, the first

method of controlled-release of dosage forms was established through coated pills over 1000 years ago (10). However, the origin of controlled delivery may have occurred inadvertently through the topical application of fatty materials containing medicinal substances (9). Nevertheless, coated pills have been documented as the first known example of controlled-release (10). Despite the discovery that a controlled-release effect could be exhibited through coated pills, the coating technology did not make any major progress until the mid- 1800's when gelatin and sugar coatings were developed, as well as the idea of using various combinations of fats and waxes to coat beads consisting of drug particles (10). Furthermore, after years of study and research, the first successful method of oral controlled drug delivery was developed and marketed by Smith Kline & French Laboratories in the 1950's; the formulation was called the "Spansule" (10). The "Spansule" consisted of 50 to 100 or more small beads within a capsule that were formulated to release drug at different times (10).

Although the majority of oral drugs are targeted to act in regions of the body other than the gastrointestinal (GI) tract, as is the case with mitomycin C, there are a number of drugs that are set-up to provide a specific site of action in a localized area of either the stomach or small intestine (1) (10-14). The rationale for utilizing site-specific release in the gastrointestinal tract is that it's the most favored region for drug absorption as far as patient compliance, cost, and convenience of administration are concerned (10). Typically, site-specific release in the upper portion of the GI tract is approached through gastric retentive delivery systems such as swelling hydrogels, high-density particles, floating systems, and polymeric bioadhesive systems (1)(5)(15). Yet, there are other ways of achieving site-specific release in the GI tract, including controlling the lag time by varying the polymer coating thickness, as well as implementing an enteric drug delivery system (14). Enteric dosage forms allow for the drug to pass through the

stomach without significant drug loss and into the small intestine where most of the absorption sites are located. The mechanism for resisting dissolution in the stomach region is through a pH sensitive (acid resistant) coating that minimizes release of the drug in the stomach, therefore decreasing local irritation and drug degradation before reaching the intended site of action (10). The functionality of the enteric coating depends on gastric and intestinal pH, gastric emptying, and enzyme activity of the GI tract (10).

While it is possible to attain site-specific release with single unit dosage forms, as demonstrated by Deshpande et al. using a swelling matrix tablet, multiple unit formulations are more advantageous (12)(16-18). Besides site-specific delivery, multiple unit dosage forms provide a more predictable gastric transit time, are less susceptible to dose dumping, minimize plasma peak fluctuations, and lessen the potential side effects without significantly diminishing the amount of drug that is available for absorption (12) (17-18). In addition, multiparticulate formulations reduce high local drug concentrations through their ability to distribute uniformly throughout the GI tract (19). Because of the many advantages offered by multiple unit delivery systems, they are gaining more importance as a safe and dependable means of controlling drug release.

In the optimization of multiparticulate controlled-release formulations, aspects such as polymer molecular weight, stirring speed, drug loading, and polymer solution phase viscosity have been investigated (20-21). Specifically, the drug release pattern of this type of dosage form can be modified by utilizing different polymer molecular weights, altering the microsphere particle size through changes in stirring speed, and/or adjusting the viscosity of the polymer phase (20-21). Previous controlled-release studies have shown that both molecular weight and polymer phase viscosity have a significant effect on dissolution rates of monolithic microspheres

(21). Therefore, considerable attention should be focused on these formulation factors in an effort to optimize the release rates of a multiparticulate controlled delivery system.

OVERVIEW OF CONTROLLED RELEASE DOSAGE FORMS

POTENTIAL ADVANTAGES AND DISADVANTAGES OF CONTROLLED DRUG DELIVERY

The primary goal of controlled-release formulations is to improve the management of disease states (3). A properly designed controlled delivery system should be capable of extending the duration of drug activity over a prolonged period of time without compromising safety. The following is a list of advantages and disadvantages of this type of dosage form (3)(10):

Advantages:

1. Reduced frequency in dosing, resulting in better patient compliance, and minimal side effects
2. Decreased fluctuation of plasma concentrations, leading to improved efficacy and less toxicity
3. Minimal drug accumulation in chronic therapy
4. Costs to the patient in terms of money and time
5. Taste and odor maskers

Disadvantages:

1. Enhanced first-pass effect
2. Longer time to achieve therapeutic blood concentrations

3. Potential for increased variation in bioavailability after oral administration

The limitations of this process are indeed significant and should not be ignored when considering the development of a controlled-release dosage form. However, the potential benefits of better patient compliance, minimal toxicity, and enhanced efficacy justify the need for controlled-release formulations in spite of their of shortcomings.

CANDIDATES FOR CONTROLLED RELEASE

The decision whether or not an active ingredient is appropriate for a controlled-release dosage form is the first step in the formulation of this type of oral dosage regimen. Drugs that are potentially harmful if given in large doses can be made safe through controlled-release formulations. In general, a candidate for controlled-release has the following attributes (1)(6)(10)(18)(22):

1. Narrow therapeutic index
2. Short elimination half-life
3. No significant first pass-effect
4. Can cause severe side effects if plasma concentrations are too high
5. Requires frequent dosing
6. Taken on a chronic or long term basis (cardiovascular, arthritic, respiratory, and analgesic therapeutic agents)

The consideration of these characteristics is pivotal to the proper development of an oral dosage form for controlled-release.

PHYSICOCHEMICAL AND BIOLOGICAL FACTORS INFLUENCING DESIGN OF CONTROLLED-RELEASE FORMULATIONS

Before preparing a controlled-release delivery system, the biological, physicochemical, and pharmacological properties of the drug must be investigated and understood. The following criteria is typically examined (3)(23-24):

Physicochemical characteristics of the drug:

Aqueous Solubility - The aqueous solubility of the active ingredient is a very important consideration in regards to its biological activity as well as in its incorporation within controlled-release dosage forms. One main reason that aqueous solubility should be taken into account is the effects that it has on the absorption process. There are two ways that aqueous solubility implements its control on absorption: 1) by affecting drug dissolution rates and thereby establishing drug concentration in solution, and 2) by its influence on the drug's ability to enter tissues, which is partially attributed to its tissue solubility (3). Furthermore, a drug's aqueous solubility can be used as a preliminary estimate to its dissolution rate because drug solubility is directly proportional to its initial time of release (3).

Previous work suggests that drugs with an aqueous solubility less than 0.1 mg/ml should be categorized as relatively insoluble compounds. Drugs that are considered to be relatively insoluble are usually not good candidates for controlled-release dosage forms. The reason being is that compounds of this nature would probably show dissolution-limited availability as well as be innately prolonged (3). However, the solubility of some relatively insoluble drug compounds has been enhanced by complex formation. For example, ibuprofen, an anti-inflammatory drug agent that is relatively insoluble in water, was complexed with B-cyclodextrin by Chow and

Karara (25) to improve solubility. The interaction of these two compounds resulted in a 10-fold improvement in drug solubility as indicated by an increase in rate of release (25).

Active ingredients that display strong pH-dependent solubility properties, specifically in the physiological pH range of interest, are usually less suitable for controlled-release formulations (26). Tetracycline, a pH-dependent drug that is best absorbed in the intestine region, dissolves to a larger scale in gastric fluid than in intestinal fluid as evident by the aqueous solubility in the highly acidic environment of the stomach being 100 times greater than at an intestinal pH 5-6 (3). Despite being more fit for uptake in the intestine, the quantity of tetracycline that is ultimately absorbed is dictated by the amount of drug release in the stomach (3).

Drug Stability – The amount of drug loss as a result of hydrolysis or metabolism in the gastrointestinal tract is proportional to the residence time in the stomach and intestine, as well as the apparent rate constant for drug degradation (3). Drugs that are in a solid form state will have only a small portion of it available in solution for possible degradation. That being said, it is very evident that in the case of drugs that are unstable in the stomach region, it is advantageous to place the active ingredient in an enteric release form to improve the bioavailability. Therefore, drug compounds of this nature are better fit for controlled-release in intestinal fluid. Obviously, drugs that are unstable in the intestinal region are not suitable for controlled-release in the small intestine considering the fact that the majority of these types of dosage forms release drug over a vast portion of the GI tract (3).

Dose Size – In the preparation of a dosage form for controlled-release, a very practical problem is the volume of drug that must be given in order to achieve the desired effect. Typically, drugs with a single oral dose greater than 0.5 g are not good candidates for a

controlled-release formulation because it usually results in a large volume as a result of the addition of the sustaining dose and probably the sustaining mechanism (3). Furthermore, for drugs that require to be dosed in huge amounts, few consumers would desire to swallow a large amount of capsules or tablets.

Partition Coefficient – During the time period between the administration of the active ingredient and its elimination from the body system, the drug compound encounters an array of physical barriers to attain access to the intended site of action. A primary factor in a drug's ability to pass through these membranes is its partition coefficient (27). Previous work has shown that a nearly linear relationship exists between a drug's partition coefficient and biological membrane permeation over a limited range (28). For the most part, drug compounds with exceedingly high partition coefficients will behave in one of the following ways: 1) either they will readily cross into the biological membranes of the body resulting in a build-up of drug in body tissues with ensuing slow elimination, or 2) they will stay localized in the lipid region of the tissue, after penetrating through the oil and water layers of the body tissues (3). Very lipophilic drugs tend to act in this manner. Nevertheless, in both situations, it is apparent that a release system for drugs with extremely high partition coefficients is not necessary.

pK_a - The pH-partition theory clearly states that the un-ionized form of drug will be preferentially absorbed into numerous tissues of the body. Furthermore, formulation and/or physiological pH can have a major impact on drug absorption due to the fact that the ionized to un-ionized ratio is typically related to pH (3). Hypothetically, ionized drug in a controlled-release situation should be capable of constant release throughout the gastrointestinal tract; however, because absorptive area varies from site to site, absorption rate may vary and potentially counteract a favorable ratio of uncharged to charged drug species (29).

Protein Binding – It is common knowledge that numerous drug compounds bind to plasma proteins with a simultaneous effect on the extent of drug activity (30). If there is a high level of drug-protein binding, then this interaction can function as a storage area for drug resulting in an extended release effect. This is made possible because plasma proteins are recirculated and not removed from the body (3).

Molecular Size – A drug's ability to pass through membranes can be affected by its molecular size (3). The influence by molecular size on drug diffusivity is revealed in equation (1) listed below:

$$\log D = -s_v \log V + k_v = -s_M \log M + k_M \ldots\ldots\ldots \quad (1)$$

Where,

D = Diffusivity

M = Molecular weight

V = Molecular volume

s_v, s_M, k_v, and k_M are constants.

The molecular size of a drug compound is an essential factor that must be accounted for when utilizing polymeric films to function as a mechanism of controlled-release. In general, this drug characteristic must be considered because of the part it plays in the ability of drug to diffuse through biological membranes.

Biological properties of the drug:

Therapeutic Index – The most commonly used method of describing the safety margin of a drug is the therapeutic index, as depicted below in equation (2):

Therapeutic index = minimum toxic dose/minimum effective dose ……. (2)

Typically, the larger the therapeutic index, the safer the drug compound; specifically, drugs with a ratio greater than 10 are regarded as reasonably safe for release into the body system (3). However, since the therapeutic index does not give a clear indication of the dose sizes that produce therapeutic and toxic effects, or the plasma drug concentrations that are relative to therapeutic and toxic levels, it can only be used as an approximation with regards to safety issues concerning the drug.

In the preparation of a controlled-release formulation for a drug with a narrow therapeutic index, it is very important that the pattern of drug release is exact so that plasma concentrations fall between the minimum effective concentration and the minimum toxic concentration; yet, this factor alone is still not enough to guarantee that the concentration of drug in the plasma will be within the therapeutically safe and effective range (3). Other aspects such as patient variability and accumulation of drug (after multiple dosing) must be taken into consideration because they can potentially affect the amount of drug in the plasma. The combination of these factors present a rather challenging ordeal when designing a controlled-release system for drugs with narrow therapeutic indices. Nevertheless, the aspect of having a drug with a narrow therapeutic index presents an enticing opportunity to develop a dosage form that precisely controls drug concentration in the blood.

Biological Half-Life – The duration of action of the active ingredient is definitely a parameter that must be considered when choosing a candidate for a controlled-release formulation. In general, a drug's biological half-life is affected by its elimination, metabolism, and distribution (31). Typically, drugs with a short biological half-life require frequent dosing; this is necessary because the repeated dosing reduces the variability in plasma levels that is usually associated with conventional oral delivery systems (32). Since frequent dosing could be

a potential inconvenience to the patient, a controlled-release dosage regimen would be most appropriate for drugs with a short biological half-life. Up until this point, there has been no established numerical value of a biological half-life. Although, Heimlich et al. have suggested a drug with a half-life value of approximately 4 hr that is a decent candidate for a controlled-release formulation (33).

Side Effects – It is assumed that for a number of drugs, the occurrence of adverse effects is directly related to their concentrations in blood (34). Hypothetically, managing the drug concentration in plasma at any given moment can lessen the frequency of side effects; therefore, a controlled-release dosage form would be a viable solution to this matter. For example, Eckstein et al. (35) demonstrated that a controlled-release form of levopoda was capable of reducing side effects caused by the drug. However, another study utilizing a controlled-release form of prednisolone reported no significant difference between a conventional tablet dosage form and the controlled-release product in minimizing the side effects of the drug (36). Nonetheless, it is apparent that success or failure of a controlled-release regimen in the reduction of side of effects is contingent on the type of formulation, in addition to how well it is designed.

Metabolism – In the process of drug metabolism, there are two possible outcomes: 1) an active drug compound can be inactivated, or 2) inactive drug can be changed into an active metabolite (3). Metabolic conversion of a drug can happen in a number of tissues, however, the organ where most metabolism processes occur is the liver. Therefore, the highest incidence of metabolic alteration of drug is after it enters the systemic circulation. If a drug undergoes extensive first pass-effect metabolism as it passes through the liver, then it is not suitable for a controlled-release product; except in situations where it can be proven that an active metabolite

was produced (6). Nevertheless, a drug's metabolic pattern must be thoroughly understood before considering it for a controlled-release formulation.

Absorption – The uniform release, and subsequent unvarying absorption of drug from a controlled-release dosage form are essential requisites for sustaining a steady tissue or plasma level (3). Ideally, the released dose would be completely absorbed, however this is typically the rate-limiting step in controlled-release regimens. It is projected that rapid absorption will immediately follow the release of drug, but of course this is not what always happens. Furthermore, drugs that are given by oral delivery can potentially have disparities in both the amount and rate of drug absorption (3). This variation could be the direct result of significant loss of drug through hydrolytic degradation within the gastrointestinal tract contents, metabolic conversion by intestinal flora, and metabolic processes that it encounters as it travels through the GI barrier (37-39). For the most part, drugs in solution are more susceptible to degradation processes than solid-state dosage forms. Thus, solid dosage regimens are usually protected from degradation and could therefore possibly enhance the amount of drug that is absorbed.

Although it is ideal for a drug to be absorbed in its entirety, it is by no means necessary in some controlled-release situations. For example, an ocular dosage form using pilocarpine as its active ingredient was able to exhibit a controlled-release effect despite having only a small fraction of drug absorbed (40).

Distribution – Drug distribution into tissues is potentially a vital feature in the overall kinetics of drug elimination. The reason is that it minimizes the drug concentration traveling through the body, and also because it can be restrictive in its equilibration with plasma and extracellular solution (3). In general, the distribution of drug is characterized by binding to tissues and proteins in the plasma. The bound fraction of drug is typically inactive and not

capable of passing through membranes. For the most part, at sites of high binding, drug activity is extended.

The apparent volume of distribution is a proportionality constant relating the drug concentration in the blood to the quantity of drug in the body system (41). It is commonly used to depict the extent of distribution and binding inside the body. When designing controlled-release formulations, the apparent volume of distribution must be taken into account because of the influence it has on both the drug concentration and the amount flowing in the blood. Although the effect of the apparent volume of distribution is often unpredictable, this pharmacokinetic parameter still warrants consideration in the development of processes for controlled-release.

METHODS OF ACHIEVING CONTROLLED-RELEASE WITH ORAL DELIVERY SYSTEMS

The process of controlled-release has a consistent theme or objective: achieve maximum therapy with minimum toxicity to the patient. In an effort to meet these criteria, the following dosage forms have been employed to attain a desired controlled-release effect for better efficacy and safety to the individual (10):

1. Prodrugs – Theses compounds result from chemical alteration of a pharmacologically active agent that will release the active ingredient *in vivo* because of enzymatic or hydrolytic cleavage. Prodrugs are useful in improving intestinal absorption as well as minimizing adverse effects through their ability to reversibly modify the physicochemical characteristics of the active drug compound.

2. Embedding in Slowly Eroding Matrix – In this process, the active agents are dissolved in a combination of fats and waxes, like beeswax, carnauba wax, hydrated fats, etc., to produce granules. Drug is released from its matrix region by steady erosion of these particles
3. Altered Density: Drug-Coated Micropellets – Spherical empty shells that have an apparent density that is less than gastric fluid are unevenly coated with a polymeric film (i.e., cellulose acetate phthalate), and then further coated with a mixture of drug and polymer, as well as any polymer material capable of controlling release in dissolution media (i.e., ethylcellulose). These globular shells function as carriers and are buoyant in gastric fluid for a prolonged length of time while gradually releasing the active ingredient into the stomach environment. Some examples of carriers for this type of controlled-release formulation are poprice, polystyrol, and conventional gelatin capsules
4. Hydrophilic Matrix – Delivery system consisting of a mixture of drug and nondigestible hydrophilic gums condensed into tablet form. Once administered, a very fast rate of drug release from the interface of the tablet is typically observed. Over time, a viscous gel layer is formed at the surface of the tablet from hydration and gelation of the hydrophilic gums, resulting in a much slower dissolution of the active ingredient.
5. pH-Independent Formulations – Dosage forms set-up to sustain a constant pH while drug is being released in a variety of pH environments. To attain release that is not pH sensitive, buffers are commonly added to the drug compound. Specifically, buffer solutions in the salt forms of phosphoric acid, citric acid,

amino acids, etc., are usually favored for these type of formulations, because they are physiologically acceptable in the body. Nevertheless, hydrophilic matrices and other systems can be made pH-independent without the use of buffers.

6. Barrier Coating – The principle of barrier coating is applicable in the formulation of beads or granules for controlled-release. In preparations where barrier-coated beads or granules are utilized, some of the particles are not coated in order to exhibit an immediate release effect, while others are coated with some variation in the amount of coating for the purpose of achieving different release profiles.
7. Embedment in Plastic Matrix – Dosage regimen that is prepared by granulating drug with inert plastic material to form a skeleton-type structure. Specifically, the active ingredient is combined with a solution of the same plastic substance within an organic solvent, and the mixture is then granulated. After the organic solvent has completely evaporated, the final product is a solid-solid structure of drug in plastic particles that is eventually compressed into tablets. Advantages of this dosage form are the inert plastic matrix remains intact throughout the GI tract; disadvantages are that slightly soluble or water-insoluble drugs are not capable of dissolution from this type of formulation.
8. Floating Delivery System – Drug delivery system intended for zero-order release in the stomach region. 3M company designed a particular type of this formulation that involves incorporating a bubble-type barrier coating around drug embedded within a matrix tablet, resulting in a floating system for controlled-release. Buoyancy is accomplished through the bubble-type membrane.

9. Hydrodynamically Balanced System – Patented controlled-release system developed by Hoffmann-La Roche for oral drug delivery that combines at least one active ingredient with a hydrocolloid in such a manner that the whole dosage form becomes hydrodynamically stable. Upon contact with the gastric media the system obtains a specific gravity less than one, which is low enough to cause it to float and remain in the stomach for an extended period of time until the entire drug dose is released.
10. Controlled-Release Capsules – Products for controlled-release that are fairly new to the drug market. They are typically pH-independent and are designed to provide reliable zero-order release of drug. Some examples are Theo-24, a dosage form marketed by Searle that uses a chemical timing complex to generate tiny particles coated with theophylline, and Inderal LA, a drug produced by Ayerst that utilizes a polymer coated controlled diffusion method to reach 12 hour release of propranolol at therapeutic levels.
11. Hydrodynamic Cushion System – A procedure implemented by the Elan Corporation that consists of a cushioned material that permits granules loaded with drug to be compressed into a distinctive tablet. This oral dosage form has a very simple mechanism of drug release in that the cushion material falls apart as soon as it comes in contact with the GI tract, and disperses drug particles to exhibit a controlled-release effect.
12. Hoffmann-La Roche's Web Delivery System – Drug technology involving an edible web produced by paper-like polymeric material where the active ingredient is placed in liquid or solid form, followed by lamination. The final product is a

multilayered configuration of 6 to 20 layers. This delivery system is designed to employ several mechanisms of drug release, including diffusion, disintegration, and erosion to attain optimal rates of controlled-release.

13. Pennkinetic Controlled-Release Systems – Liquid system developed by Pennwalt that combines two processes for controlled-release: membrane diffusion control and ion exchange. The basic set-up of this formulation is mixing ionized drug with an appropriate polymer matrix, and subsequently adding polyethylene glycol (PEG) 4000 and ethylcellulose to the drug-polymer complex. PEG 4000 is added to the dosage form to bring plasticity and stability to the structure; ethylcellulose is utilized to produce a water-insoluble coating that is permeable to the active ingredient. The ionic interaction between drug and ions in the gastrointestinal fluid is essential to the effectiveness of this delivery system. Some advantages of this liquid dosage form are extended and specific drug release, and the ability to mask bitter or bad tasting drugs. This tasteless feature is very useful when preparing formulations for young children.
14. Passage-Sponge Formation - An innovative method for controlled-release that involves the preparation of soft gelatin capsules by dissolving or suspending drug agents in a polyethylene glycol solution of polyvinyl acetate or shellac; within the capsule is gelatin material. Upon coming in contact with the GI media, the gelatin goes into solution and forms a sponge-like interior, which eventually becomes a sponge-like skeleton as the fluids move in deeper into the capsule. Finally, the drug is released through the mechanism of diffusion.

15. Bioadhesives – A concept in which drug is bound to a specific area to extend the duration of drug activity and produce a localized effect within the gastrointestinal tract. Although it is a fairly old idea, improvements in polymer technology have provided a renewed interest in bioadhesive dosage forms for controlled delivery. In particular, it has been shown that quite a few polymers can be attached to mucous tissue in a noncovalent manner for a prolonged period of time. Bioadhesive dosage forms are commonly used for administration in the buccal cavity.
16. Polymer Resin Beads – In this process, epoxy resins are used to place active ingredients within plastic material for controlled-release purposes. There are two basic ways of incorporating drugs into the plastic material: 1) suspending the active agent in the liquid plastic monomer, or 2) dissolving the drug in the liquid plastic monomer. After drug inclusion, the mixture is dissolved in a hydrophilic or lipophilic solution to form an emulsion. Once the emulsion is heated to 50-60 °C, polymerization occurs and within a 2 to 4 hour time frame the droplets become solid and beads are formed.
17. Drug Complex Formation – Drug complex formulations for controlled delivery can be prepared with active ingredients that have an amine group, such as alkaloids, antihistamines, and amphetamine. In most cases, the amine is combined with tannic acid in an alcoholic solution to form a drug complex. This multi-faceted structure is then washed, dried, and mixed with other materials. Finally, the drug complex can either be compressed into tablets or granulated and placed inside of capsules.

POLYMERIC MICROPARTICULATE SYSTEMS FOR CONTROLLED-RELEASE

Reservoir system with rate controlling membrane:

This microparticulate system can be described as core reservoirs of drug enclosed by polymeric membranes that control the rate of diffusion of the active agents into the surrounding medium (Figure 2.1) (9). Reservoir microcapsules are advantageous in that they offer low polymer to core ratios and the potential for a zero-order release effect. However, they tend to be less rugged than monolithic microspheres and therefore cannot be compressed into tablet form because pressure could possibly alter zero-order release properties. In order for reservoir microspheres to achieve zero-order release, the following conditions must be met (9):

1. Comparable drug loads and release rates among all the microparticles in the dose
2. Drug core concentrations remain constant
3. The rate limiting step is the transit of drug particles through the membrane
4. The rate controlling membrane remains intact and unaffected throughout the duration of drug release

Furthermore, to sustain zero-order release factors that affect the rate of drug diffusion such as membrane thickness and permeability, as well as the concentration gradient between inner and outer portion of the shell, must be carefully monitored and controlled.

Matrix system:

This multiple-unit system is depicted as drug materials incorporated throughout a rate-controlling polymer matrix in a more or less uniform fashion (Figure 2.2) (9)(42). For the most part, the drug-polymer matrix can be either biodegradable or non-biodegradable. The dissolution profile of this system is dependent on a number of variables, including the membrane thickness, surface area, drug loading, drug particle size, and the characteristics of the polymer. In

comparison to reservoir microcapsules, the drug release from monolithic microspheres is more challenging to model due to the numerous aspects that must be taken into consideration (9). Also, except for unique situations, drug liberation from matrix microspheres does not exhibit zero-order release characteristics. In most cases, the dissolution of the matrix system is described by Higuchi models (9). Nevertheless, this system is advantageous over the reservoir system because it is more rugged; thus, monolithic microcapsules can be compressed into tablets because the release properties are less likely to be affected by pressure.

Miscellaneous Systems:

Besides the aforementioned reservoir and matrix systems, other forms of microparticulate drug delivery have been established. Some examples are osmotic systems, biodegradable systems, buoyant systems, and miniature mechanical pumps. In addition to these methods for controlled-release, reservoir systems without a rate controlling membrane have been designed as well. Porous plastic and hollow fiber schemes are two primary examples of this type of system.

Osmotic devices have only come into existence in recent years. The Alza Corporation developed the first commercially available product that utilizes a tiny osmotic pump to control the release of drug; it was introduced in 1977 (43). In addition, mini-mechanical devices have been employed to disperse the active ingredient over an extended period of time (44).

There have been numerous attempts to effectively improve gastric retention of drug in the stomach (1)(5). One approach that appears to be the most promising is the buoyant system. As demonstrated by S. Stithit et al. (1), floating theophylline microspheres with densities less than 1 g/cm^3 displayed near zero-order release characteristics and remained buoyant for more than 24 hours in both gastric and intestinal fluid. These microspheres can be described as spherical with smooth surfaces and internal cavities formed by entrapped bubbles of carbon dioxide,

surrounded by a drug-polymer type matrix (Figure 2.3) (1). The near zero-order release kinetics of buoyant microspheres is similar to the drug release behavior of reservoir microcapsules with rate controlling membranes.

Yolles and Sartori made the first acknowledgement of the use of an artificial biodegradable polymer system for drug delivery in 1970 (45). Since this disclosure, many processes of biodegradation utilizing polymers have come about. In these systems, drug is distributed within the polymer. Once the polymer is placed inside of the body, it slowly erodes and releases the active ingredient. Thus, the biodegradation of the polymer directly affects the release pattern of the drug.

MICROENCAPSULATION PROCESSES FOR CONTROLLED-RELEASE

Historically, the first instance of microencapsulation was achieved by NCR in the development of carbonless paper (46). For the most part, microencapsulation can be defined as the incorporation of particles within a coating material (3)(6). This method provides a means to control the release of active ingredients into the body system. Furthermore, since the particles from microencapsulation are typically small in nature, they are readily dispersed throughout the GI tract, potentially enhancing the absorption of drug (47). The following is a list of microencapsulation processes that have been designed for the purpose of coating active pharmaceutical agents (48):

1. Coacervation – The process of coacervation in an aqueous solution can be described as a frequently used method that involves the addition of a substance that competes for water molecules within a colloid solution, resulting in the formation of two phases; one phase rich in colloid particles, the other phase poor

in colloid droplets (3). There are two primary types of coacervation: simple and complex. The basic difference is that simple coacervation uses one colloid, while complex coacervation utilizes two. The technique of using complex coacervation for the coating of active agents was first disclosed by Phares and Sperandio (49), and further analyzed and expanded on by both Luzzi and Gerraughty (50, 51) and Madan et al. (52, 53). Methods of coacervation may use aqueous or non-aqueous solvents, depending on the substance to be coated and the polymer used for coating. For the most part, moderate to very water-soluble drugs are used with non-aqueous vehicles, while active agents that are not water-soluble are utilized with aqueous solvents. Polymers that are usually associated with non-aqueous coacervatio processes are ethylcellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, and cellulose acetate phthalate. Gelatin and other water-soluble gums are typically associated with aqueous coacervation processes. In either situation, the polymer functions as the membrane surrounding the drug core material.

2. Emulsion-Solvent Evaporation Method – This process involves dissolving an active ingredient in a polymer solution, then mixing this internal phase with an external phase, e.g. light or heavy mineral oil, to form an emulsion. In general, a surfactant agent of low concentration is incorporated within the external phase to stabilize the mixture. A closer look at how this method works is in the formation of matrix microspheres. During the early stages of emulsification, globules of liquid containing suspended drug particles and/or dissolved drug are formed in the external oil phase simultaneously as solvent is removed from the globules and

eventually out of the emulsion, resulting in an initial gel matrix. As more and more solvent is removed from the globules, the viscosity of the internal polymer solution phase increases. Finally, after the solvent has completely evaporated, the gel structure becomes rigid and firm matrix microspheres are produced. The final product is then centrifuged, washed with volatile hydrocarbons (i.e. heptane, hexane, etc.), filtered, dried, and collected for observation and characterization studies. Quite a few scientists have implemented this method in the preparation of microsphere formulations, including Dubernet et al. (54) and Arnaud et al. (55). In addition, Bodmeir and Chen (56) formulated ethylcellulose microspheres loaded with anti-inflammatory drugs using this technique.

3. Interfacial Polymerization – In this process of microencapsulation, a reaction of two monomers occurs at the interface between two incompatible phases resulting in a polymer layer that surrounds the disperse phase that consists of a solution or distribution of active agents. The aqueous disperse phase contains one reactive monomer, and the non-aqueous continuous phase contains the other (48). In general, interfacial polymerization forms very thin-walled, porous microspheres that are not appropriate for controlled-release dosage forms.
4. Spray Congealing, Spray Embedding, Spray Drying, and Spray Poly Condensation –
    a. The processes of spray drying and congealing have been employed for the microencapsulation of numerous drug agents (48). Spray congealing involves using a non-aqueous coating substance that melts at high temperatures and solidifies when the atomized molecules come in contact

with cool air in a spray dryer; this process is typically used with moisture sensitive drugs. On the other hand, spray drying can be described as a system that distributes the active ingredients in a solution of the coating substance. Subsequently, the solution is atomized and the solvent evaporated away by heated air.

b. Other methods that are based on spray drying are spray poly condensation and spray embedding. Spray poly condensation can be depicted as drug material dispersed in a continuous phase reactive monomer with catalyst mixed in with additional membrane forming agents like polyvinyl alcohol. In the process of spray embedding, a mixture of drug and dissolution limiting polymer in solution within an aqueous or organic solvent is spray dried.

5. Congealable Disperse Phase Encapsulation – This system is an uncomplicated type of microencapsulation that distributes or dissolves fine drug particles under high temperature conditions within a hydrophobic or hydrophilic aqueous carrier that congeals when brought down to normal ambient temperature (57, 58).

Through these methods, microencapsulation has proven to be a good means of extending the release rate of active ingredients, as well as an adequate solution to some of the drugs' undesirable bioavailability and manufacturing issues (59).

CHARACTERIZATION AND RELEASE KINETICS OF MATRIX MICROSPHERES

Characterization of monolithic microspheres:

During the development and evaluation of a matrix microsphere system for controlled delivery, characterization of the particles for size, surface area, density (as a function of porosity), drug loading, and dissolution is a very important and necessary ordeal to undertake. This is mainly due to the numerous factors possible while formulating monolithic microspheres (9). The following is a brief description of each characterization aspect involved in matrix microsphere formulations (9):

1. Particle Size – In many microsphere systems, rate of drug dissolution is inversely proportional to the square of the microcapsule size. Thus, any alteration in the size of the microspheres or size distribution can result in changes in drug release rate. In order to determine particle size distribution, sieves of various dimensions are commonly used. However, since aggregates are not clearly visible, microscopic detection methods must be employed as well on all microsphere samples. Typically, the particle size distribution of matrix microspheres can be described as log-normal.
2. Drug Loading – Under ideal circumstances, the actual amount of drug present in a microsphere is similar to its theoretical drug content. However, there are several factors that can cause variation in drug loading, including drug particle size, microsphere size, preparation temperature and time, drug loss in the external mineral oil phase (depends on how soluble the drug is in mineral oil), as well as an unfavorable suspension when dissolving both the polymer and drug in the internal phase solvent. When performing drug content analysis, the active

ingredient can be dissolved in a suitable solvent to determine the amount of drug present in the microcapsule. This is possible only if the polymer or other aspects of the microsphere do not interact with the chosen solvent. To avoid this problem, a solvent that does not affect the polymer is utilized. Furthermore, in many cases it is convenient to use a solvent that dissolves both the polymer and drug.

3. Dissolution – The release rate of active agents is typically measured in this manner. Dissolution testing is a very good indicator of how fast or slow the dosage form releases drug in comparison to other formulations. It is an *in vitro* process that is performed in low pH (simulated gastric fluid, pH ~ 1.2) and slightly alkaline (simulated intestinal fluid, pH ~ 7.2) media, without enzymes present. In most cases, a small amount of nonionic surfactant is added to the buffer solution to aid in wetting the microspheres so that its entire surface area is completely exposed to the surrounding environment. Samples from the dissolution medium are generally taken at specific time intervals and analyzed by ultraviolet spectrophotometer devices.
4. Surface Area – In general, the smaller the microcapsule, the greater the surface area for a given amount of drug. The main reason being, there is an inverse relationship between microcapsule diameter and the surface area per unit weight of the microsphere. This is typically true for nonporous, round microspheres with smooth surfaces. However, a porous and abnormal microcapsule surface can alter the amount of surface area exposure, potentially affecting the rate of drug release.

5. Density (Porosity) – The porosity of a microcapsule can adversely affect the drug release kinetics. It is defined as the percent or fraction of void space present in microspheres. In situations where a significant area of the void space is sealed off, changes in surface area would only be evident from the measurement and calculation of density. So in order to get an approximation of the porosity, the actual measured density of the microspheres is compared to its calculated density average based on actual drug content (24).

Release kinetics of monolithic microspheres:

Drug release from a microsphere can be described as diffusion of drug from an area of high concentration (core material) to a region of low concentration (dissolution medium). Typically, mathematical models and/or equations are utilized to depict drug release from a delivery system. In the process of developing formulations for controlled-release, it is desirable to design mathematical models that are straightforward, yet complicated to describe release kinetics (10). The following equations are used to portray the drug release behavior from monolithic microspheres (9):

Higuchi model for homogeneous matrix microspheres –

$$1 + 2F - 3F^{2/3} = (6\,DC_s/Ar_o^2)t \ldots\ldots\ldots\ldots \quad (3)$$

Where,

D = diffusion coefficient

C_s = drug solubility in the matrix

A = initial concentration of drug in the matrix

r_o = radius of matrix microsphere

Higuchi model for non-homogeneous (granular) matrix microspheres –

$$1 + 2F - 3F^{2/3} = (6 DC_sV_{sp}/\tau Ar_o^2)t \ldots\ldots\ldots \quad (4)$$

Where,

D = diffusion coefficient

C_s = drug solubility in the matrix

V_{sp} = specific volume of the drug

τ = tortuosity of the porous system

A = initial concentration of drug in the matrix

r_o = radius of matrix microsphere

The exact conditions for these Higuchi models are: 1) a pseudo-steady state occurs soon after the extraction of drug commences, and 2) initial drug concentration in the matrix is considerably greater than the solubility of drug in the matrix ($C_s << A$). Nevertheless, for a given situation the variables within parentheses on the right side of equations (3) and (4) can be incorporated into a single constant as in equation (5) below:

Basic Higuchi model for spherical matrix microspheres –

$$1 + 2F - 3F^{2/3} = Kt \ldots\ldots\ldots\ldots \quad (5)$$

Where, F represents the fraction of drug remaining as a function of time, t.

VISCOSITY AND CONTROLLED-RELEASE MICROSPHERE FORMULATION AND MANUFACTURE

Microsphere properties are significantly influenced by processing and formulation factors like stirring speed, solvent type, drug loading, temperature, morphology, and drug solubility. These variables have been frequently examined and reported in previous studies. Specifically,

several scientists have investigated the effects of polymer molecular weight and viscosity grade. In a study performed by Dortunc and Gunal (60), it was discovered that release of acetazolamide from hydroxypropylmethylcellulose (HPMC) was slower when higher viscosity grades of polymer were used for a swellable tablet dosage form. Chattaraj and Das (61) had a similar finding in that as they increased the viscosity grade of ethylcellulose in hydrophilic matrix tablets, the release rate decreased. In another study by Tefft and Friend (62), controlled-release herbicide microspheres were prepared using an assortment of viscosity grades of ethylcellulose; as expected, the higher viscosity grades led to lower drug release rate. In addition to influencing the release rate of microspheres, the viscosity grade is also known to affect particle size and matrix swelling properties. For example, Sanghvi and Nairn (63) were able to control the particle size of cellulose-acetate trimellitate microspheres by increasing the viscosity ratio (internal phase/external phase) before and after mixing. Besides viscosity grade studies, previous work has been performed that involves examining the effect of other formulation aspects like polymer molecular weight on microsphere characteristics. For example, Shukla and Price (64) investigated the effect of polymer molecular weight and drug loading of cellulose acetate propionate on the release properties of theophylline microspheres, and found that the higher polymer molecular weight had the slower release.

Although there have many studies on the effect of viscosity grade on rate of release, not much attention has been dedicated to how the polymer solution phase viscosity influences release kinetics and other microsphere characteristics. However, there are a few situations where it has been investigated. For example, Obeidat and Price (21) have suggested that release rates of theophylline loaded matrix microspheres could be predictably optimized by adjusting the viscosity of the polymer solution phase. From their results it was evident that both the polymer

solution phase viscosity and the polymer molecular weight have an effect on drug release from monolithic microspheres. In another example, Bittner and Kissel (65) found that by increasing the polymer concentration of poly(lactide-co-glycolide), and thereby increasing the viscosity, they could produce spherical microspheres with smooth surfaces. Furthermore, the effect of the polymer solution phase viscosity was also demonstrated by Jeyanthi et al. (66) using peptide-containing poly(lactide-co-glycolide) microspheres. In this experiment, increase in the viscosity of the polymer solution resulted in an increase in microsphere size. Thus, in summary, the morphology and particle size of the microspheres respectively, were influenced by the changes in polymer phase viscosity. Nevertheless, more study is needed on the aspect of the dependency of microsphere properties on the viscosities of both the polymer solution phase and the continuous phase, especially their effect on release kinetics where not a lot of substantial research has been reported.

Theophylline

Theophylline is a xanthine derivative that is widely used in the treatment of asthma and bronchospasm. It functions as a diuretic, cardiac stimulant, and smooth muscle relaxant of the respiratory tract; small quantities occur naturally in tea (67). Theophylline was first disclosed in 1900 to treat asthma, but its use did not become prevalent until 1936; the FDA approved it in 1940. Since theophylline has a narrow therapeutic index range of 10 – 20 μg/ml, it is typically formulated in a controlled-release dosing regimen to prevent adverse side effects that are associated with high plasma concentrations (1) (68). The morphology of an anhydrous theophylline drug crystal resembles a long strand or rod-like object (Figure 2.4). Typically, a micronized form of anhydrous theophylline is used in monolithic microspheres because it's

easier to encapsulate within the matrix (Figure 2.5). The chemical structure of theophylline is 1,3 – dimethylxanthine (Figure 2.6) (67). It has a pK_a value of 8.79 as well as a low aqueous solubility of 8.3 mg/ml (69). In addition, theophylline solutions are usually relatively stable over the whole pH range of the GI tract.

Eudragit® polymers

Eudragit products are commercial products commonly known as polymethacrylates. They are available in different grades such as Eudragit® RL 100, Eudragit® RS 100, and Eudragit® RL PO, to name a few. Eudragit® RL 100 and Eudragit® RS 100 are pH – independent copolymers synthesized from acrylic acid and methacrylic acid esters (70). Their chemical name is poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) (Figure 2.7). The difference between Eudragit® RL 100 and Eudragit® RS 100 is that Eudragit® RL 100 has a slightly larger amount of trimethylammonioethyl methacrylate chloride present, as well as more hydrophilic groups and a greater percentage of functional quartenary ammonium groups (10 % in comparison to 5 %) (70). They are primarily used to form water insoluble coating agents for controlled-release dosage forms. In general, Eudragit® RL 100 films have a higher permeability than Eudragit® RS 100 films (70). Furthermore, they are both soluble in acetone and their pH-independent nature is a result of the presence of salt forms of their ammonium groups (70).

Ethylcellulose

Ethylcellulose can be described as a cellulose ethyl ether that is extensively used in oral formulations for controlled-release. It is prepared by treating wood pulp or cotton with alkali and ethylation of the alkali cellulose with ethyl chloride (67). Chemically, ethylcellulose is a long-chained polymer of β-anhydroglucose units attached together by acetal linkages (Figure

2.8) (70). It functions as a coating agent, tablet filler, and a viscosity-increasing agent. However, it is mainly used as a water insoluble coating agent to modify the release of the active ingredient (70). Drug release from microspheres coated with ethylcellulose is influenced by microsphere wall thickness and surface area (70). For the most part, high viscosity grades of ethylcellulose tend to produce stronger and more robust coatings. Commercial ethyl cellulose (i.e. ETHOCEL® Standard 20 and ETHOCEL® Standard 100) has an ethoxyl content ranging from 43 % to 50 % (67). Ethylcellulose that consists of more than 46.5 % of ethoxyl content are freely soluble in solvents such as methanol, chloroform, ethyl acetate, toluene, and acetone (67)(70).

Heavy Mineral Oil

Heavy mineral oil is a combination of refined liquid saturated aliphatic (C_{14} to C_{18}) and cyclic hydrocarbons taken from petroleum. It functions as an emollient, lubricant, and solvent. In more recent years, heavy mineral oil has been utilized in the preparation of microspheres (72). Heavy mineral oil is slightly soluble in acetone, and completely miscible with benzene, chloroform, and ether; it is insoluble in glycerin and water.

Light Mineral Oil

Light mineral is a mixture of refined liquid saturated hydrocarbons attained from petroleum. It functions as an emollient, solvent, tablet and capsule lubricant, and therapeutic agent. In pharmaceutical formulations, it is used in a similar manner to heavy mineral oil. For example, it functions as the oily medium in the microencapsulation of numerous drug compounds (72). Light mineral is partly soluble in acetone, and completely miscible with chloroform, ether, and hydrocarbons; it is sparingly soluble in ethanol (95 %), and practically insoluble in water. It is less viscous than heavy mineral oil.

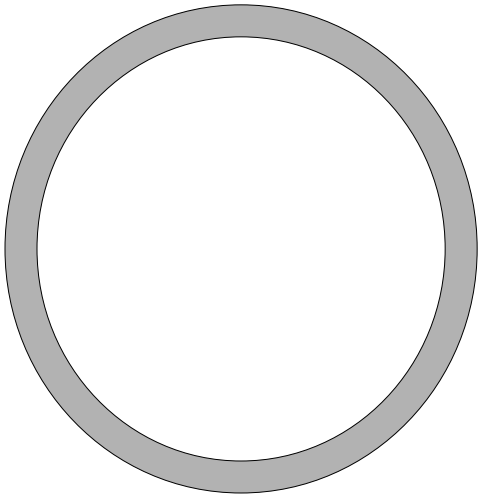


Figure 2.1. Cross-sectional diagram of reservoir microsphere with a spherical core (drug core = white inner region, polymeric membrane = gray outer layer).

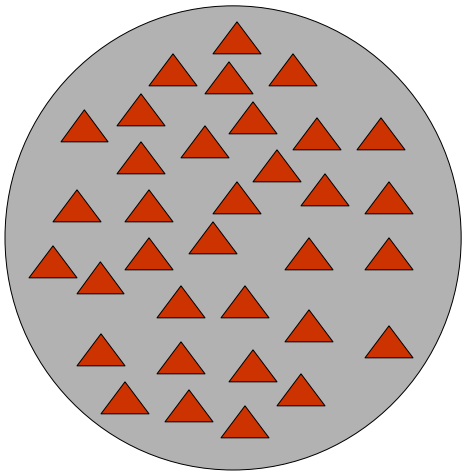


Figure 2.2. Cross-sectional diagram of matrix microsphere (drug core = triangles, polymeric membrane = gray area).

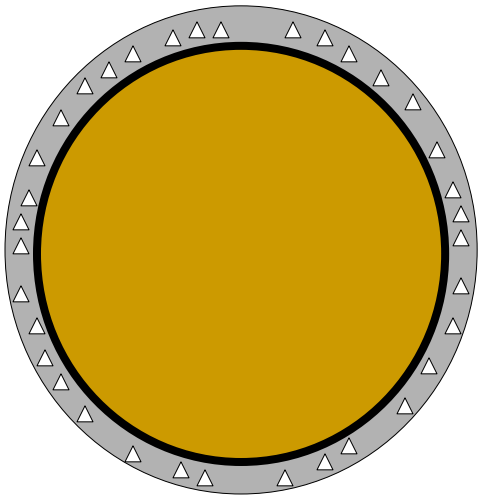


Figure 2.3. Cross-sectional diagram of buoyant microsphere (drug = triangles, polymer = gray outer layer, bubble = region within black circle).

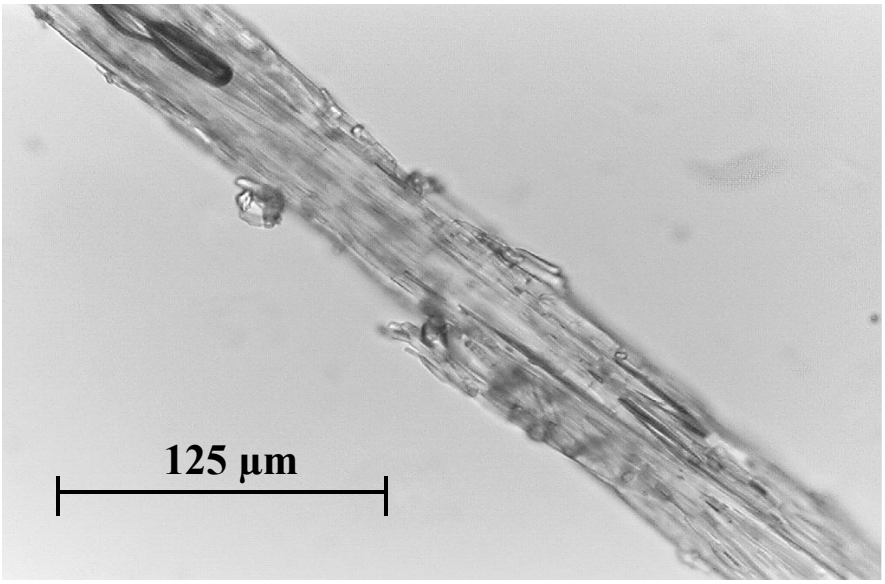


Figure 2.4. Physical appearance of an anhydrous theophylline crystal (microscopic observation at 400X).

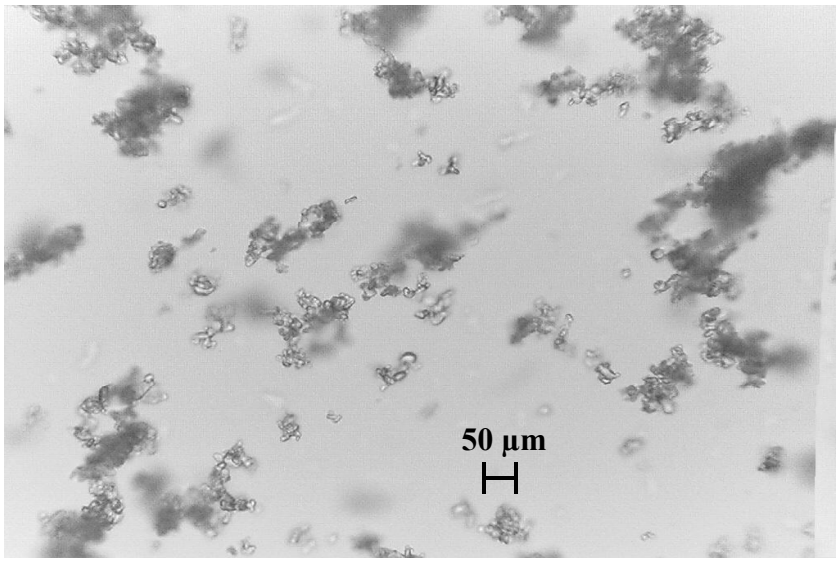


Figure 2.5. Physical appearance of micronized anhydrous theophylline (microscopic observation at 100X).

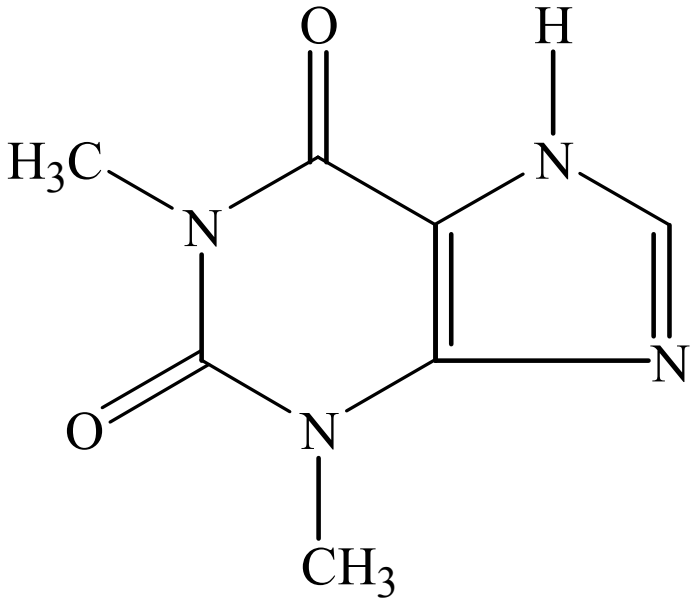
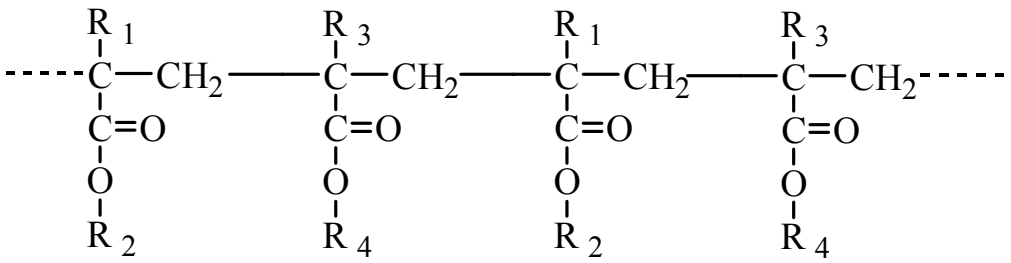


Figure 2.6. Chemical structure of theophylline ($C_7H_8N_4O_2$).



R_1 = H, CH_3

R_2 = CH_3, C_2H_5

R_3 = CH_3

R_4 = $CH_2CH_2N(CH_3)_3^+Cl^-$

Figure 2.7. Chemical structure of Eudragit® RL 100 and Eudragit® RS 100 (Eudragit® RL 100 has a higher percentage of R_4 groups).

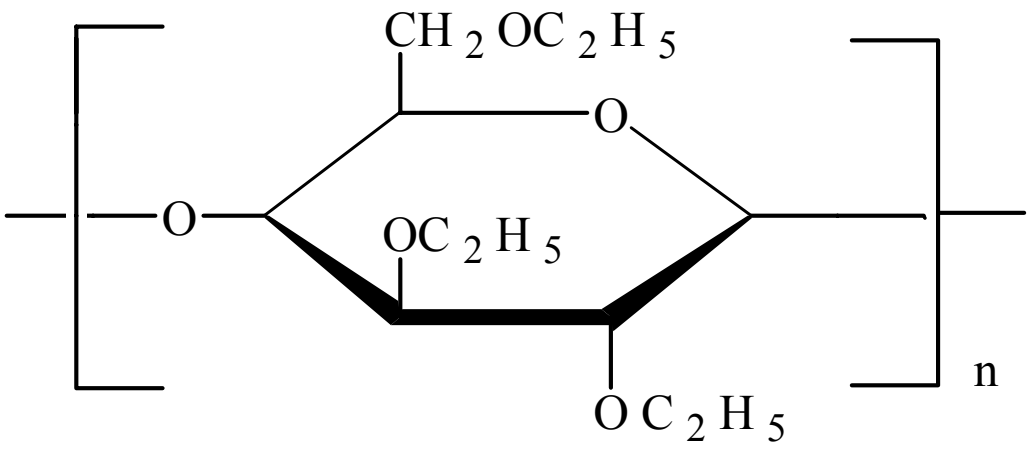


Figure 2.8. Chemical structure of ethylcellulose.

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CHAPTER 3

EFFECT OF CONTINUOUS PHASE VISCOSITY, ETHOCEL® POLYMER PHASE VISCOSITY, AND OTHER FORMULATION FACTORS ON THE PROPERTIES OF THEOPHYLLINE MATRIX MICROSPHERES PREPARED BY EMULSION-SOLVENT EVAPORATION

Introduction

Ethylcellulose, a water insoluble polymer, has been commonly employed in studies examining the effect of formulation parameters such as polymer viscosity grade, morphology, solvent type and polymer molecular weight on microsphere characteristics (1-4). Dashevsky and Zessin (4) investigated the effect of ethylcellulose molecular weight on theophylline microsphere properties and found that different molecular weight ethylcellulose mixtures of EC-100 and EC-7 ensured better hardness and elasticity of the polymer matrix, as well as a more uniform particle size distribution of theophylline microspheres. Nevertheless, not much has been reported on the effect of the continuous phase viscosity or polymer phase viscosity on ethylcellulose microsphere properties. Therefore, the objectives of this study were to 1) examine the effect of using heavy mineral oil (high viscosity) versus light mineral oil (low viscosity) as the external phase on the properties of matrix microspheres prepared by emulsion-solvent evaporation, 2) evaluate the effect of the apparent viscosities of the polymer phase of ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) on matrix microsphere properties, 3) investigate the effect of the interaction between polymer molecular weight and apparent viscosity on matrix microsphere

properties. Theophylline was used as a model drug because it is good candidate for controlled-release due to its low therapeutic index.

Experimental

Materials

Ethylcellulose (ETHOCEL® Standard 20, Dow Chemical Co., lot no. MF09013T01, M.W. 109,500 – 124,400), ethylcellulose (ETHOCEL® Standard 100, Dow Chemical Co., lot no. LI29013T02, M.W. 218,300 – 223,200), theophylline (Knoll AG, lot no. 93237), magnesium stearate, acetone, and methylene chloride (Fisher Scientific Co., Fair Lawn, NJ), mineral spirits (W. M. Barr & Co. Inc., Memphis, TN), heavy mineral oil and light mineral oil (Witco Co., Greenwich, CT), polysorbate 80 (Tween 80) (Ruger Chemical Co. Inc., Irvington, NJ). Monobasic potassium phosphate and sodium hydroxide 50 % w/w solution (J. T. Baker Inc., Phillipsburg, NJ).

Instruments

Stirrer (Lab. Stirrer, LR 400D, Yamato Scientific Co., LTD., Tokyo, Japan), stirrer, (Lab. Stirrer, LR 400C, Fisher Scientific Co., Japan), USP Dissolution Apparatus II (Dissolution test system 5100, Distek, Inc., North Brunswick, NJ), UV spectrophotometer (Spectronic 2000, Bausch & Lomb, Rochester, NY), Accumet pH meter 5 (Fisher Scientific Co., NJ), Standard sieves series, viscometer model DV-II with UL adapter (Brookfield Engineering Laboratories, Inc., Stoughton, MA), LEO 982 Field emission scanning electron microscope (FE-SEM, LEO Electron Microscopy, Inc., Thornwood, NY).

Preparation of microspheres

In this study microspheres containing micronized anhydrous theophylline were prepared by emulsion-solvent evaporation using polymers ETHOCEL® 100 (M.W. 218,300-223,200) at concentrations 5 %, and 7 % (w/w), ETHOCEL® 20 (M.W. 109,500-124,400) at concentrations 7% and 9 % (w/w), as the organic phase in acetone. Each formulation was prepared using both heavy mineral oil and light mineral oil, in separate instances, as the external oil phase. Theophylline powder was incorporated into each solution to yield the required drug to polymer ratios. The internal phase (drug/polymer) and external phase (heavy or light mineral oil) were mixed together using a stirrer consisting of a single shaft with three propellers attached; each propeller had a diameter of 25 mm and contained three blades. 0.5 % magnesium stearate was used as an emulsion stabilizer. The emulsion system was continuously stirred at a constant designated speed for each polymer solution (see Tables 3.1-3.2). After the formation of microspheres and complete evaporation of the acetone solvent, the microspheres were collected by centrifugation, washed with mineral spirits to remove the mineral oil, filtered, and dried in a Fisher Isotemp® oven at 50 °C ± 0.5 °C.

Viscosity of the polymer organic phase

The apparent viscosities of the polymer solutions and both the light and heavy mineral oil continuous phases were determined with a Brookfield DV-II viscometer using a UL adapter with spindle No. 00 at 20 rpm. All viscosities were determined at 25 °C ± 0.5 °C.

Particle size distribution

The particle size distributions were evaluated by sieve analysis using a set of standard sieves from 45 to 1000 μm. Each batch of microspheres was placed on the uppermost sieve and

tapped by hand. The weight of the microspheres retained on each individual sieve was then recorded and placed in collection vials.

Drug loading

Drug content analysis of the microspheres was performed by placing an accurately weighed amount (~ 5 mg) in a 10 ml volumetric flask. Methylene chloride was then added to dissolve both the polymer and the drug. Drug concentrations were determined spectrophotometrically at a wavelength of 274 nm. At this wavelength, no spectrophotometric interferences were observed from blank microspheres (microspheres without drug).

In vitro dissolution analysis

In vitro dissolution studies were performed on the microspheres at 37 °C ± 0.5 °C in vessels filled with 900 ml of simulated intestinal fluid (SIF) USP without enzymes at 100 rpm using a USP dissolution apparatus II. Samples of microspheres were accurately weighed (20-30 mg) and suspended in the dissolution media. A 5 ml sample of fluid was withdrawn at specified time intervals to assay the released drug spectrophotometrically at 271 nm; calculated drug concentrations were corrected for drug removed by sampling. Dissolution was carried out for at least 24 hours. Each graphical point of the dissolution data was an average of three samples of microspheres in separate vessels.

Results and Discussion

Viscosity determinations

The relationship between the apparent viscosity and the concentration of the ETHOCEL® polymer solutions is shown in Table 3.3 and illustrated in Figure 3.1. As expected, the apparent viscosity increased as the polymer concentration increased. Furthermore, it is

Table 3.1. Preparation conditions used in the formulation of ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) microspheres (heavy mineral oil, 145 cps).

Polymer	**Concentration in acetone (w/w)**	**Stirrer speed (rpm)**
EC-100	5 % 7 %	800 500
EC-20	7 % 9 %	400 700

Table 3.2. Preparation conditions used in the formulation of ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) microspheres (light mineral oil, 46 cps).

Polymer	**Concentration in acetone (w/w)**	**Stirrer speed (rpm)**
EC-100	5 % 7 %	950 1100
EC-20	7 % 9 %	900 1000

evident that ETHOCEL® 100 has higher apparent viscosity than ETHOCEL® 20 at the same concentration (7 %) in acetone; this is due to the higher molecular weight of ETHOCEL® 100.

Effect of formulation and processing factors on particle size distribution

One of the methods employed to control the particle size distribution of microspheres prepared by emulsion-solvent evaporation was to adjust the stirring speed during the emulsification process. Typically, higher polymer concentrations produce larger particle sizes. The particle size distribution of microspheres prepared from different polymer concentrations could be altered by adjusting the agitation intensity (see Table 3.1 and Table 3.2) to obtain similar or relatively close particle size distributions. For the most part, in this study, similar particle size distributions were prepared in both heavy and light mineral oil preparations at all ETHOCEL® concentrations. However, for light mineral oil preparations, the particle size range for 5 % ETHOCEL® 100 was slightly smaller (45-500 μm) as compared to the 45-710 μm particle size range produced from the 7-9 % ETHOCEL® polymer solutions. Despite the adjustments made in the agitation intensity, the particle size range of 5 % ETHOCEL® 100 was limited to no greater than 500 μm due to the low concentration of polymer in acetone. Typical log-probability plots of particle size distribution of microspheres prepared from concentrations of ETHOCEL® 100 and ETHOCEL® 20 polymers in acetone are shown in Figures 3.2 (heavy mineral oil) and 3.3 (light mineral oil); the geometric mean and geometric standard deviations are given in Table 3.4. The size distributions of the microspheres, in light or heavy mineral oil preparations, were generally narrow as indicated by the geometric standard deviations calculated from 50 % oversize/ 84 % oversize (see Table 3.4).

It is very clear from looking at Figures 3.2 and 3.3 and the geometric mean data that there was a significant difference in both particle size range and average microsphere diameter (see

Table 3.4) between microspheres prepared using heavy mineral oil and microspheres prepared using light mineral oil at all ETHOCEL® polymer concentrations. Microspheres prepared using heavy mineral oil as the external phase, had a narrow particle size range 45-150 μm in comparison to light mineral oil preparations, which had a substantially larger particle size range of 45-710 μm and average microsphere diameter (see Table 3.4). It is evident from these figures that light mineral oil has a significant influence on the particle size distribution of microspheres prepared from ETHOCEL® polymers in acetone. This difference in particle size range may be attributed to light mineral oil being more soluble in acetone than in heavy mineral oil, causing the acetone in the emulsion globules to go into the light mineral oil rapidly and the quick formation of a gelled-matrices resulting in a wide range of particle sizes. It was observed for heavy mineral oil preparations in acetone that there was a lot of aggregation of small particles during the emulsification process, causing the mixture to break-up and result in smaller range of particle sizes. The solubility of light mineral oil and heavy mineral oil in acetone and vice versa, has been investigated.

Drug loading

Tables 3.5 and 3.6 show the drug content of microspheres with a theoretical drug loading of 33.3 % calculated from the weight of drug and polymers (the ratio of weights of theophylline: ETHOCEL® 100 or ETHOCEL® 20 was 1:2) in light and heavy mineral oil preparations. In heavy mineral oil preparations, drug content was determined collectively at one size fraction of ≤ 150 μm due to the low yields in each respective concentration. The 5 % ETHOCEL® 100 concentration had the highest drug content in heavy mineral oil primarily because of the high number of aggregates present formulation; there was not much variability in the drug loading of other concentrations prepared in heavy mineral oil, as well as those prepared in light mineral oil.

It was apparent that the drug loading of ETHOCEL® 100 polymers was higher than ETHOCEL® 20 polymers (see Table 3.6); this was attributed to the high molecular weight of ETHOCEL® 100.

Effect of polymer phase viscosity and other formulation aspects on dissolution properties

Dissolution profiles of different size fractions of theophylline microspheres prepared from 5 % and 7 % concentrations of ETHOCEL® 100 and 7 % and 9 % concentrations of ETHOCEL® 20 are shown in Figures 3.4 (heavy mineral oil) and 3.5-3.8 (light mineral oil). In the heavy mineral oil preparations, it is evident that most of the drug was released immediately (see Figure 3.4). Initial release was close to 100 % for most these microsphere formulations. Typically, as you increase the polymer phase viscosity, the initial release of drug decreases. However, in most of the heavy mineral oil preparations the effect of viscosity was negligible. There are several potential reasons why the microspheres from most of these preparations released most of the drug in less than 1 hour. Hollow shell-like particles, smaller particles attached to larger particles, as well as aggregates of smaller particles are possible explanations for this rapid dissolution of drug (see Figures 3.9 and 3.10). The presence of these types of particles increased the surface area available to the dissolution and subsequently increased the release of drug.

For light mineral oil preparations of ETHOCEL® polymer microspheres, the initial release of drug was not as pronounced as seen in the heavy mineral oil formulations (see Figures 3.5-3.8). For the most part, in these dissolution profiles, release was faster for smaller particle sizes and slower for larger particle sizes as expected. However, at the largest particle size of each concentration, the release was typically not the slowest. This was due to the attachment of smaller microspheres to the larger particle sizes, aggregates of smaller particles that were

retained on the larger sieves, and the presence of hollow shell-like particles in this fraction. Microscopic observations support these conclusions (see Figures 3.11 and 3.12).

When comparing the release between different concentrations of the same polymer, the dissolution from the higher concentration (higher apparent viscosity) should be slower at comparable particle sizes. It is thought that as you increase the polymer phase viscosity the drug would be held more firmly inside the microsphere and the release of drug is slowed. However, this was not the case for the lower molecular weight ETHOCEL® 20 polymer concentrations prepared in light mineral oil. At the lowest concentration of 7 %, the release was slower than the 9 % concentration over larger particle sizes as shown in Figures 3.13 and 3.14. Again, this faster release was probably associated with the presence of aggregates of small particles and smaller particles attached to the larger microspheres that negate the effect of polymer phase viscosity on microsphere properties. This is very evident in Figure 3.15 that shows the relation between T50 % and the square of the microsphere diameter. In Figure 3.15, from 63-355 μm microsphere sizes there is a linear relationship for both 7 % and 9 % ETHOCEL® 20 polymer concentrations. Yet, with the addition of a larger size fraction (600 μm) the relationship is no longer linear because the release was not typical of a larger sized particle.

In Figure 3.16, T50 % plots of ETHOCEL® 20 polymer concentrations and ETHOCEL® 100 polymer concentrations are shown (light mineral oil conditions). The results indicate a more linear relationship for the concentrations of the lower molecular weight polymer (significantly higher R^2 values were observed), which was not expected because the higher molecular weight polymers tend to produce higher polymer phase viscosities that essentially function as a retardant agent to drug release. However, these high molecular weight polymers may also induce a substantial amount of aggregation that may result in unusual or uncharacteristic release behavior.

Furthermore, dissolution profiles of microspheres prepared from ETHOCEL® 20 polymer (low molecular weight) exhibited release profiles that suggest that these microspheres could be described by the Higuchi spherical matrix model as shown in Figure 3.17 (light mineral oil conditions). In addition, when comparing the release profiles of similar concentrations (7 %) of ETHOCEL® 20 polymer and ETHOCEL® 100 polymer (light mineral oil preparations), the dissolution was slower in the lower molecular weight polymer as depicted in Figures 3.18-3.21, and a more linear relationship between T50 % and particle diameter was observed (see Figure 3.22). Also, dissolution from 7 % ETHOCEL® 20 (low MW) microspheres could be better described by the Higuchi spherical matrix model than 7 % ETHOCEL® 100 (high MW) (see Figures 3.23-3.24). Although aggregates of small particles were found in microsphere preparations from lower molecular weight ETHOCEL® 20, it could be that higher molecular weight polymers have the tendency to produce a substantially higher amount of aggregates that are primarily responsible for the uncharacteristic release behavior of matrix microspheres prepared from ETHOCEL® 100 concentrations in this study.

Table 3.3. Apparent viscosities of different concentrations of ETHOCEL® 20 (EC-20) and ETHOCEL® 100 (EC-100) polymers in acetone.

Formulation	**Concentration % w/w**	**Viscosity of polymer phase (cps) ± Std Dev**
PA LPA	5 % EC-100	59.3 ± 0.30
PC LPC	7 % EC-100	206 ± 0.60
PB LPB	7 % EC-20	34.9 ± 0.30
PD LPD	9 % EC-20	66.5 ± 0.50

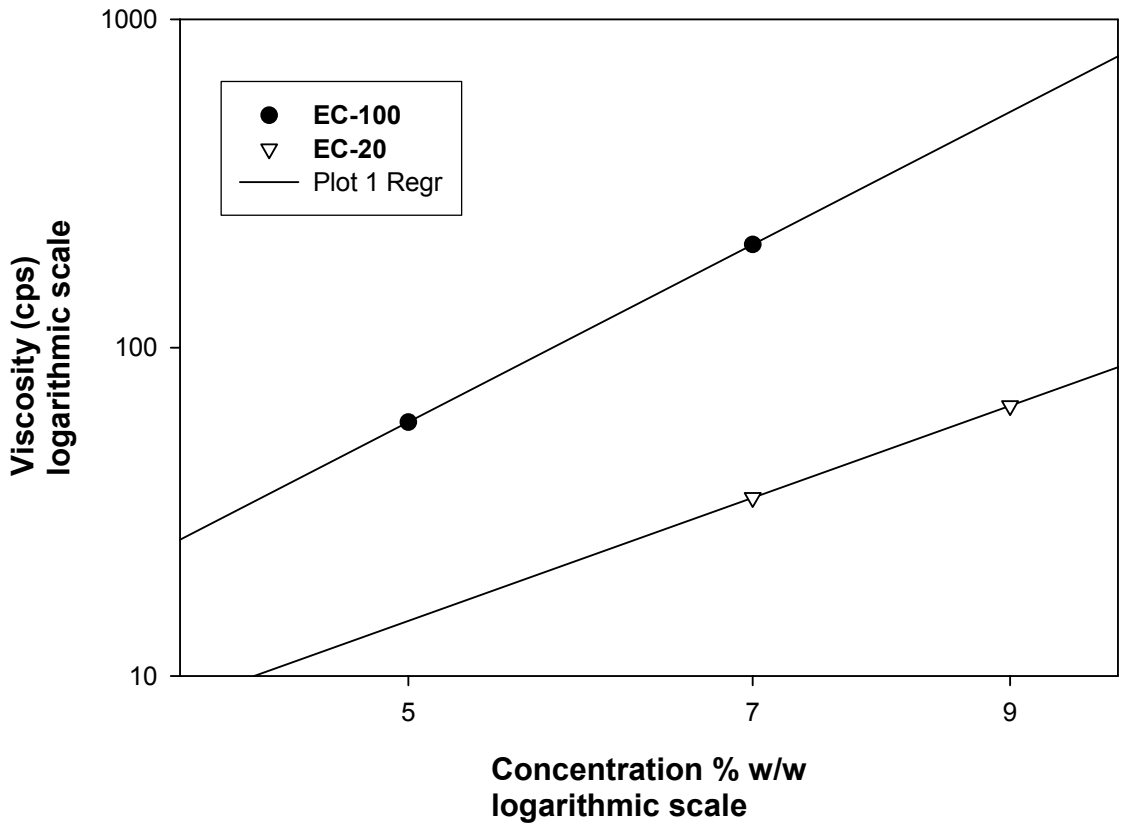

Figure 3.1. Apparent viscosities of different concentrations of ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) in acetone.

Table 3.4. Particle size analysis of microspheres prepared using ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) in acetone.

Polymer concentration in acetone (w/w)	**Geometric mean diameter (d_g) (µm)**	**Geometric standard deviation (σ_g)**	**External phase**
5 % EC-100	55	1.53	heavy mineral oil
5 % EC-100	160	1.45	light mineral oil
7 % EC-100	60	1.33	heavy mineral oil
7 % EC-100	250	1.67	light mineral oil
7 % EC-20	58	1.38	heavy mineral oil
7 % EC-20	240	1.58	light mineral oil
9 % EC-20	55	1.41	heavy mineral oil
9 % EC-20	280	1.47	light mineral oil

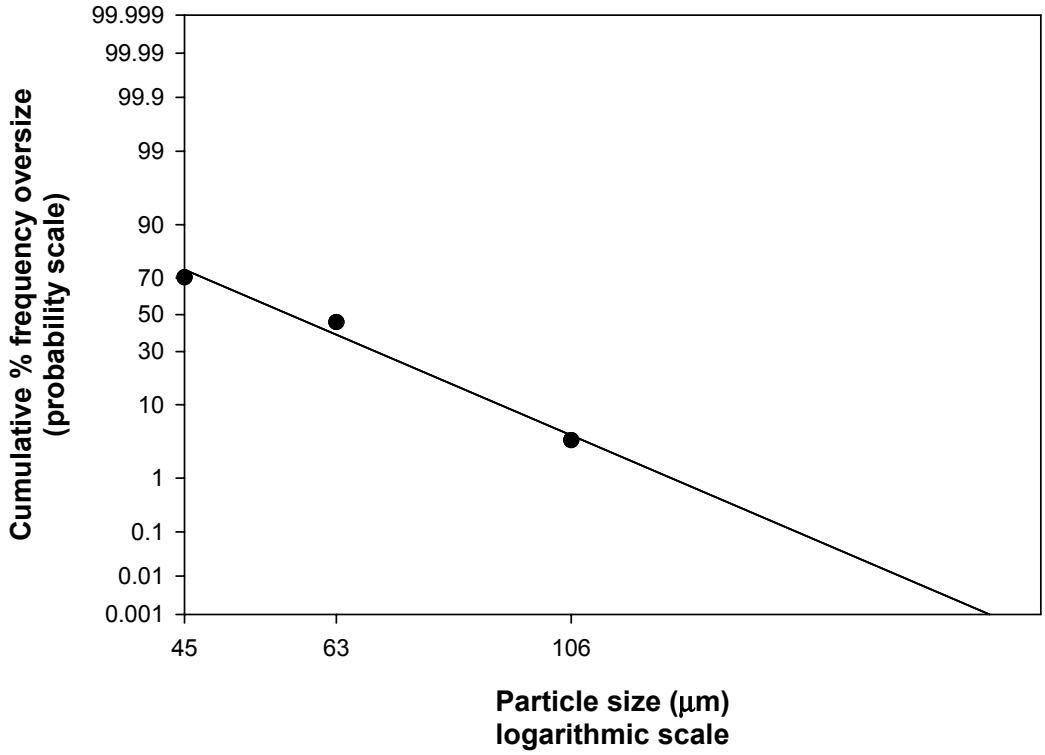

Figure 3.2. Log-normal particle size distribution of microspheres prepared from 9 % ETHOCEL® 20 (PD/heavy mineral oil).

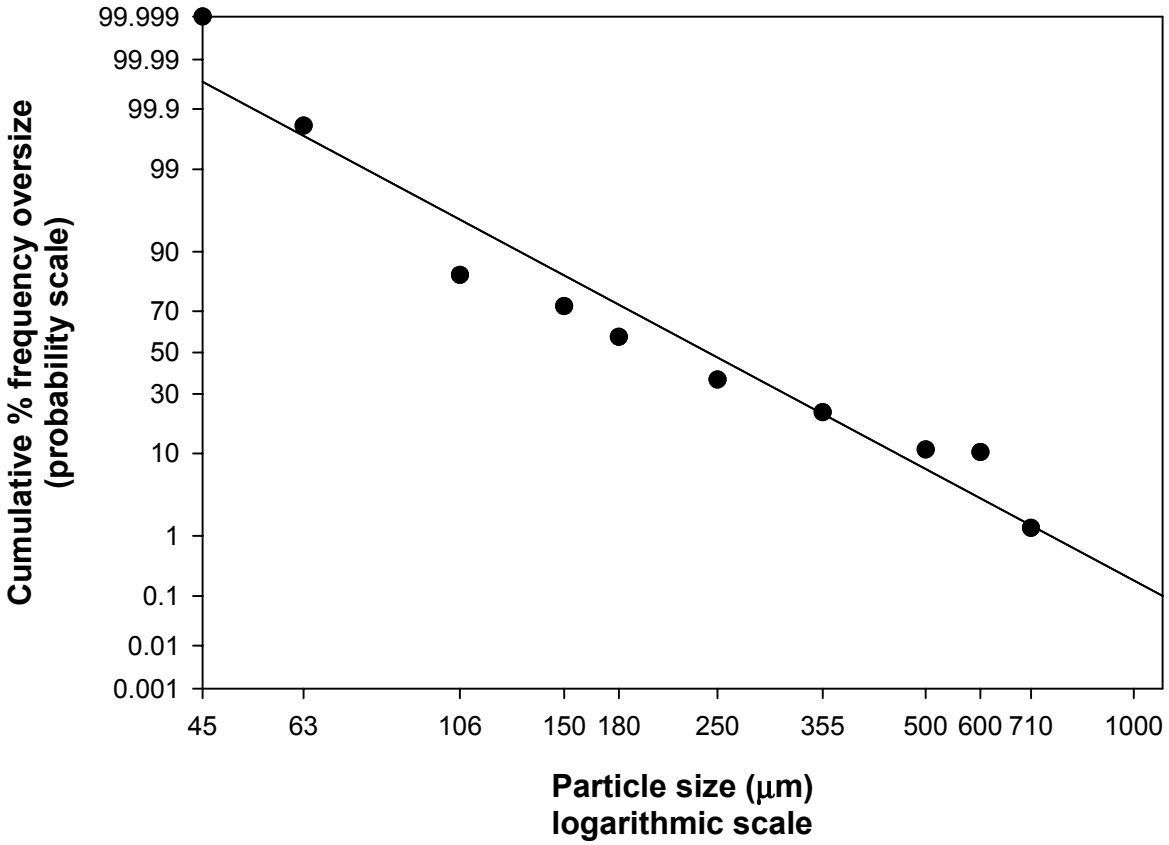

Figure 3.3. Log-normal particle size distribution of microspheres prepared from 7 % ETHOCEL® 100 (LPC/light mineral oil).

Table 3.5. Drug contents of different size fractions of theophylline microspheres prepared using ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) in acetone (heavy mineral oil: theoretical drug loading = 33.3 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (μm)**	**Drug content (%) ± Std Dev**
5 % EC-100	≤150	31 ± 2.31
7 % EC-100	≤ 150	27 ± 0.00
7 % EC-20	≤ 150	26 ± 1.53
9 % EC-20	≤ 150	27 ± 1.53

Table 3.6. Drug contents of different size fractions of theophylline microspheres prepared using ETHOCEL® 100 (EC-100) and ETHOCEL® 20 (EC-20) in acetone (light mineral oil: theoretical drug loading = 33.3 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (μm)**	**Drug content (%) ± Std Dev**
5 % EC-100	355-500	28 ± 2.08
	250-355	27 ± 1.00
	180-250	27 ± 1.00
	150-180	26 ± 0.58
	63-150	27 ± 1.00
7 % EC-100	600-710	27 ± 1.15
	500-600	27 ± 1.53
	355-500	27 ± 0.58
	250-355	27 ± 1.00
	180-250	28 ± 0.00
	150-180	28 ± 1.73
	63-150	27 ± 0.58
7 % EC-20	600-710	24 ± 1.53
	500-600	22 ± 0.58
	355-500	24 ± 0.58
	250-355	24 ± 1.53
	180-250	25 ± 0.58
	150-180	24 ± 0.58
	63-150	24 ± 0.00
9 % EC-20	600-710	23 ± 0.58
	500-600	23 ± 0.00
	355-500	24 ± 0.58
	250-355	22 ± 1.15
	180-250	23 ± 2.00
	150-180	24 ± 1.73
	63-150	23 ± 0.58

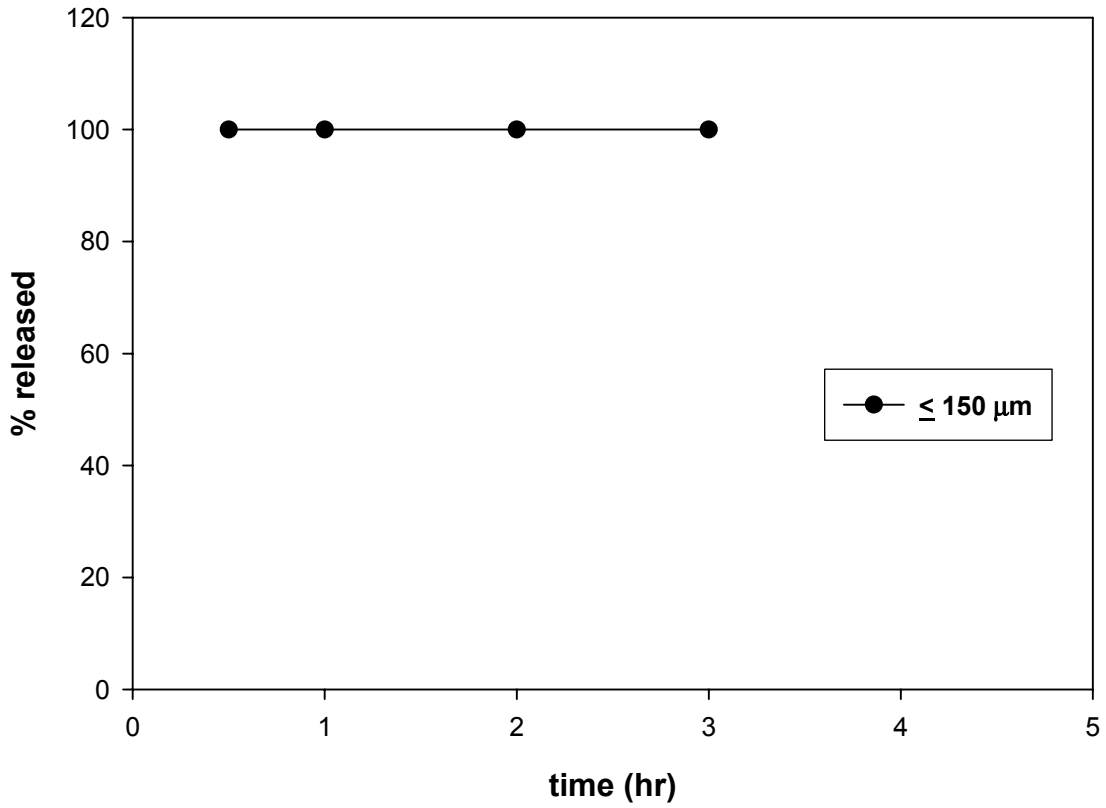

Figure 3.4. Release profile of ≤ 150 μm size fraction of theophylline microspheres prepared using 9 % ETHOCEL® 20 in acetone (PD/heavy mineral oil).

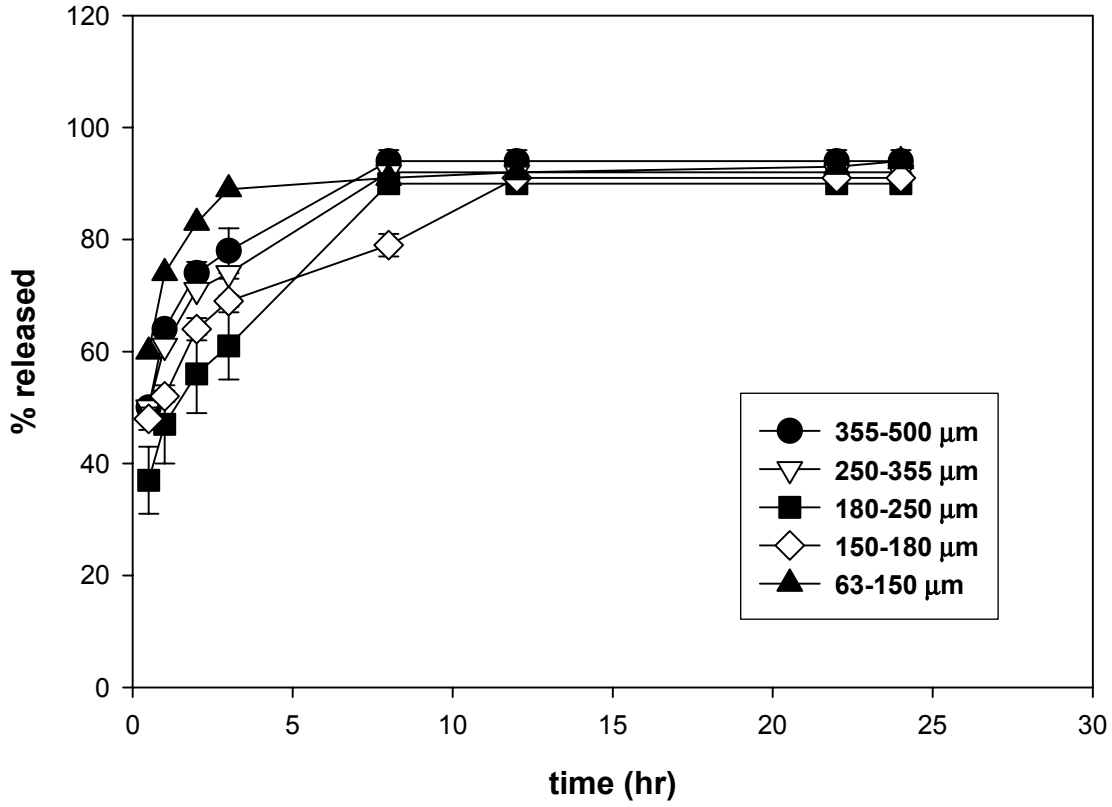

Figure 3.5. Release profiles of size fractions of theophylline microspheres prepared using 5 % ETHOCEL® 100 in acetone (LPA/light mineral oil).

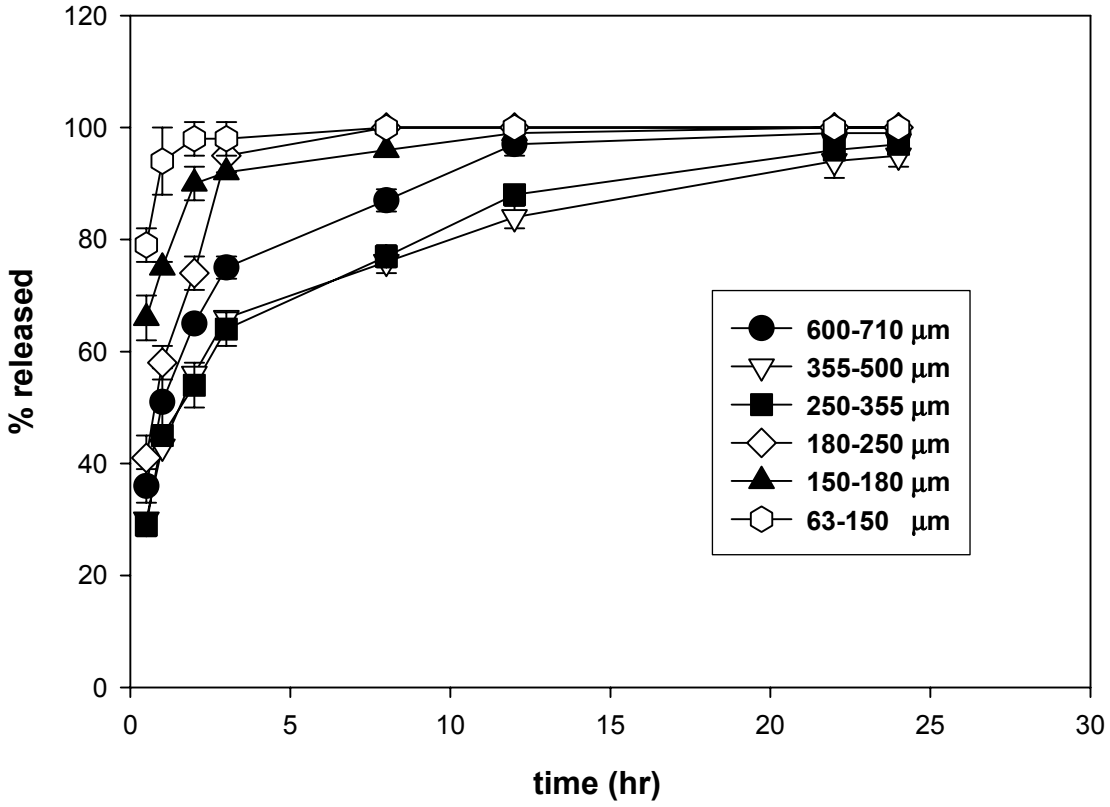

Figure 3.6. Release profiles of size fractions of theophylline microspheres prepared using 7 % ETHOCEL® 100 in acetone (LPC/light mineral oil).

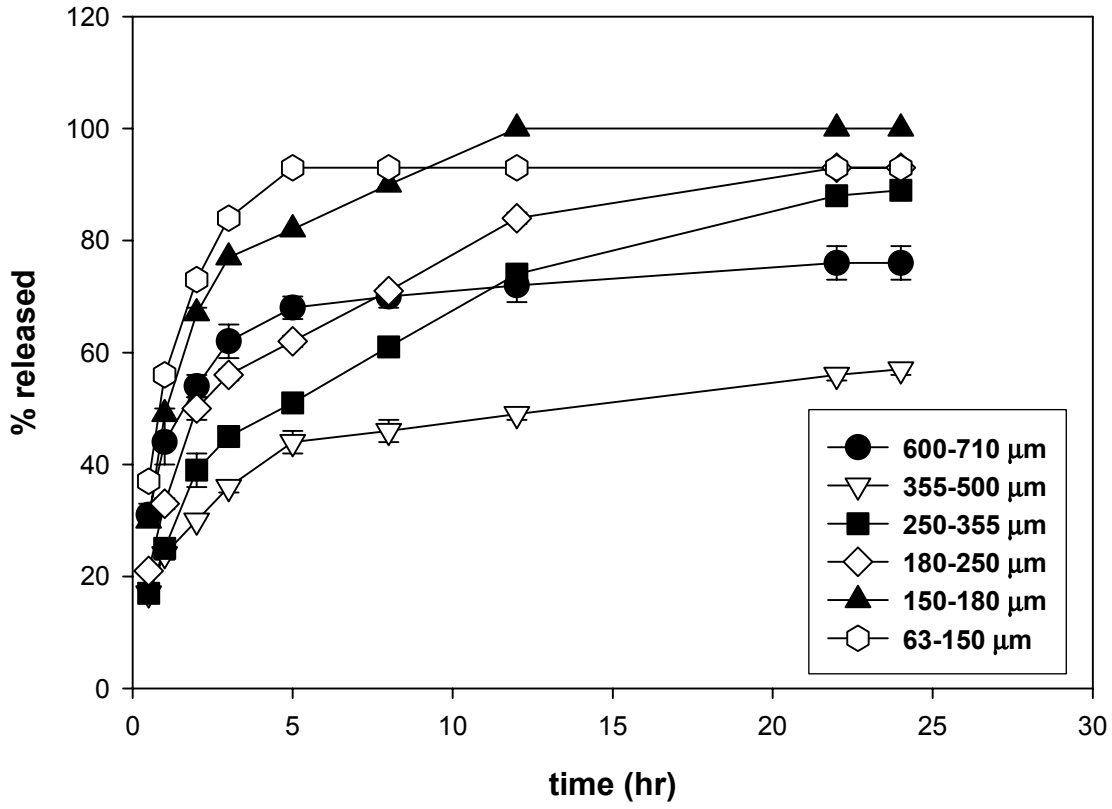

Figure 3.7. Release profiles of size fractions of theophylline microspheres prepared using 7 % ETHOCEL® 20 in acetone (LPB/light mineral oil).

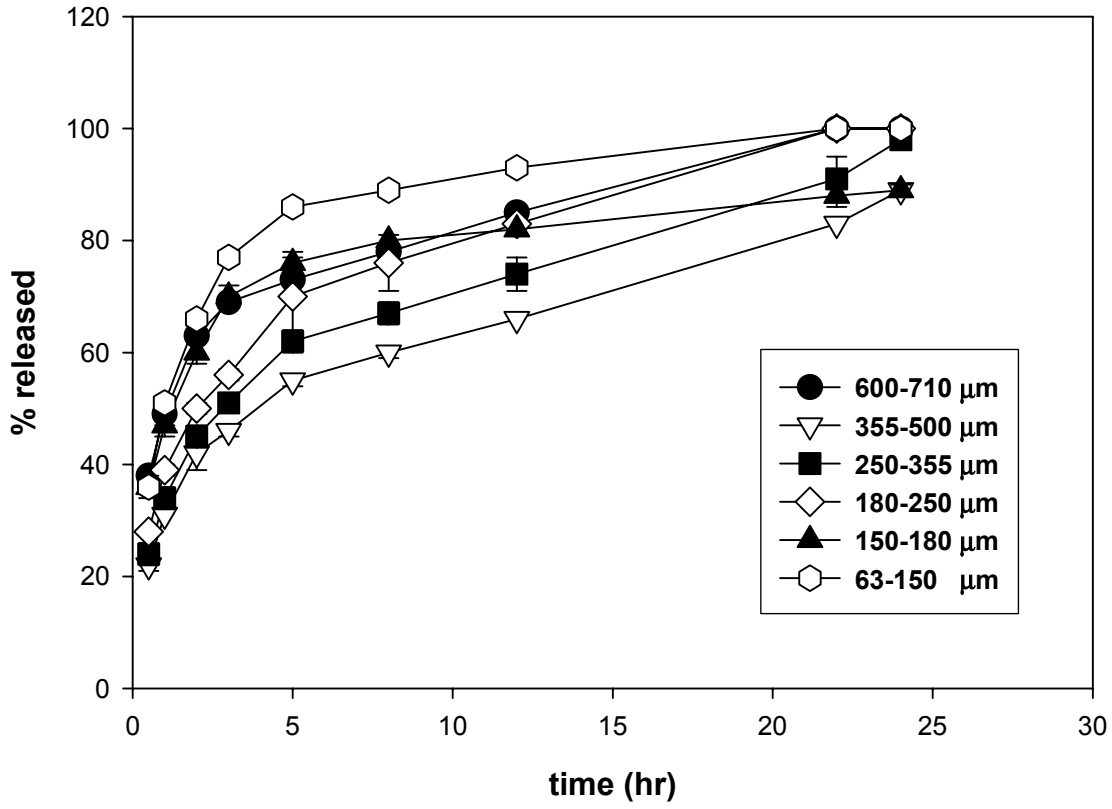

Figure 3.8. Release profiles of size fractions of theophylline microspheres prepared using 9 % ETHOCEL® 20 in acetone (LPD/light mineral oil).

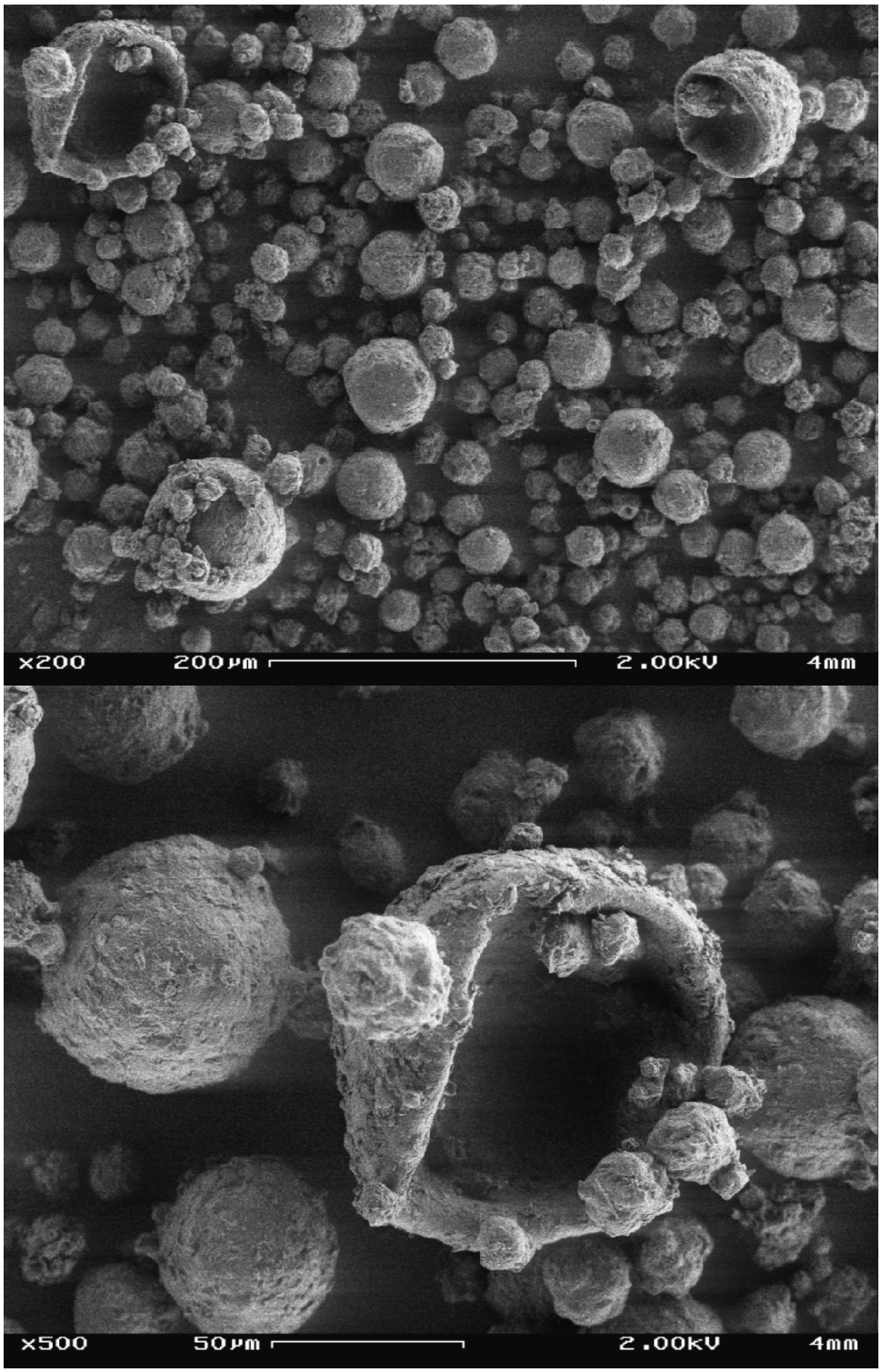

Figure 3.9. ≤ 150 µm size fraction of 7 % ETHOCEL® 100 polymer microspheres (heavy mineral oil).

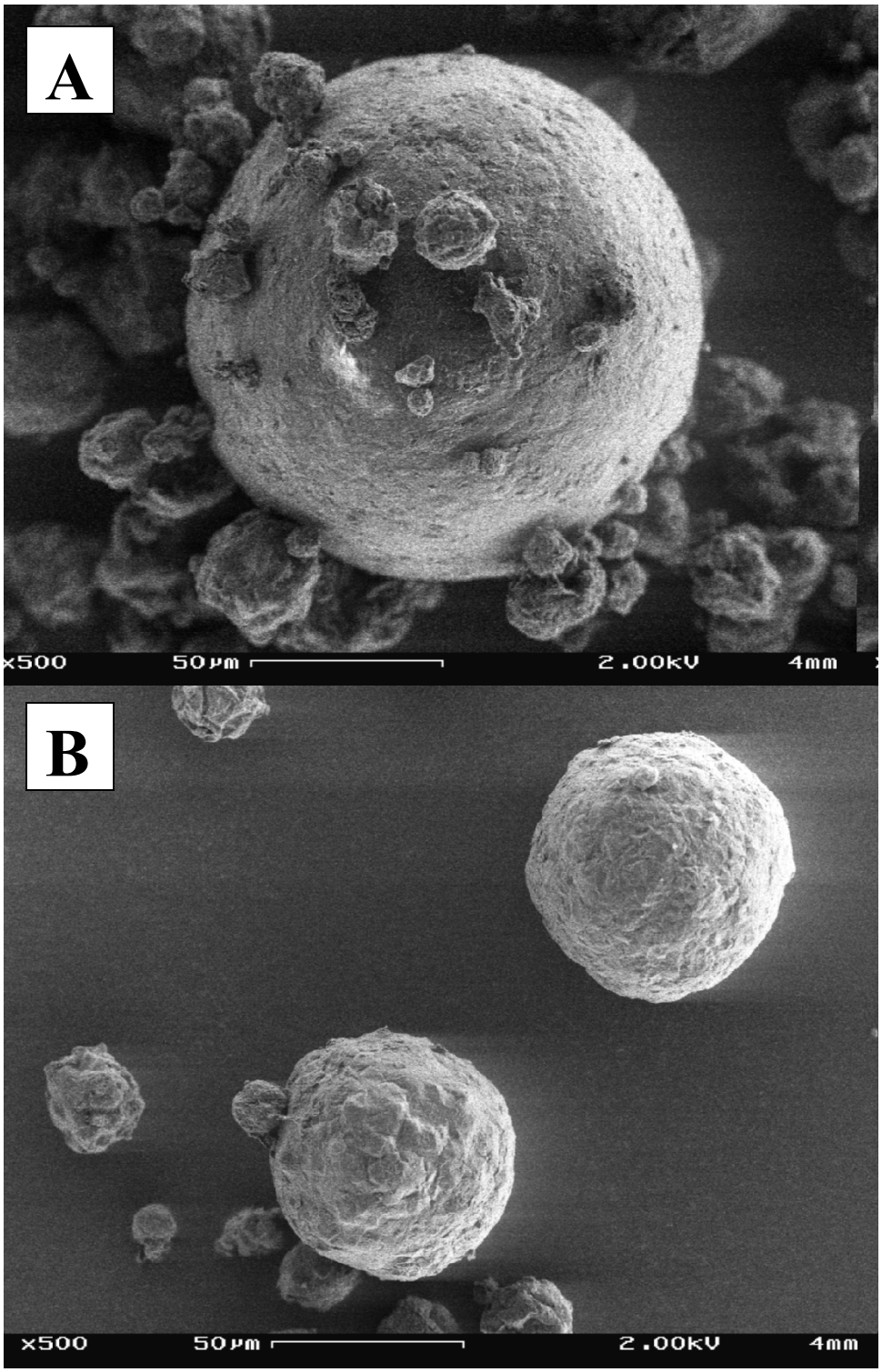

Figure 3.10. ≤ 150 µm size fraction of ETHOCEL® polymer microspheres (heavy mineral oil): (A) 7 % ETHOCEL® 100, (B) 9 % ETHOCEL® 20.

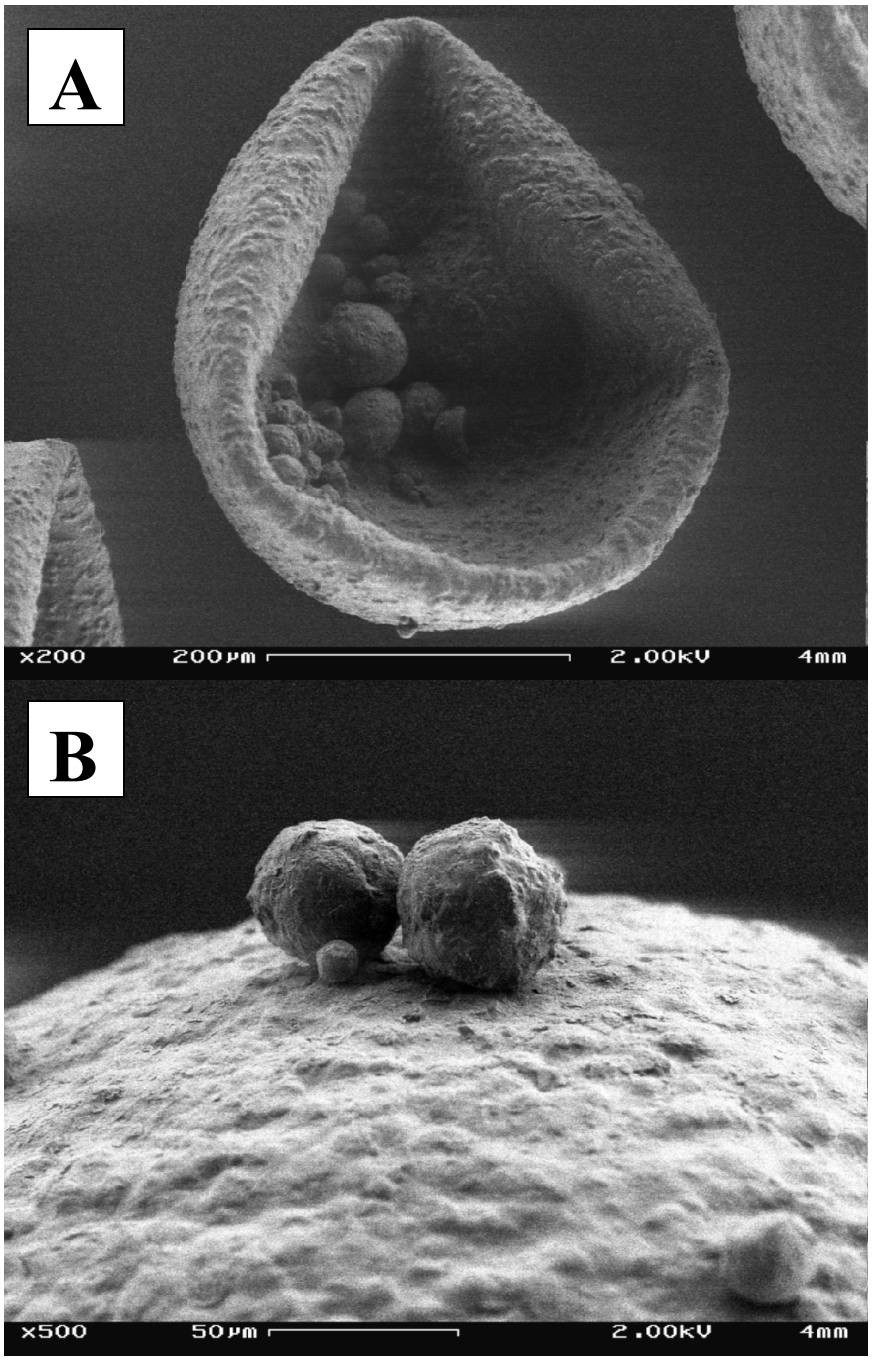

Figure 3.11. ETHOCEL® polymer microspheres (light mineral oil): (A) Hollow shell-like particle with small particles inside from 5 % ETHOCEL® 100 (355-500 µm), (B) Small particles attached to larger particle from 7 % ETHOCEL® 20 (600-710 µm).

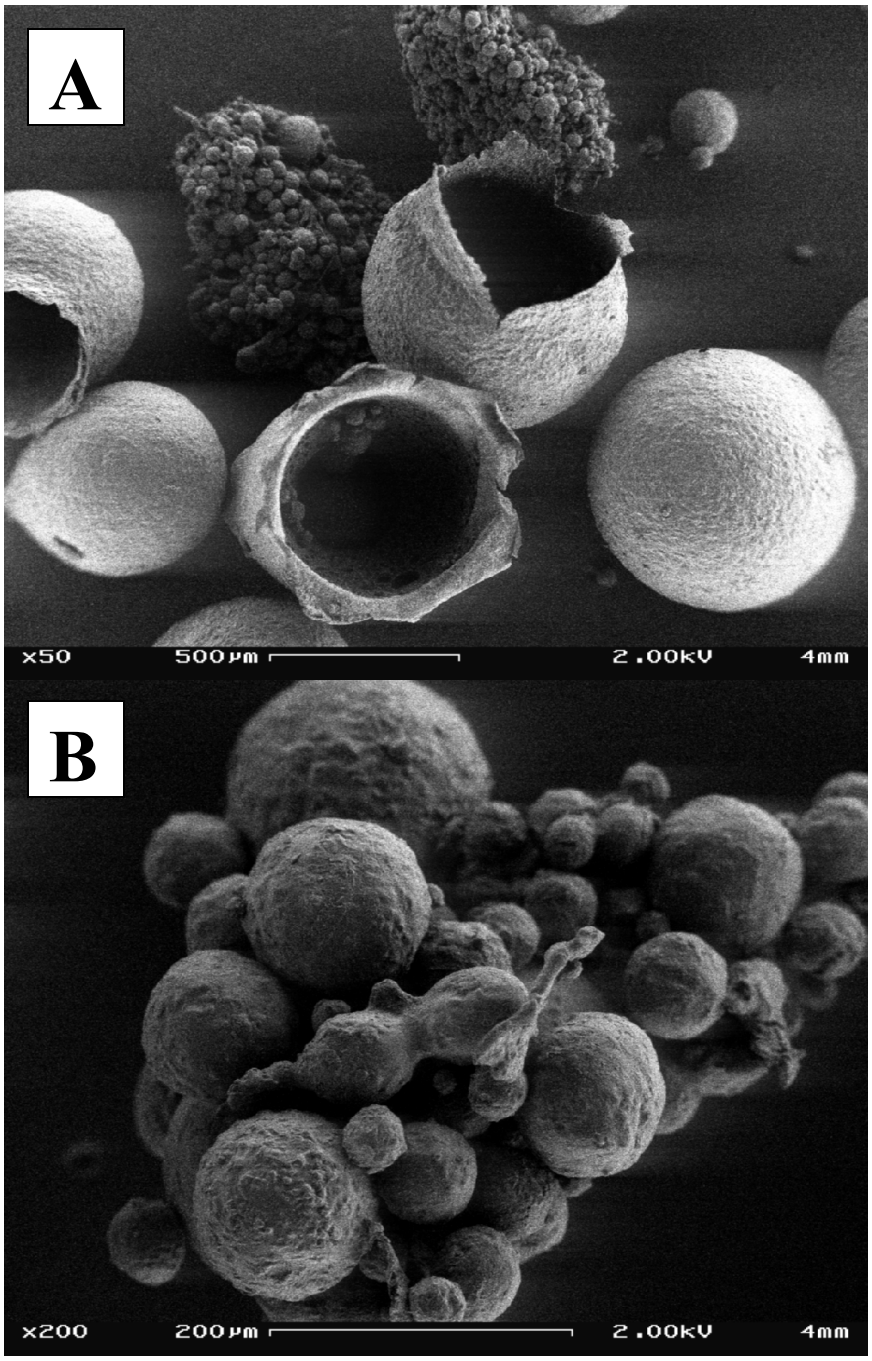

Figure 3.12. ETHOCEL® polymer microspheres (light mineral oil): (A) Hollow shell-like particles from 7 % ETHOCEL® 100 (600-710 µm), (B) Aggregates of small particles from 7 % ETHOCEL® 20 (600-710 µm).

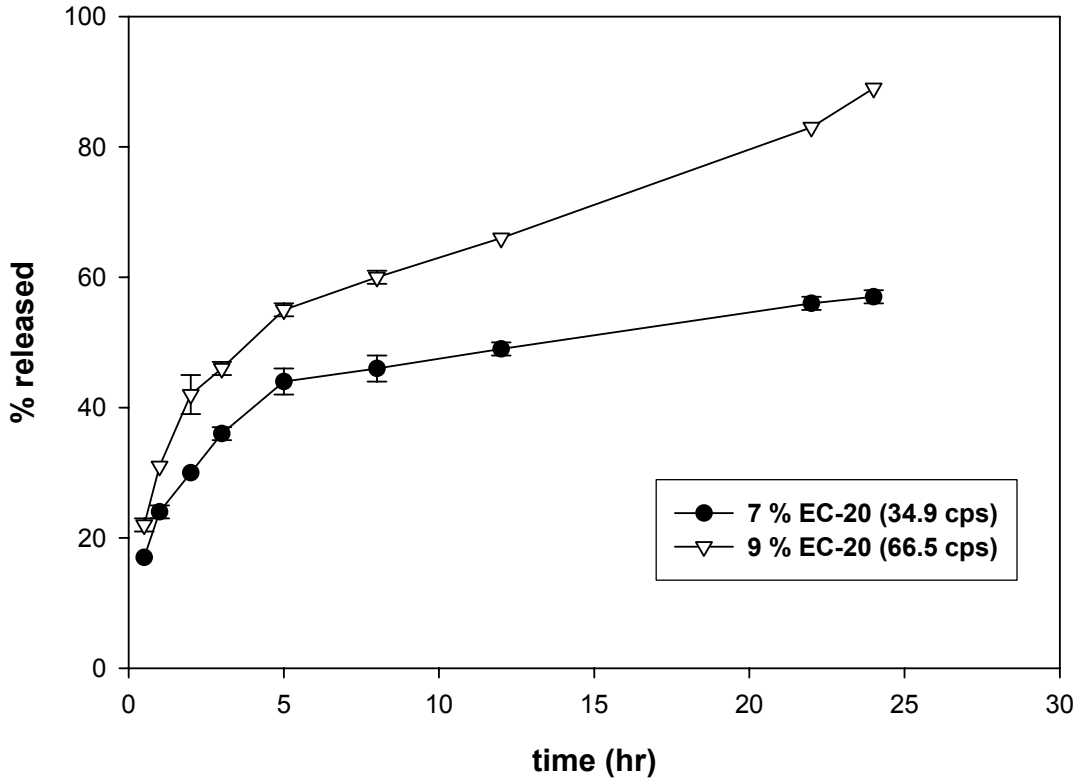

Figure 3.13. Release profiles of 355-500 μm theophylline microspheres prepared from different concentrations of ETHOCEL® 20 in acetone (7 %, 9 %), with respective viscosities (34.9, 66.5 cps) (light mineral oil).

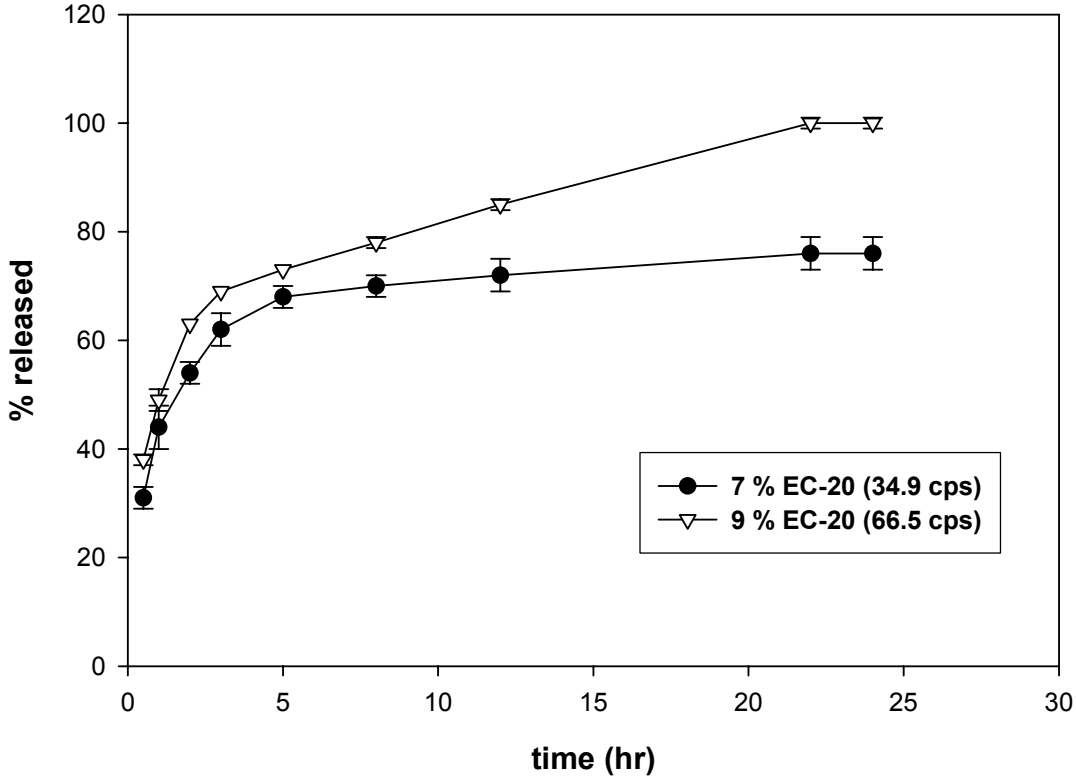

Figure 3.14. Release profiles of 600-710 μm theophylline microspheres prepared from different concentrations of ETHOCEL® 20 in acetone (7 %, 9 %), with respective viscosities (34.9, 66.5 cps) (light mineral oil).

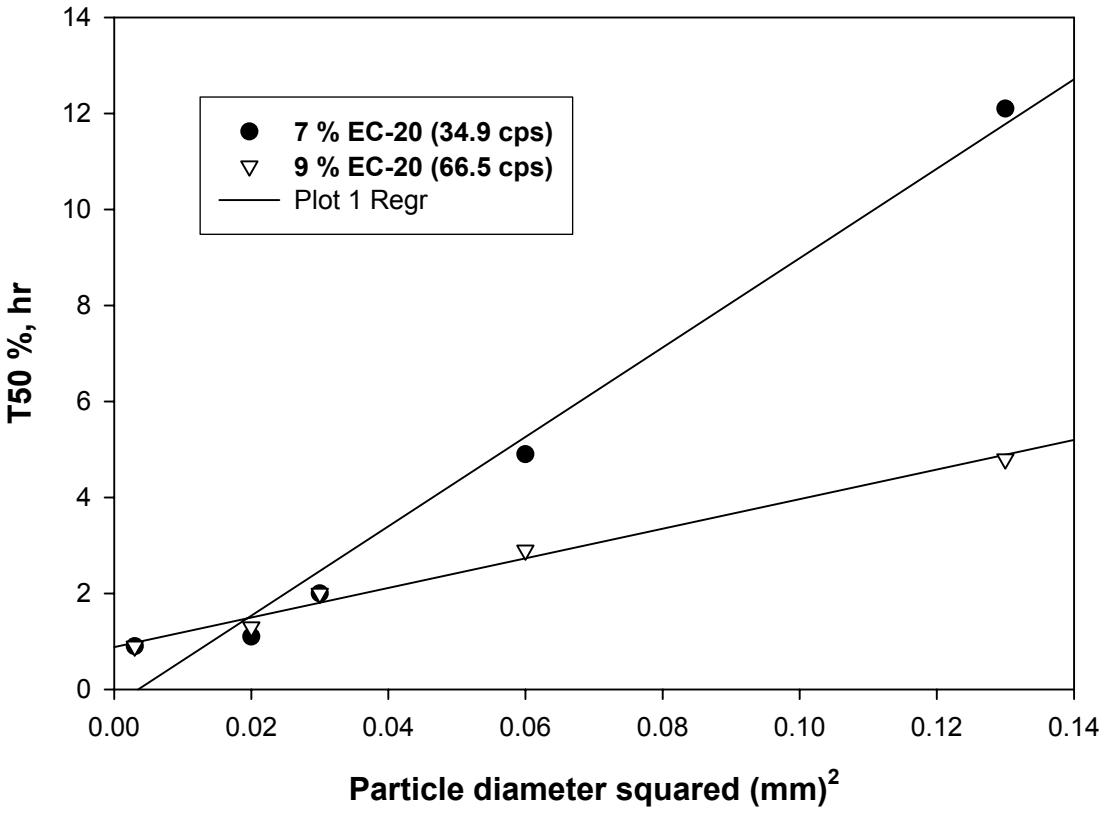

Figure 3.15. The relation between T50 % and the square of the microsphere diameter prepared from ETHOCEL® 20 polymer.

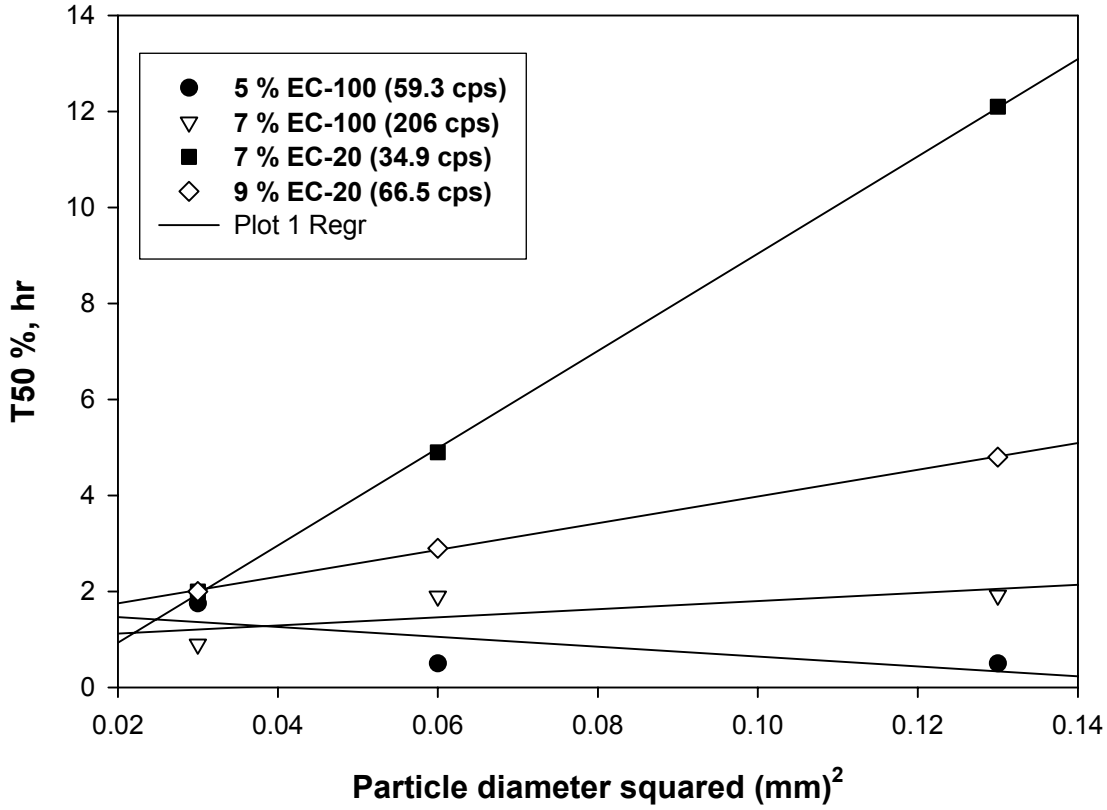

Figure 3.16. The relation between T50 % and the square of the microsphere diameter prepared from ETHOCEL® 20(EC-20) and ETHOCEL® 100 (EC-100) polymers.

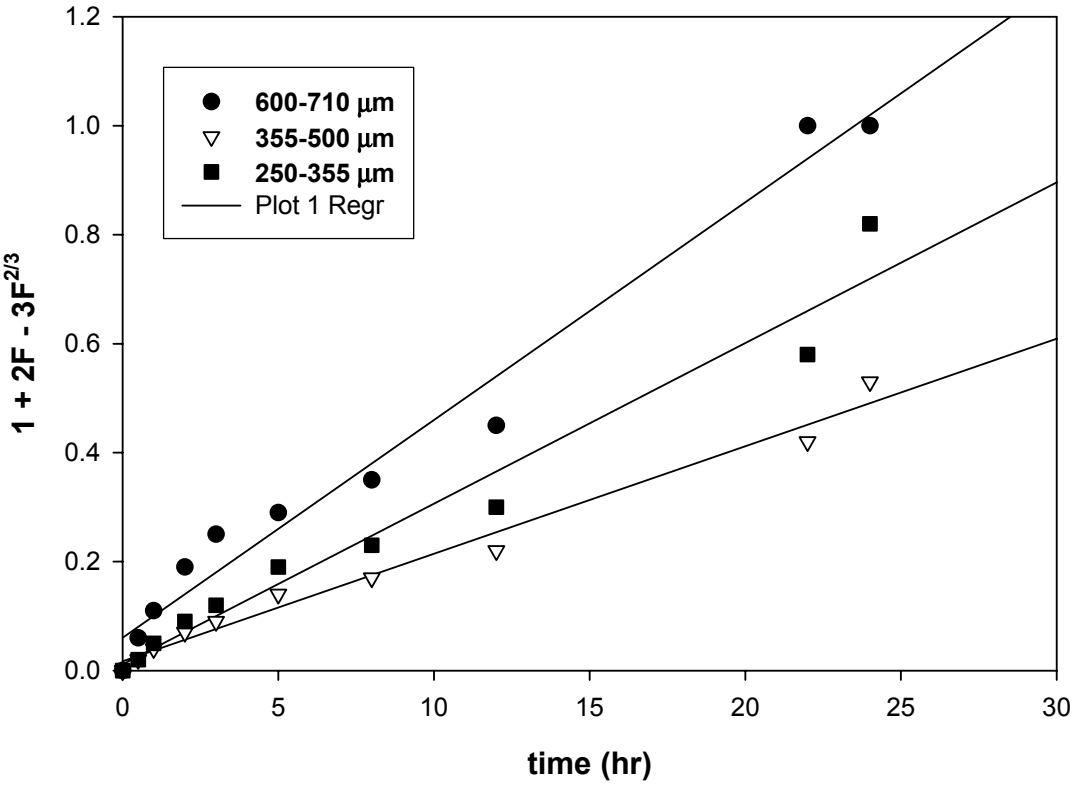

Figure 3.17. Higuchi plots for dissolution of different size fractions of theophylline microspheres prepared from 9 % ETHOCEL® 20 in acetone (light mineral oil).

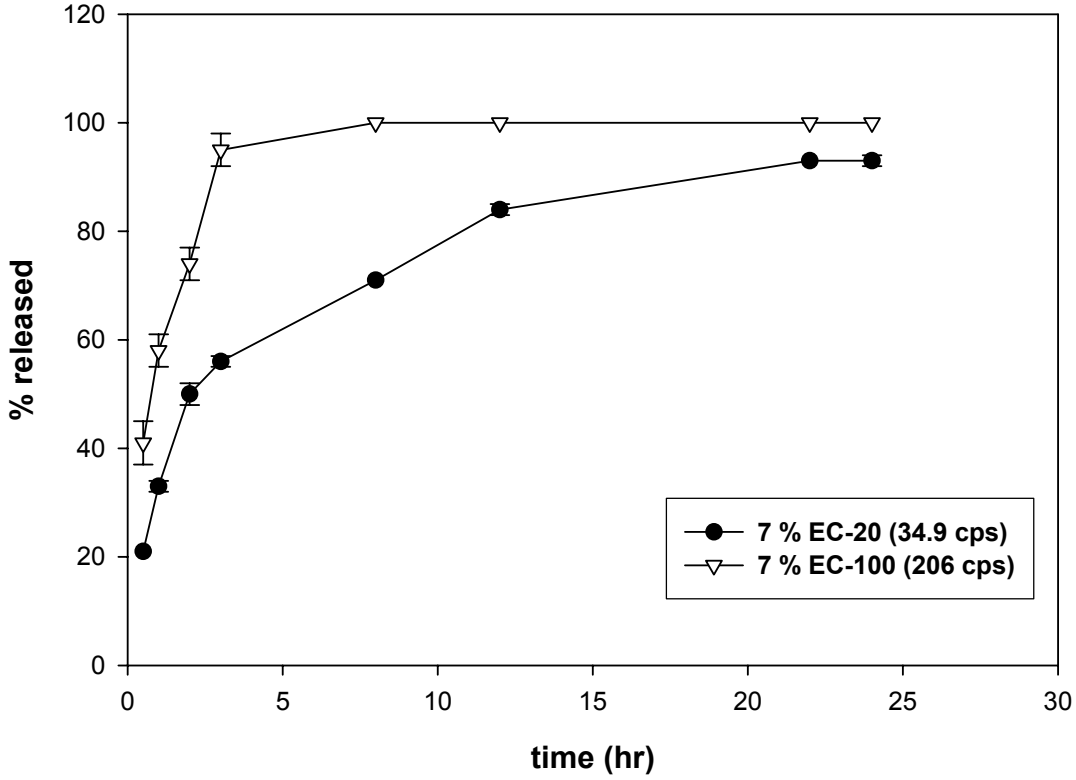

Figure 3.18. Release profiles of 180-250 μm theophylline microspheres prepared from similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

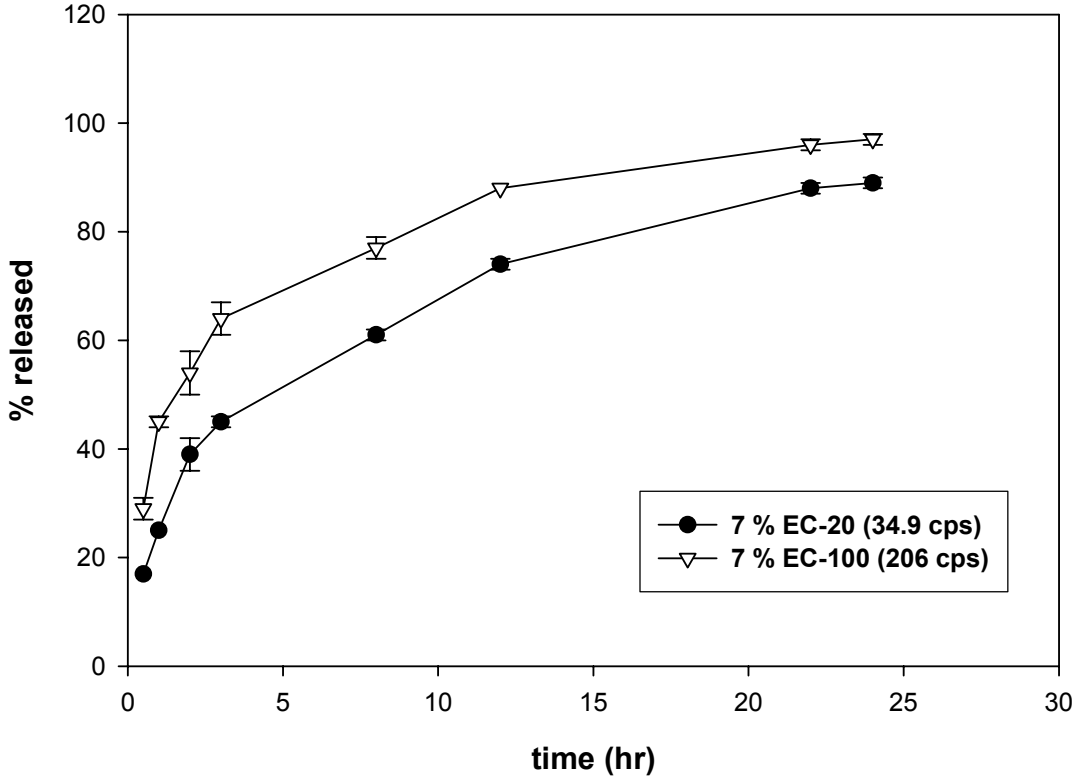

Figure 3.19. Release profiles of 250-355 μm theophylline microspheres prepared from similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

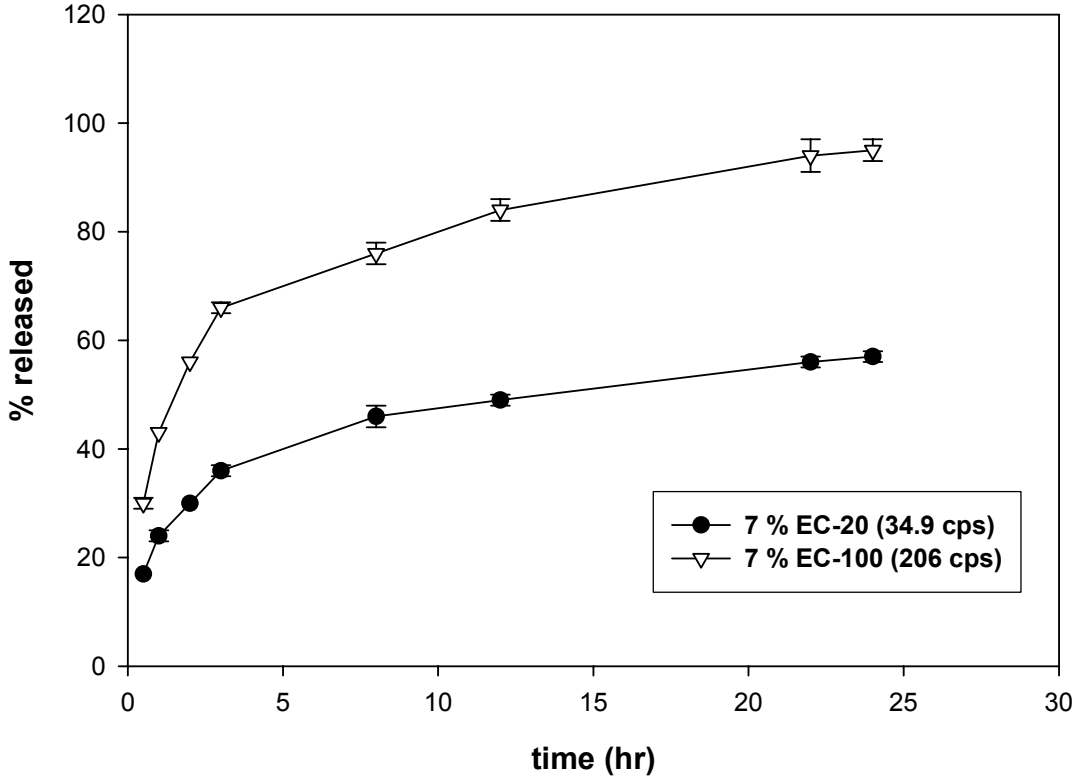

Figure 3.20. Release profiles of 355-500 μm theophylline microspheres prepared from similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

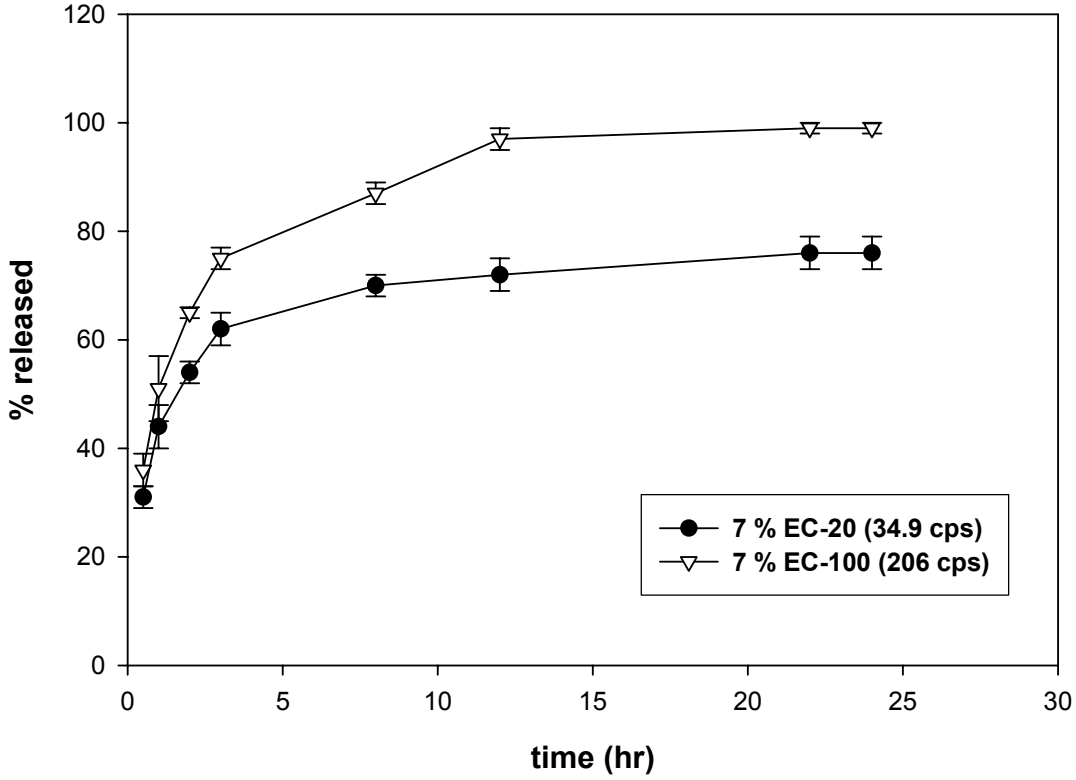

Figure 3.21. Release profiles of 600-710 μm theophylline microspheres prepared from similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

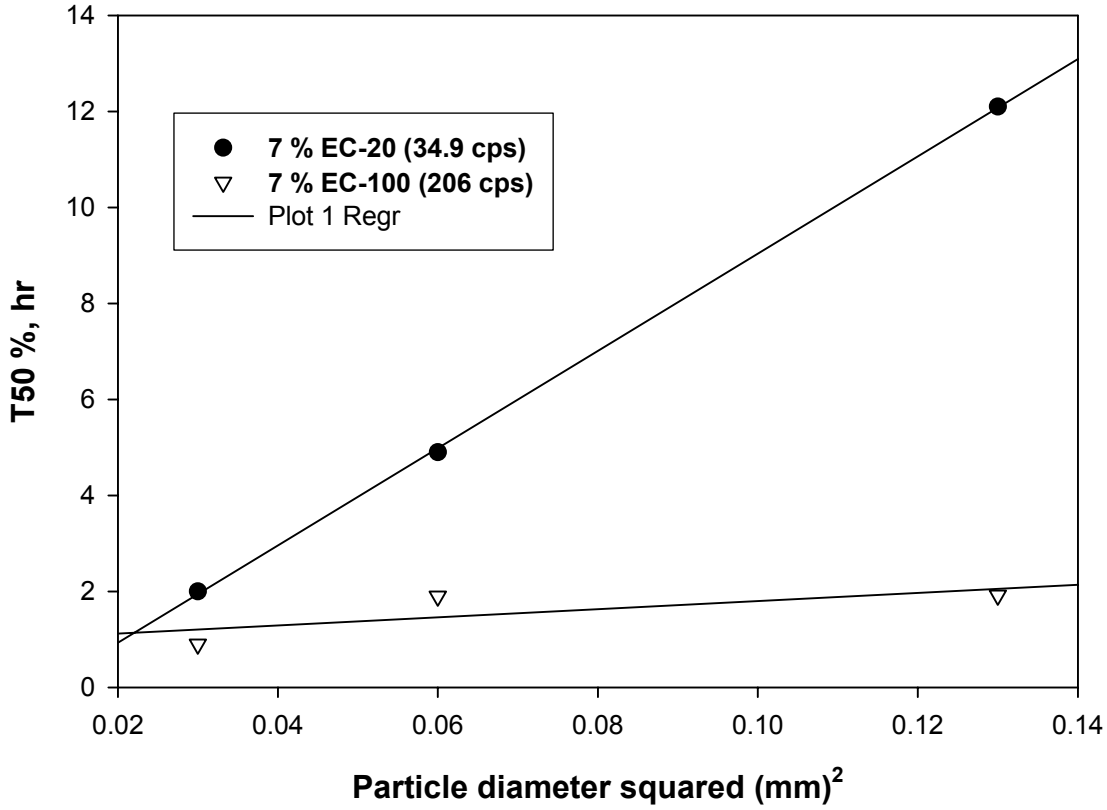

Figure 3.22. The relation between T50 % and the square of the microsphere diameter from similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

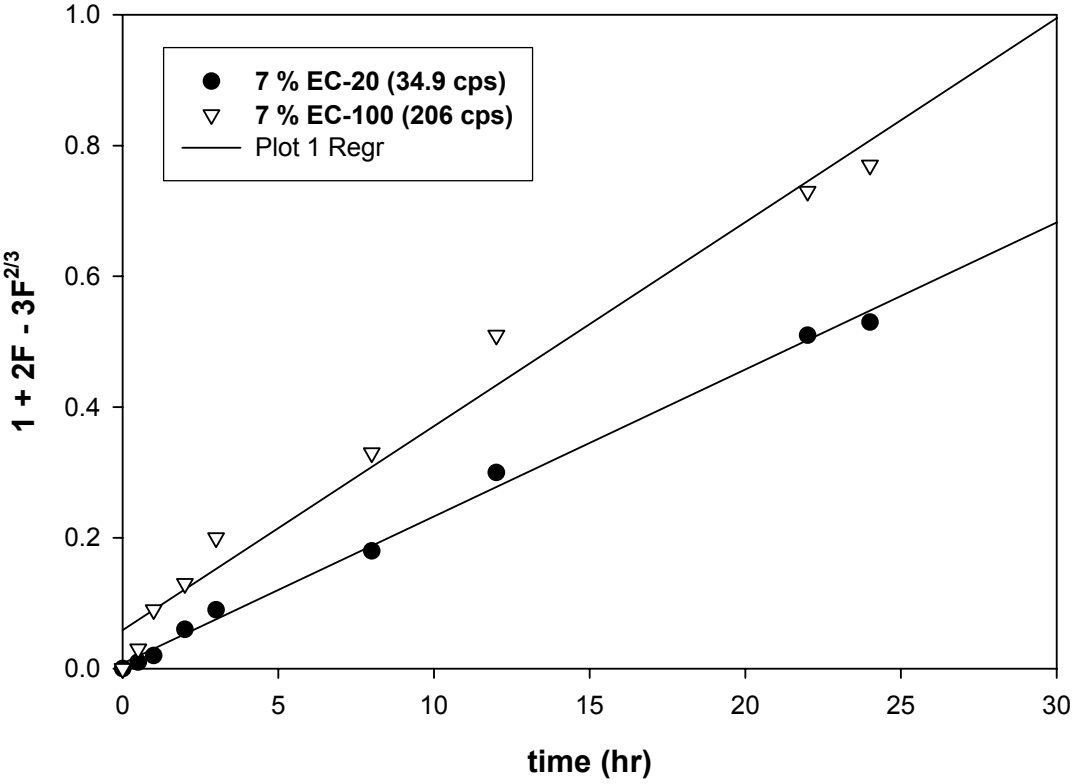

Figure 3.23. Higuchi plots for dissolution of 250-355 μm theophylline microspheres prepared using similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

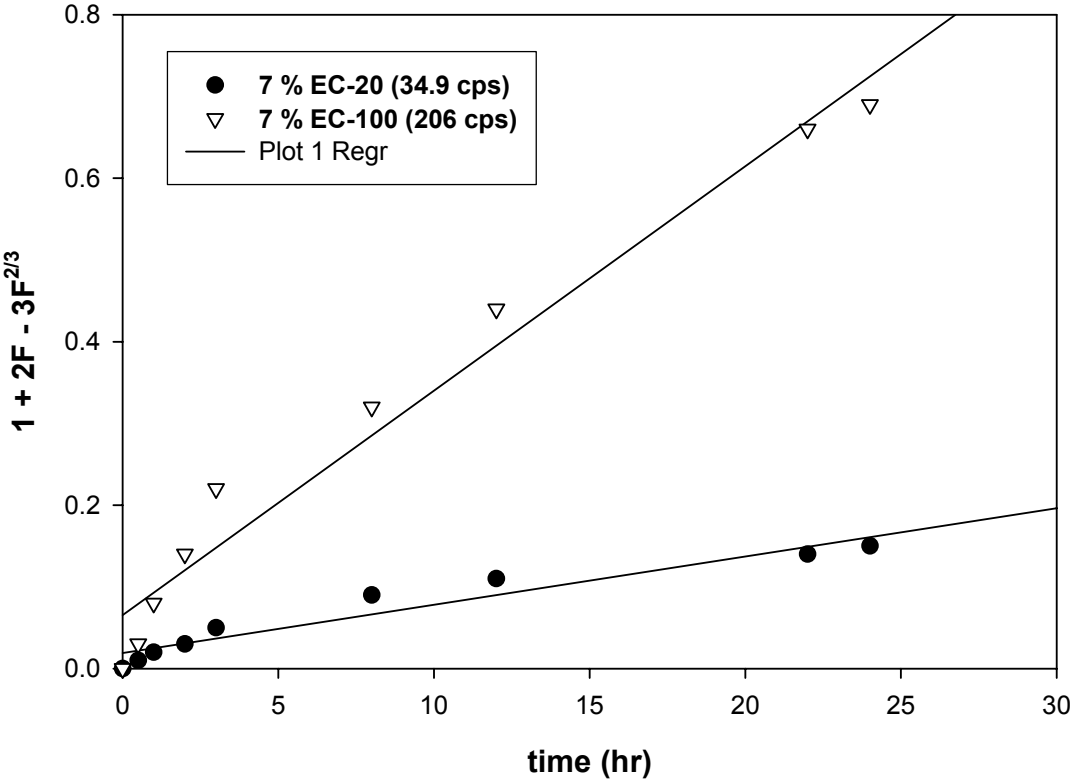

Figure 3.24. Higuchi plots for dissolution of 355-500 µm theophylline microspheres prepared using similar concentrations of ETHOCEL® polymers with high molecular weight (EC-100), and low molecular weight (EC-20).

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1. Shlieout, G., and Zessin, G., Investigation of ethylcellulose as a matrix former and a new method to regard and evaluate the compaction data. *Drug Dev. Ind. Pharm.*, 22, 313-319, 1996.
2. Bain, D. F., Munday, D. L., and Smith, A., Solvent influence of spray-dried biodegradable microsperes. *J. Microencapsulation*, 16, 4, 453-474, 1999.
3. Alpar, H. O., and Walters, V., The prolongation of the in vitro dissolution of a soluble drug (phenethicillin potassium) with ethyl cellulose. *J. Pharm. Pharmacol*., 33, 419-422, 1981.
4. Dashevsky, A., and Zessin, G., The effect of ethylcellulose molecular weight on the properties of theophylline microspheres, *J. Microencapsulation,* 14, 273-280, 1997.

CHAPTER 4

EFFECT OF CONTINUOUS PHASE VISCOSITY, EUDRAGIT® POLYMER PHASE VISCOSITY, AND OTHER FORMULATION FACTORS ON THE PROPERTIES OF THEOPHYLLINE MATRIX MICROSPHERES PREPARED BY EMULSION-SOLVENT EVAPORATION

Introduction

Oral delivery is the most commonly used method of drug administration (1). The rationale for using the oral route over other routes is that it is considered the safest and most convenient means of delivering the active agent (2). Over the years, oral controlled-release dosage forms have been frequently employed because of their many advantages over conventional dosing regimens. Some of these advantages include better patient compliance through a reduction in the number of doses taken, as well as minimal side effects that are typically associated with high drug concentrations in the blood (3-4). Controlled-release formulations are especially beneficial to drugs that have narrow therapeutic indexes such as theophylline, a bronchodilator that has been shown to be well absorbed in the gastrointestinal tract (5). However, at high plasma concentrations this drug can cause severe toxicity to the body (3). Thus, the importance of safety alone warrants the use of drug agents of this nature in controlled delivery systems (4).

Multiple-unit dosage forms are often preferred over single-unit formulations in situations where a controlled-release effect is desired (5). One of the main reasons for using this type of

dosage form is that the small particles can potentially disperse uniformly throughout the gastrointestinal tract and prevent high local concentrations that can cause adverse local effects (5-8). Furthermore, with many small units distributed throughout the GI tract, a more predictable release profile can be provided because of the reduction in local variability in the surrounding medium (5). In addition, multiple-unit dosage forms are less susceptible to dose dumping (5-8). Some examples of multiple-unit systems that have been used for controlled drug delivery are pellets, reservoir microparticles, and monolithic (matrix) microspheres (9-11). In particular, matrix microspheres can be formulated for many drugs and are very durable components (12). A popular method for preparing matrix microspheres is through emulsion-solvent evaporation (13). It is a simple process that can be performed at low or moderate temperatures, with no pH adjustment. Furthermore, catalysts or reactive agents are not required as well.

Microsphere properties are greatly influenced by processing and formulation factors, such as drug loading, stirring speed, solvent type, viscosity, molecular weight, and morphology (14). Specifically, several studies have been performed on the effects of polymer viscosity grade and polymer molecular weight. For example, Shukla and Price (15) investigated the effect of polymer molecular weight and drug loading of cellulose acetate propionate on the release properties of theophylline microspheres, and found that the higher polymer molecular weight had the slower release. Despite these findings, not much emphasis has been placed on how the viscosity of the polymer solution phase affects microsphere characteristics. Also, the effect of continuous phase viscosity on microsphere properties has not been reported. Obiedat and Price (14) demonstrated that both the molecular weight and solution viscosity of cellulose acetate butyrate polymers (CAB381-2 and CAB381-20) are influential in the release kinetics of

microspheres. However, further investigation of other polymer classes and the effect of influence of continuous phase viscosity should be undertaken. For example, Eudragit® polymers have been employed in microencapsulation techniques, but not much research has been reported on how its polymer solution phase and/or other formulation parameters affect microsphere properties (16-19). Therefore, the objectives of this study were to 1) examine the effect of using heavy mineral oil (high viscosity) versus light mineral oil (low viscosity) as the external phase on the properties of matrix microspheres prepared by emulsion-solvent evaporation, 2) investigate the effect of the apparent viscosities of the polymer phase of Eudragit® RS 100 (ERS 100) and Eudragit® RL 100 (ERL 100) on matrix microsphere properties, and 3) evaluate matrix microspheres prepared from a combination of two polymers (Eudragit® RL 100 (ERL 100)/ETHOCEL® 100 (EC-100), 1:1 ratio) at different polymer concentrations and how they effect microsphere characteristics. Theophylline was used as a model drug because it is good candidate for controlled-release due to its low therapeutic index.

Experimental

Materials

Eudragit® polymer (Eudragit® RL 100, Rohm, lot no. 8370706071, M.W. 150,000), Eudragit® polymer (Eudragit® RS 100, Rohm, lot no. 8370408031, M.W. 150,000) ethylcellulose (ETHOCEL® Standard 100, Dow Chemical Co., lot no. LI29013T02, M.W. 218,300 – 223,200), theophylline (Knoll AG, lot no. 93237), magnesium stearate, acetone, and methylene chloride (Fisher Scientific Co., Fair Lawn, NJ), mineral spirits (W. M. Barr & Co. Inc., Memphis, TN), heavy mineral oil and light mineral oil (Witco Co., Greenwich, CT),

polysorbate 80 (Tween 80) (Ruger Chemical Co. Inc., Irvington, NJ). Monobasic potassium phosphate and sodium hydroxide 50 % w/w solution (J. T. Baker Inc., Phillipsburg, NJ).

Instruments

Stirrer (Lab. Stirrer, LR 400D, Yamato Scientific Co., LTD., Tokyo, Japan), stirrer, (Lab. Stirrer, LR 400C, Fisher Scientific Co., Japan), USP Dissolution Apparatus II (Dissolution test system 5100, Distek, Inc., North Brunswick, NJ), UV spectrophotometer (Spectronic 2000, Bausch & Lomb, Rochester, NY), Accumet pH meter 5 (Fisher Scientific Co., NJ), Standard sieves series, viscometer model DV-II with UL adapter (Brookfield Engineering Laboratories, Inc., Stoughton, MA), LEO 982 Field emission scanning electron microscope (FE-SEM, LEO Electron Microscopy, Inc., Thornwood, NY).

Preparation of microspheres

In this study, matrix microspheres containing micronized anhydrous theophylline were prepared by emulsion-solvent evaporation using Eudragit® RL 100 (M.W. 150,000) at concentrations 10 %, 20 %, 23 %, 25 %, and 27 % (w/w), Eudragit® RS 100 (M.W. 150,000) at concentrations 10 %, 20 %, 23 %, 25 %, and 27 % (w/w), and a (1:1) combination of Eudragit® RL 100 and ETHOCEL® 100 at concentrations of 8 %, 10 %, 12 %, and 14 % (w/w) as the internal phase dissolved in acetone. Each formulation was prepared using both heavy mineral oil and light mineral oil, in separate instances, as the external phase; however, microsphere preparations from 10 % concentrations of Eudragit® RL 100 and Eudragit® RS 100 in acetone were formulated using only heavy mineral oil. Theophylline powder was incorporated into each solution to yield the required drug to polymer ratios. The internal phase (drug/polymer) and external phase (heavy or light mineral oil) were mixed together using a stirrer consisting of a single shaft with three propellers attached; each propeller had a diameter of 25 mm and

contained three blades. 0.5 % magnesium stearate was used as an emulsion stabilizer. The emulsion system was continuously stirred at a constant designated speed for each polymer solution (see Tables 4.1-4.3). After the formation of microspheres and complete evaporation of the acetone solvent, the microspheres were collected by centrifugation, washed with mineral spirits to remove the mineral oil, filtered, and dried in a Fisher Isotemp® oven at 50 °C ± 0.5 °C.

Viscosity of the polymer organic phase

The apparent viscosities of the polymer solutions and both the light and heavy mineral oil continuous phases were determined with a Brookfield DV-II viscometer using a UL adapter with spindle No. 00 at 5 to 100 rpm. The speed required to obtain an apparent viscosity reading depended on how viscous the solution was; more viscous solutions required a low rpm, while less viscous solutions required a higher rpm (≥ 50 rpm). All viscosities were determined at 25 °C ± 0.5 °C.

Particle size distribution

The particle size distributions were evaluated by sieve analysis using a set of standard sieves from 45 to 1000 μm. Each batch of microspheres was placed on the uppermost sieve and tapped by hand. The weight of the microspheres retained on each individual sieve was then recorded and placed in collection vials.

Drug loading

Drug content analysis of the microspheres was performed by placing an accurately weighed amount (~ 5 mg) in a 10 ml volumetric flask. Methylene chloride was then added to dissolve both the polymer(s) and the drug. Drug concentrations were determined spectrophotometrically at a wavelength of 274 nm. At this wavelength, no spectrophotometric interferences were observed from blank microspheres (microspheres without drug).

Table 4.1. Preparation conditions used in the formulation of Eudragit® RL 100 (ERL 100) and Eudragit® RS 100 (ERS 100) microspheres (heavy mineral oil, 145 cps).

Polymer	**Concentration in acetone (w/w)**	**Stirrer speed (rpm)**
ERL 100	10 %	750
	20 %	700
	23 %	950
	25 %	1000
	27 %	1200
ERS 100	10 %	750
	20 %	650
	23 %	700
	25 %	750
	27 %	850

Table 4.2. Preparation conditions used in the formulation of Eudragit® RL 100 (ERL 100) and Eudragit® RS 100 (ERS 100) microspheres (light mineral oil, 46 cps).

Polymer	**Concentration in acetone (w/w)**	**Stirrer speed (rpm)**
ERL 100	20 %	800
	23 %	850
	25 %	900
	27 %	1000
ERS 100	20 %	850
	23 %	900
	25 %	930
	27 %	950

Table 4.3. Preparation conditions used in the formulation of Eudragit® RL 100 (ERL 100)/ETHOCEL® 100 (EC-100) (1:1) microspheres (heavy mineral oil, 145 cps and light mineral oil, 46 cps).

Polymers	**Concentration in acetone (w/w)**	**Stirrer speed (rpm)**
ERL 100/EC-100	8 %	1000
	10 %	1100
	12 %	1200
	14 %	1300

In vitro dissolution analysis

In vitro dissolution studies were performed on the microspheres at 37 °C ± 0.5 °C in vessels filled with 900 ml of simulated intestinal fluid (SIF) USP without enzymes at 100 rpm using a USP dissolution apparatus II. Samples of microspheres were accurately weighed (20-30 mg) and suspended in the dissolution media. A 5 ml sample of fluid was withdrawn at specified time intervals to assay the released drug spectrophotometrically at 271 nm; calculated drug concentrations were corrected for drug removed by sampling. Dissolution was carried out for at least 24 hours. Each graphical point of the dissolution data was an average of three samples of microspheres in separate vessels.

Results and Discussion

Viscosity determinations

The relationship between the apparent viscosity and the concentration of the Eudragit® polymer solutions is shown in Table 4.4 and illustrated in Figure 4.1. As expected, the apparent viscosity increased as the polymer concentration increased. Furthermore, despite having similar molecular weight specifications (150,000) and chemical structures, it was very evident that Eudragit® RL 100 polymer solutions had higher apparent viscosities than Eudragit® RS 100 polymer solutions at the same concentrations in acetone, especially at the highest concentration of 27 % (see Table 4.4). The differences in apparent viscosity could be attributed to Eudragit® RL 100 having slightly more trimethylammonioethyl methacrylate chloride content and a higher percentage of functional quarternary ammonium groups present.

Effect of formulation and processing factors on particle size distribution

One of the methods employed to control the particle size distribution of microspheres prepared by emulsion-solvent evaporation was to adjust the stirring speed during the emulsification process. Typically, higher polymer concentrations produce larger particle sizes. With the exception of 10 % concentrations of Eudragit® RL 100 and Eudragit® RS 100 in acetone, particle size distribution of microspheres prepared from different polymer concentrations could be altered by adjusting the agitation intensity (see Table 4.1 and Table 4.2) to obtain similar or relatively close particle size distributions. The inability to yield similar particle size distributions at 10 % could be attributed to the concentration in acetone being too low. At this concentration, smaller particle size was favored regardless of the intensity of the agitation because smaller particle size distributions are typically associated with lower polymer concentrations (~ 45-106 μm). Similar particle size distributions were only achieved from microspheres prepared with 20 %, 23 %, 25 %, and 27 % Eudragit® polymers in acetone using heavy mineral oil as the external phase. At 25 % or lower Eudragit® polymer concentrations in acetone, formulations prepared using light mineral oil as the external phase produced irregular-shaped microspheres, aggregates, loose drug and polymer, minimal yields, and smaller particle sizes (see Figure 4.2), while 27 % concentrations produced a wider range of particle sizes; in this situation, adjustments in agitation intensity did not yield similar particle size distributions. The difference in similar particle size distributions using heavy mineral oil and the lack thereof using light mineral oil may come down to external phase viscosity; especially since the internal phase viscosities of the concentrations are the same in either situation. Regardless of the concentration, heavy mineral oil preparations had the tendency to break-up resulting in smaller particle sizes and similar particle size ranges; this was also evident for Eudragit® polymer concentrations of

25 % or less in light mineral oil preparations. For light mineral oil preparations, this is probably attributed to the polymer phase viscosity being too low to produce larger size microspheres as well as larger particle size ranges. However, at 27 % Eudragit® polymer concentrations using light mineral oil as the external phase, the polymer phase viscosity was high enough to produce larger size microspheres as well as wider range of particle sizes. The typical log-probability plot of the particle size distribution of microspheres prepared from Eudragit® polymer concentrations of 20 %, 23 %, 25 %, and 27 % in acetone (heavy mineral oil), and 20 %, 23 %, and 25 % in acetone (light mineral oil) is shown in Figure 4.3.

For Eudragit® polymer concentrations of 20 %, 23 %, and 25 % in acetone using heavy mineral oil and light mineral oil as the external phase, the range in particle size was generally the same (~ 45-250 μm) (see Figures 4.3-4.4). However, there was a significant difference in both particle size range and geometric mean (see Table 4.5) between microspheres prepared using heavy mineral oil and microspheres prepared using light mineral oil at Eudragit® polymer concentrations of 27 % in acetone (see Figure 4.5). Microspheres prepared using heavy mineral oil as the external phase, had a particle size range of 45-250 μm, while light mineral oil preparations had a particle size range of 106-1000 μm, at 27 % Eudragit® polymer concentrations in acetone (see Figures 4.5-4.6). Furthermore, the geometric mean was substantially higher in the light mineral oil preparations than in the heavy mineral oil preparations, at 27 % Eudragit® polymer concentrations in acetone (see Table 4.5). It is evident from Figures 4.5-4.6 and Table 4.5 that light mineral oil has a significant influence on the average particle size and the particle size distribution of microspheres prepared from Eudragit® RL 100 and Eudragit® RS 100 polymer concentrations of at least 27 % in acetone. This difference in particle size range may be attributed to light mineral oil being more soluble in

acetone than in heavy mineral oil, causing the acetone in the emulsion globules to go into the light mineral oil rapidly and the quick formation of a gelled-matrices resulting in a wide range of particle sizes. It was observed for concentrations below 27 % Eudragit® polymer in acetone, that that there was a lot of aggregation of small particles during the emulsification process, causing the mixture to break-up and result in smaller range of particle sizes. The solubility of light mineral oil and heavy mineral oil in acetone and vice versa, has been investigated.

Drug loading

In Tables 4.6-4.7 the drug content of microspheres with a theoretical drug loading of 40 % calculated from the weight of theophylline and polymers Eudragit® RL 100 or Eudragit® RS 100 (the ratio of drug to polymer was 2:3) is shown; Table 4.8 shows the drug content of microspheres with a theoretical drug loading of 33.3 % (drug to polymer ratio was 1:2). Microsphere preparations using heavy mineral oil had a theoretical drug loading of 40 %; microsphere preparations using light mineral oil had a theoretical drug loading of 33.3 %.

Effect of polymer phase viscosity and other formulation aspects on dissolution properties

The typical dissolution profile of different size fractions of theophylline microspheres prepared from 10 %, 20 %, 23 %, 25 %, and 27 % concentrations of both Eudragit® RL 100 and Eudragit® RS 100 is shown in Figure 4.7 (light and heavy mineral oil preparations); however, the dissolution profiles for 27 % Eudragit® polymer concentrations using light mineral oil as the external phase, are depicted in Figures 4.8-4.9. With the exception of 27 % Eudragit® polymer concentrations (light mineral oil), it is evident from Figure 4.7 that most of the drug was released immediately, and the initial release was close to 100 %. Typically, as you increase the polymer phase viscosity, the initial release of drug decreases. However, in most of these concentrations, it is clear that viscosity was not factor. There are several potential reasons

Table 4.4. Apparent viscosities of different concentrations of Eudragit® RL 100 (ERL 100) and Eudragit® RS 100 (ERS 100) in acetone.

Formulation	**Concentration % w/w**	**Viscosity of polymer phase (cps) ± Std Dev**
P1	10 % ERL 100	1.92 ± 0.00
P2	10 % ERS 100	1.02 ± 0.00
P3 LMP3	25 % ERL 100	22.6 ± 0.06
P4 LMP4	25 % ERS 100	12.4 ± 0.10
P5 LMP5	20 % ERL 100	9.73 ± 0.17
P6 LMP6	20 % ERS 100	5.10 ± 0.00
P7 LMP7	23 % ERL 100	19.1 ± 0.15
P8 LMP8	23 % ERS 100	8.6 ± 0.03
P9 LMP9	27 % ERL 100	41.2 ± 0.00
P10 LMP10	27 % ERS 100	15.0 ± 0.06

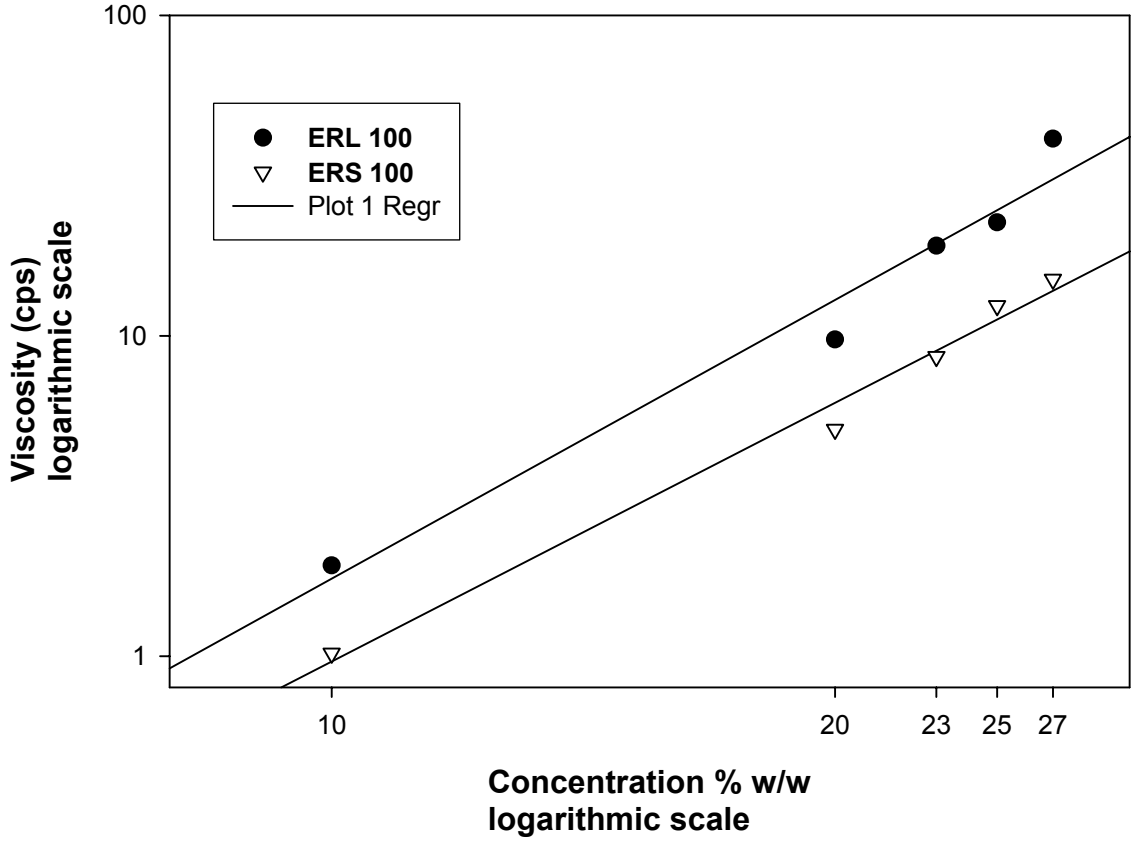

Figure 4.1. Apparent viscosities of different concentrations of Eudragit® RL 100 (ERL 100) and Eudragit® RS 100 (ERS 100) in acetone.

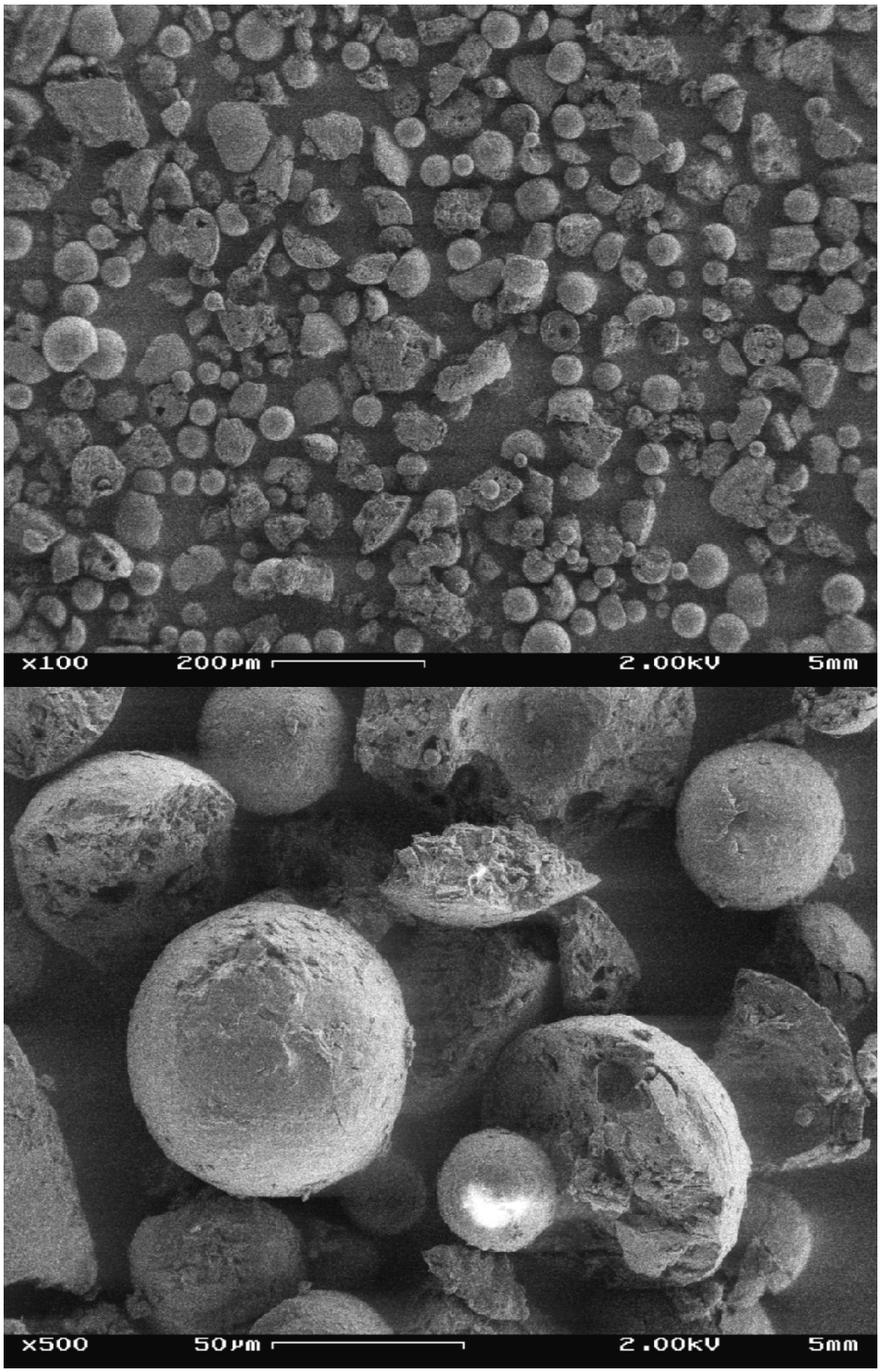

Figure 4.2. Microspheres prepared from 25 % Eudragit® RL 100 in acetone using light mineral oil as the external phase (63-106 µm).

Table 4.5. Particle size analysis of microspheres prepared from Eudragit® RL 100 (ERL 100) and Eudragit® RS 100 (ERS 100) in acetone.

Polymer concentration in acetone (w/w)	**Geometric mean diameter (d_g) (µm)**	**Geometric standard deviation (σ_g)**	**External phase**
27 % ERL 100	220	1.63	heavy mineral oil
27 % ERL 100	700	1.79	light mineral oil
27 % ERS 100	130	1.35	heavy mineral oil
27 % ERS 100	480	1.66	light mineral oil

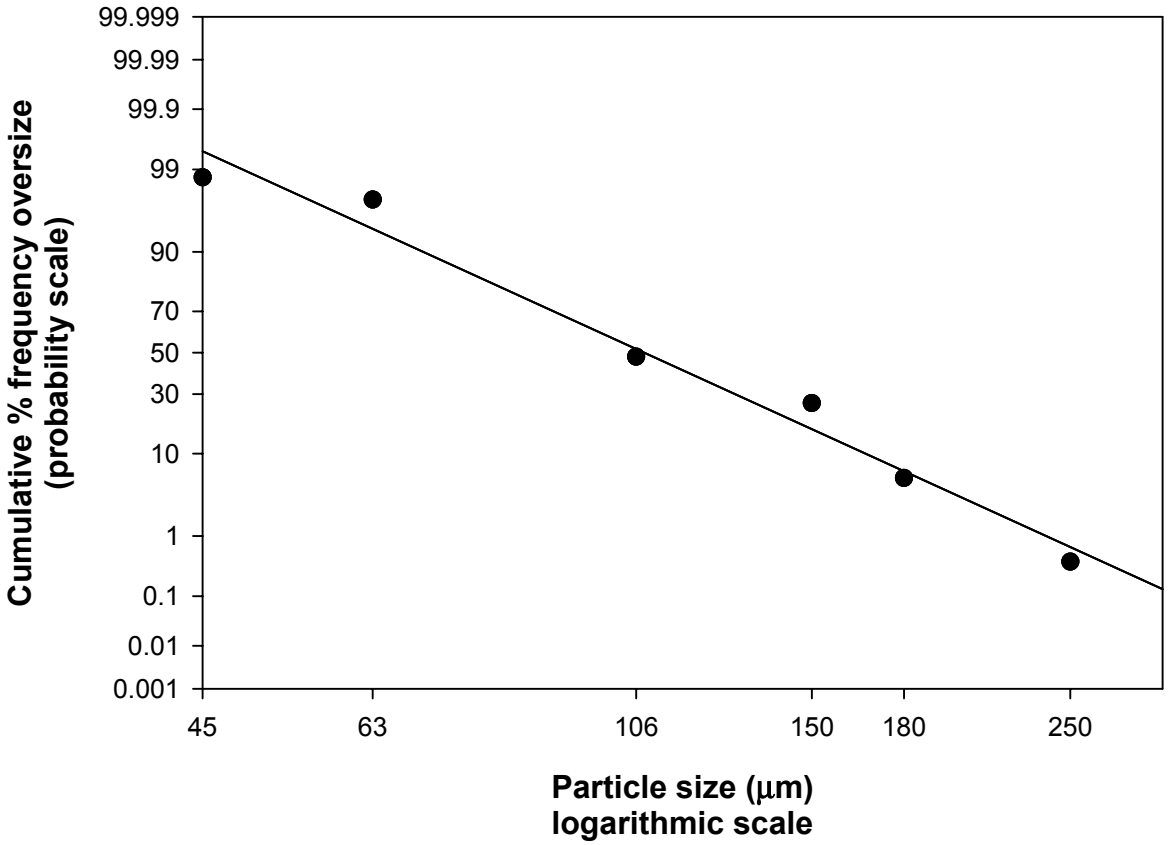

Figure 4.3. Log-normal particle size distribution of microspheres prepared from 25 % Eudragit® RL 100 (P3/heavy mineral oil).

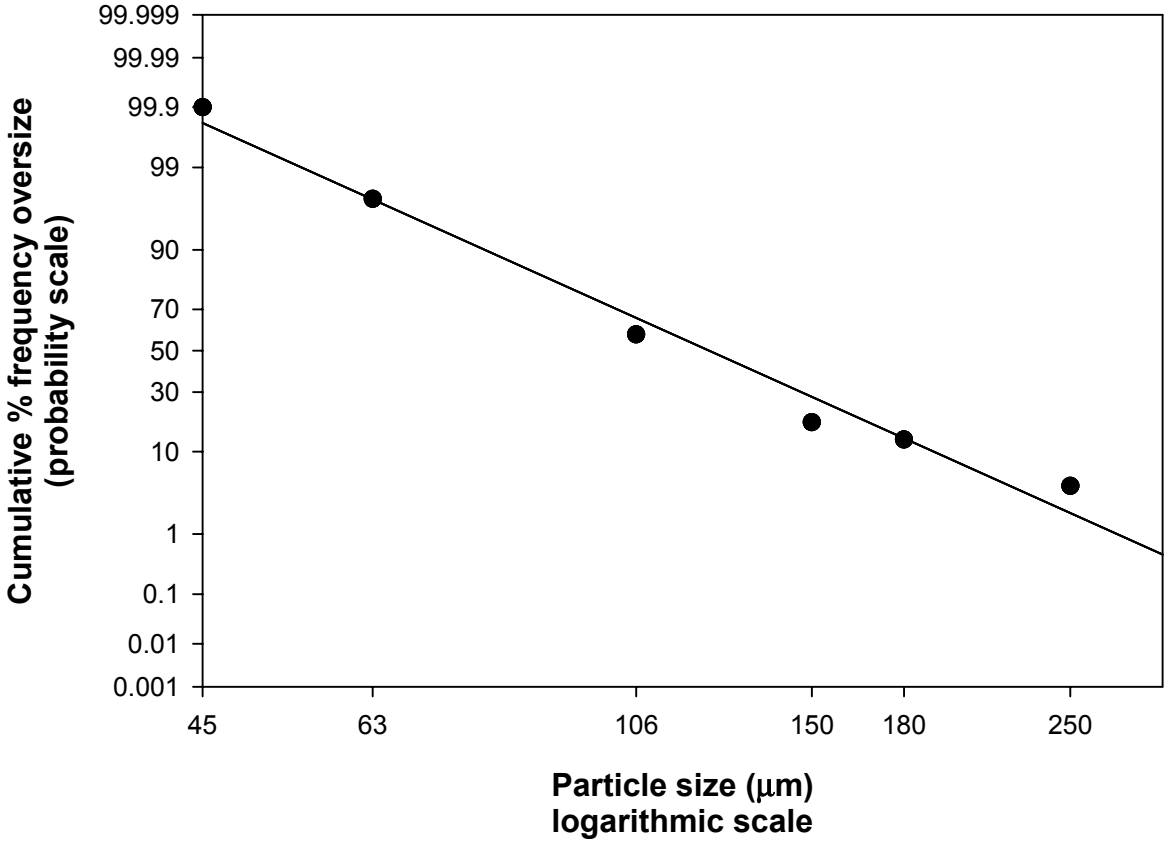

Figure 4.4. Log-normal particle size distribution of microspheres prepared from 25 % Eudragit® RL 100 (LMP3/light mineral oil).

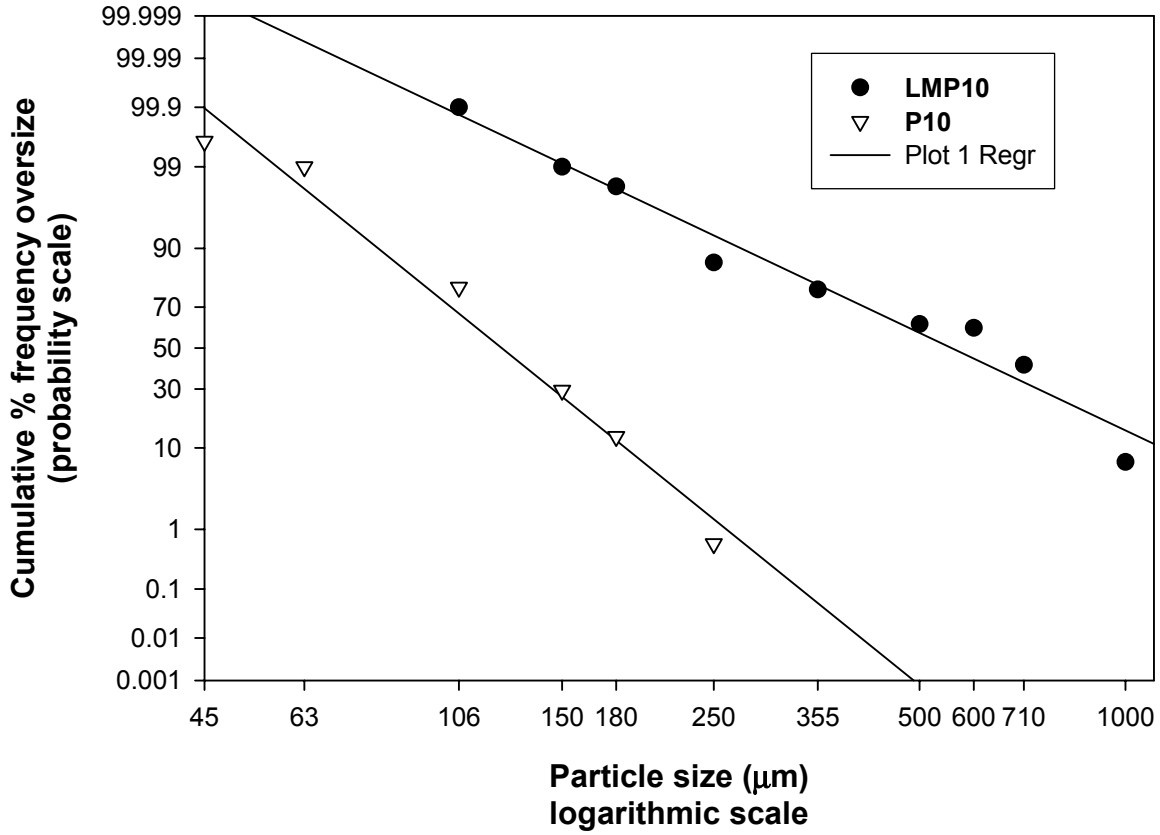

Figure 4.5. Log-normal particle size distribution of microspheres prepared from 27 % Eudragit® RS 100 (LMP10/light mineral oil, P10/heavy mineral oil).

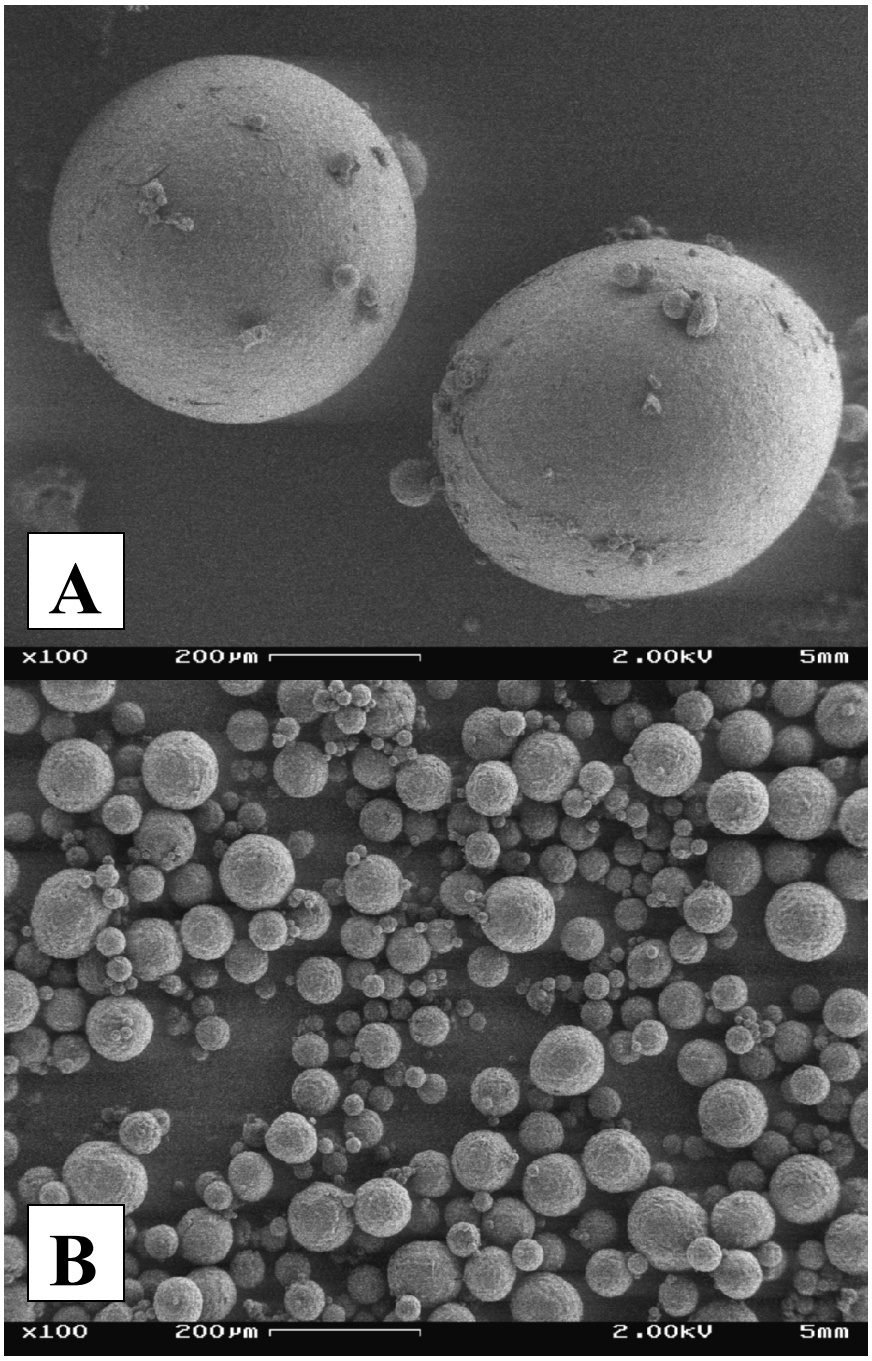

Figure 4.6. Microspheres prepared from 27 % Eudragit® RS 100 in acetone: (A) 600-710 µm (light mineral oil), (B) 180-250 µm (heavy mineral oil).

why the microspheres from most of these preparations released most of the drug in less than 1 hour. For one, aggregates of small particles was quite prevalent in light and heavy mineral oil preparations; especially at polymer concentrations less than or equal to 25 %. This crowding of particles increased the dissolution of drug because it essentially increased the surface area available to the dissolution; free drug was also commonly found in theses preparations, especially at the lower concentrations. This definitely could have contributed to rapid release of drug because there was no barrier to control the rate of release. In addition, smaller particle sizes were typical of these formulations (≤ 25 % polymer concentrations). In general, with smaller particle sizes, the release is usually faster. This is because there is an inverse relationship between the surface area of microspheres and the statistical diameter (for nonporous, smooth, and spherical microcapsules). Another potential reason for the immediate release behavior of these microspheres is that the polymer phase viscosity was not viscous enough to prevent the loss of drug. It is thought that as you increase the polymer phase viscosity the drug would be held firmly inside the microsphere and the release of drug is slowed. However, it is possible that during the emulsification process that the polymer phase viscosity was unable to inhibit the migration of drug to the surface of the microspheres, and therefore the drug was more prevalent in this area and readily available for dissolution. Nevertheless, at the highest polymer concentrations of 27 % with light mineral oil as the external phase, release was slower in comparison to the ≤ 25 % polymer concentrations (see Figures 4.8 and 4.9). However, at the smaller particle sizes of 27 % Eudragit® RL 100, the release was relatively the same as the other concentrations in acetone. Nonetheless, the release was slower as the particle size increased, which is typical with larger particle sizes. Also, the slower release of the 27 % polymer concentrations may be attributed to having the highest polymer phase viscosities. The polymer

phase viscosity of these concentrations was more effective in prohibiting drug migration to the surface of microsphere during the emulsification process.

When comparing microspheres from the two best release situations in this study (27 % Eudragit® RL 100 and 27 % Eudragit® RS 100 in light mineral oil), the release was more pronounced from microspheres prepared from 27 % Eudragit® RL 100 as depicted in Figures 4.10 and 4.11 at different size fractions of 180 μm, 250 μm, 355 μm, and 600 μm. Despite having a significantly higher apparent viscosity in acetone than 27 % Eudragit® RS 100 (41.2 cps to 15 cps), the release was still significantly faster. The obvious reason for this discrepancy in release behavior is that Eudragit® RL 100 has more permeability than Eudragit® RS 100. However, it was thought that with Eudragit® RL 100 having a substantially higher polymer phase viscosity (in addition to basically the same molecular weight and chemical structure) that the difference in release profiles at similar size fractions would not be as large as the results indicated. Nevertheless, there was another contributing factor to the significant disparity in release behavior between the two polymers. Microscopic observations indicated the presence of aggregates that in some instances completely covered microspheres prepared from Eudragit® RL 100, which was not as prevalent in those formulated from Eudragit® RS 100 (see Figure 4.12). Combining the fact that Eudragit® RL 100 is already a highly permeable membrane, with the addition of numerous aggregates that effectively increased the surface area available to the dissolution media, it is understandable why the release from Eudragit® RL 100 microspheres was significantly faster in comparison to microsphere preparations from Eudragit® RS 100. Furthermore, the release profiles of microspheres prepared from 27 % Eudragit® RL 100 could not be described by the Higuchi spherical matrix model as indicated by low R^2 values of less than .28. However, dissolution rates of 27 % Eudragit® RS 100 microspheres exhibited a

release profile that could be described by the Higuchi spherical matrix model, but only at size fractions ≥ 355 μm (R^2 values were in the 90 percentile) (see Figure 4.13).

The effect of using different external phases, on release kinetics was not factor at Eudragit® polymer concentrations ≤ 25 %. It was thought that by formulating microspheres at a lower theoretical drug loading (33.3 %) in light mineral (as opposed to 40 % in heavy mineral oil as in the previous formulations), that there would be some difference in the release profile. However, for particle size fractions of similar size (63 μm and 106 μm) the release was exactly the same in both light mineral oil and heavy mineral oil. Typically, for microspheres of the same size, the ones with the higher drug loading release drug at a faster rate; but, in this study a difference of 6.7 % in theoretical drug content wasn't much of factor because the release was still immediate for most of the Eudragit® polymer concentrations, regardless of what external phase was used. Nonetheless, at the highest concentrations of Eudragit® polymers (27 %) the type of external phase used in the preparation of microspheres did have an influence on dissolution rates, in a sense that light mineral oil formulations effectively increased the size of the particles, as well as the range of particle sizes (63 μm to greater than 1000 μm). Eudragit® polymer concentrations of 27 % that utilized heavy mineral oil produced smaller particles and a smaller particle size range (63-250 μm), in comparison to light mineral oil preparations of the same concentration (see Figures 4.7-4.9). As stated earlier, larger particle sizes tend to promote slower release of drug than smaller particle sizes. This is typically due to less surface area available to the dissolution. Moreover, although the dissolution profile of 27 % Eudragit® RL 100 in light mineral oil was an improvement over of the dissolution profile of 27 % Eudragit® RL 100 in heavy mineral oil, the release behavior in either situation was not very good. The dissolution profile of 27 % Eudragit® RS 100 (light mineral oil) demonstrated the best release

behavior out of all the matrix microsphere formulations. Microspheres prepared from 27 % Eudragit® RS 100 using light mineral oil was the only formulation to show a linear relationship between the square of particle diameter and the T50 % (the time at which 50 % of the drug is released) as illustrated in Fig. 4.14 (R^2 = .95).

Effect of incorporating a hydrophobic polymer (ETHOCEL® 100) with a highly permeable polymer (Eudragit® RL 100) on microsphere properties

Viscosity determinations – ETHOCEL® 100 was combined with Eudragit® RL 100 to form total polymer solutions of 8 %, 10 %, 12 %, and 14 % in acetone (polymer ratio is 1:1). The apparent viscosity of each concentration is given in Table 4.9. In Figure 4.15 the relation between apparent viscosity and the concentration of the polymer solutions is shown. As expected the apparent viscosity increased with increase in polymer concentrations. It is evident that the addition of ETHOCEL® 100 caused a considerable increase in the apparent viscosity of the polymer phase. Previously, using solely Eudragit® RL 100 in acetone, in order to produce a polymer phase of sufficient viscosity, high concentrations of the polymer had to be dissolved into the solvent. The addition of ETHOCEL® 100 with Eudragit® RL 100 allows for lower concentrations and substantially higher viscosities, in comparison to using Eudragit® RL 100 as the lone polymer agent in acetone. Furthermore, in comparing the 10 % Eudragit® RL 100/ ETHOCEL® 100 polymer concentration and the 10 % Eudragit® RL 100 polymer concentration, there is a very large disparity in the apparent viscosities (113 cps to1.92 cps) (see Table 4.4 and 4.9). The significant difference in viscosity is more than likely due to the higher molecular weight of ETHOCEL® 100 (218,300-223,200) and perhaps other molecular characteristics.

Table 4.6. Drug contents of different size fractions of theophylline microspheres prepared using Eudragit® RS 100 in acetone (heavy mineral oil: theoretical drug loading = 40 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (µm)**	**Drug content (%) ± Std Dev**
10 % ERS 100	63-106	34 ± 1.00
	≤ 63	28 ± 0.00
20 % ERS 100	106-150	38 ± 0.58
	63-106	39 ± 0.58
	45-63	38 ± 1.73
	≤ 45	32 ± 1.53
23 % ERS100	180-250	38 ± 1.53
	150-180	38 ± 1.00
	106-150	40 ± 1.53
	63-106	38 ± 1.15
25 % ERS 100	180-250	37 ± 2.08
	150-180	34 ± 1.15
	106-150	34 ± 0.58
	63-106	33 ± 2.65
27 % ERS 100	180-250	38 ± 1.53
	150-180	35 ± 2.52
	106-150	36 ± 2.52
	63-106	31 ± 5.51

Table 4.7. Drug contents of different size fractions of theophylline microspheres prepared using Eudragit® RL 100 in acetone (heavy mineral oil: theoretical drug loading = 40 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (μm)**	**Drug content (%) ± Std Dev**
10 % ERL 100	63-106	33 ± 1.53
20 % ERL 100	150-180	35 ± 2.08
	106-150	38 ± 1.15
	63-106	36 ± 2.52
23 % ERL 100	250-355	39 ± 2.08
	180-250	38 ± 2.08
	150-180	39 ± 2.00
	106-150	36 ± 1.00
	63-106	39 ± 1.15
25 % ERL 100	180-250	31 ± 3.21
	150-180	33 ± 1.53
	106-150	30 ± 6.03
	63-106	27 ± 3.21
27 % ERL 100	250-355	35 ± 6.03
	180-250	35 ± 6.25
	150-180	38 ± 2.65
	106-150	25 ± 5.51
	63-106	31 ± 3.21

Table 4.8. Drug contents of different size fractions of theophylline microspheres prepared using Eudragit® RL 100 and Eudragit® RS 100 in acetone (light mineral oil: theoretical drug loading = 33.3 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (μm)**	**Drug content (%) ± Std Dev**
27 % ERS 100	710-1000	22 ± 1.15
	600-710	23 ± 0.58
	355-500	23 ± 1.00
	250-355	22 ± 2.00
	180-250	24 ± 1.53
	106-250	21 ± 1.00
27 % ERL 100	≥ 1000	26 ± 0.58
	710-1000	28 ± 1.00
	600-710	26 ± 0.00
	500-600	27 ± 1.15
	355-500	29 ± 4.62
	250-355	27 ± 1.15
	180-250	27 ± 0.58
	150-180	27 ± 2.52
	63-150	26 ± 0.58
25 % ERL 100	106-150	21 ± 2.65
	63-106	24 ± 1.53

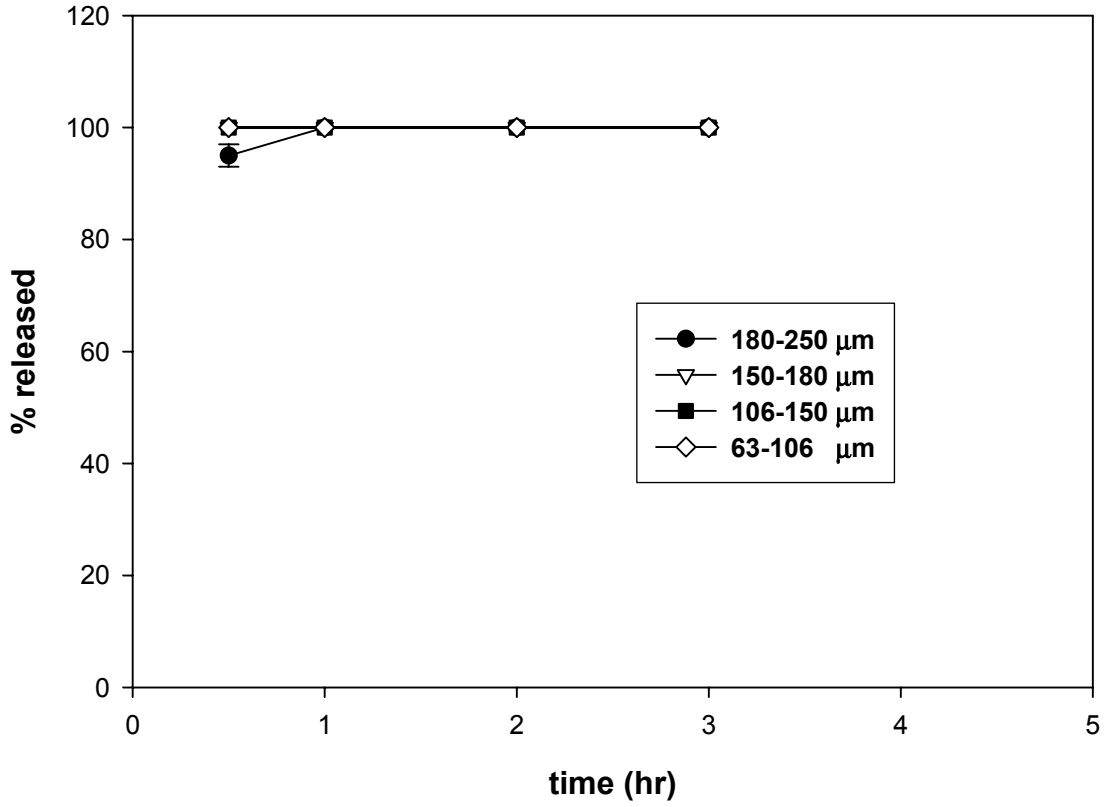

Figure 4.7. Release profiles of different size fractions of theophylline microspheres prepared using 27 % Eudragit® RS 100 in acetone (P10/heavy mineral oil: theoretical drug loading = 40 %).

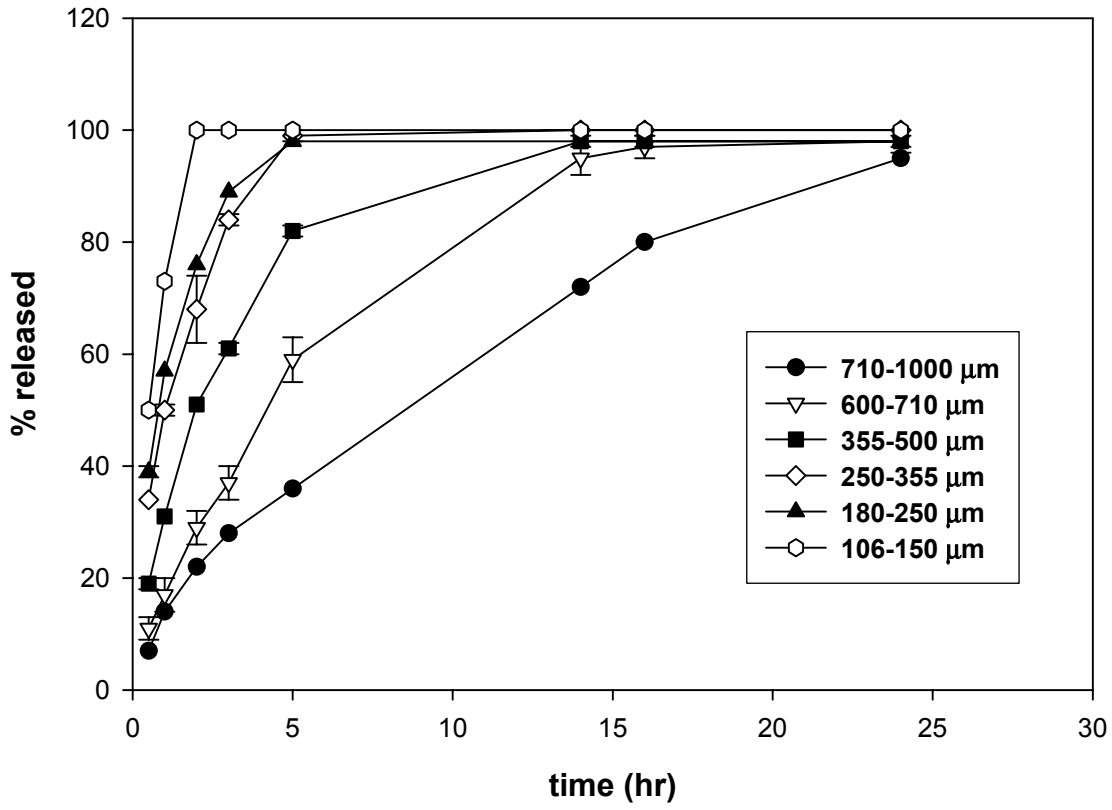

Figure 4.8. Release profiles of different size fractions of theophylline microspheres prepared using 27 % Eudragit® RS 100 in acetone (LMP10/light mineral oil: theoretical drug loading = 33.3 %).

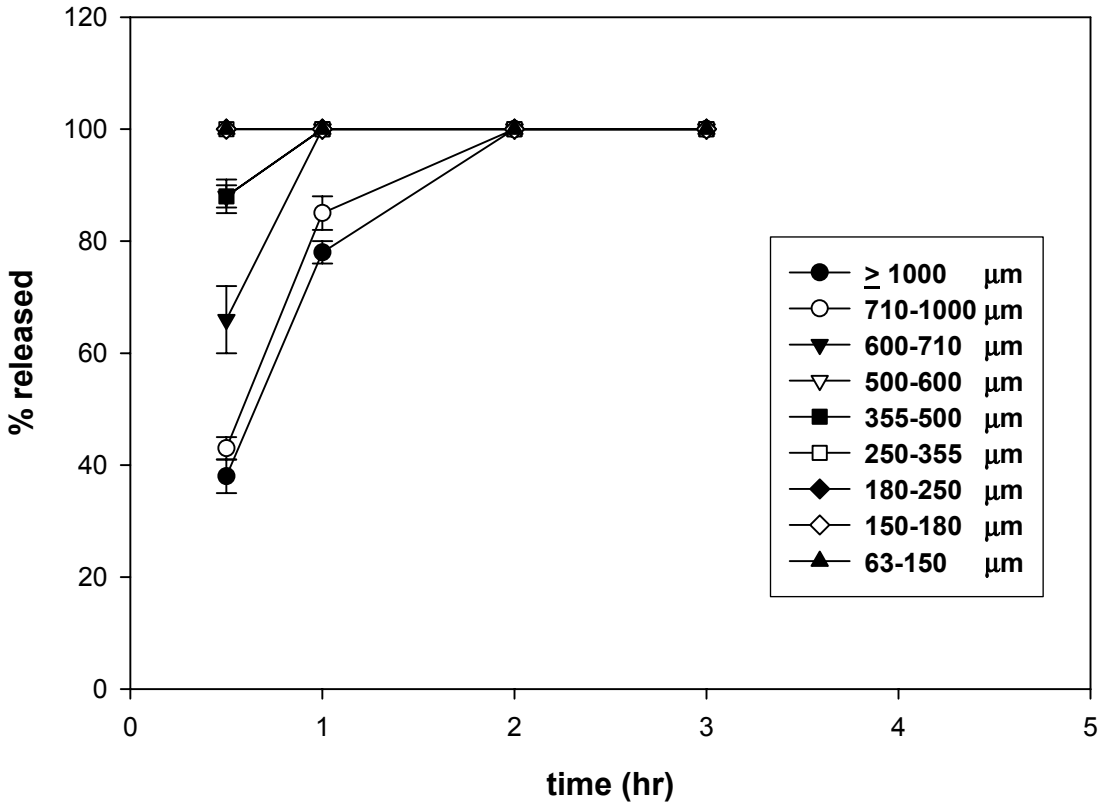

Figure 4.9. Release profiles of different size fractions of theophylline microspheres prepared using 27 % Eudragit® RL 100 in acetone (LMP9/light mineral oil: theoretical drug loading = 33.3 %).

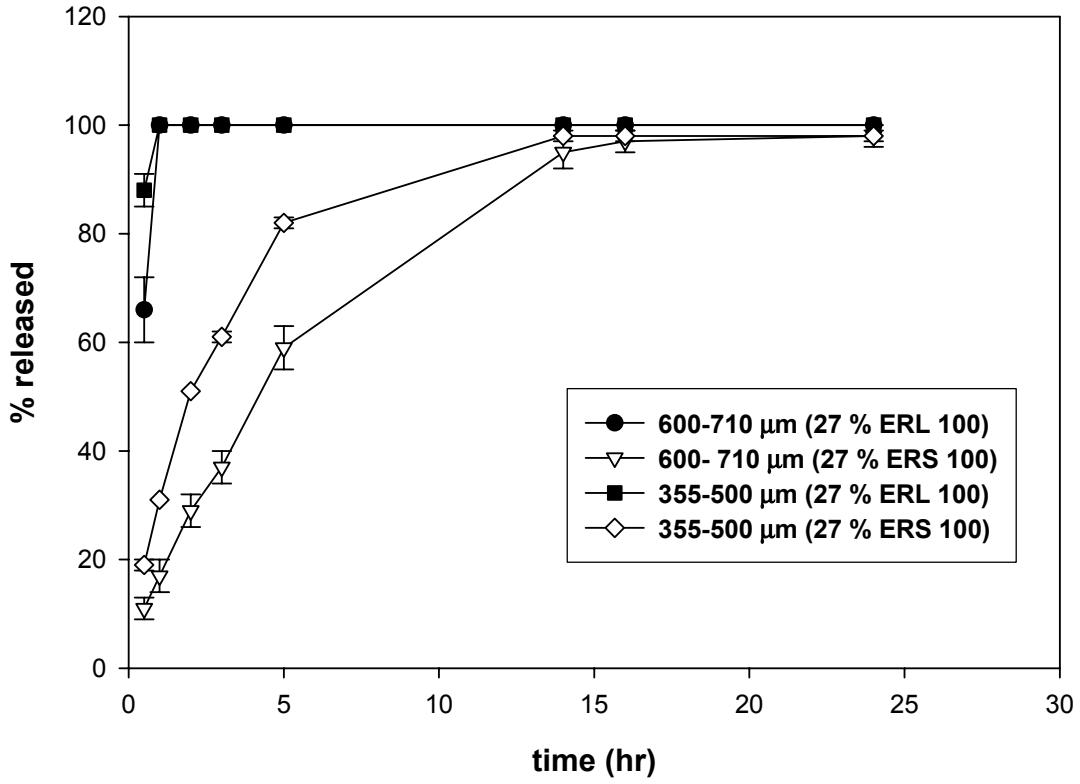

Figure 4.10. Release profiles of different size fractions of theophylline microspheres prepared using similar concentrations and molecular weights of Eudragit® polymers [Eudragit® RL 100 (ERL 100), Eudragit® RS 100 (ERS 100)] with respective viscosities (41.2 cps, 15.0 cps).

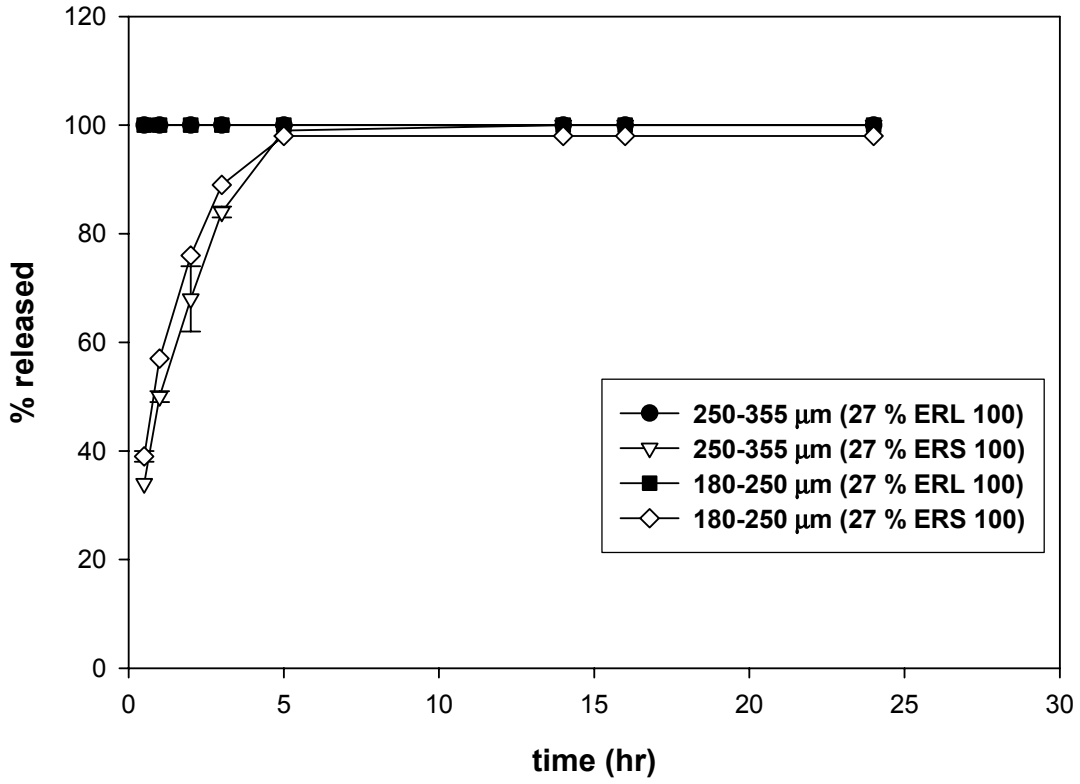

Figure 4.11. Release profiles of different size fractions of theophylline microspheres prepared using similar concentrations and molecular weights of Eudragit® polymers [Eudragit® RL 100 (ERL 100), Eudragit® RS 100 (ERS 100)] with respective viscosities (41.2 cps, 15.0 cps).

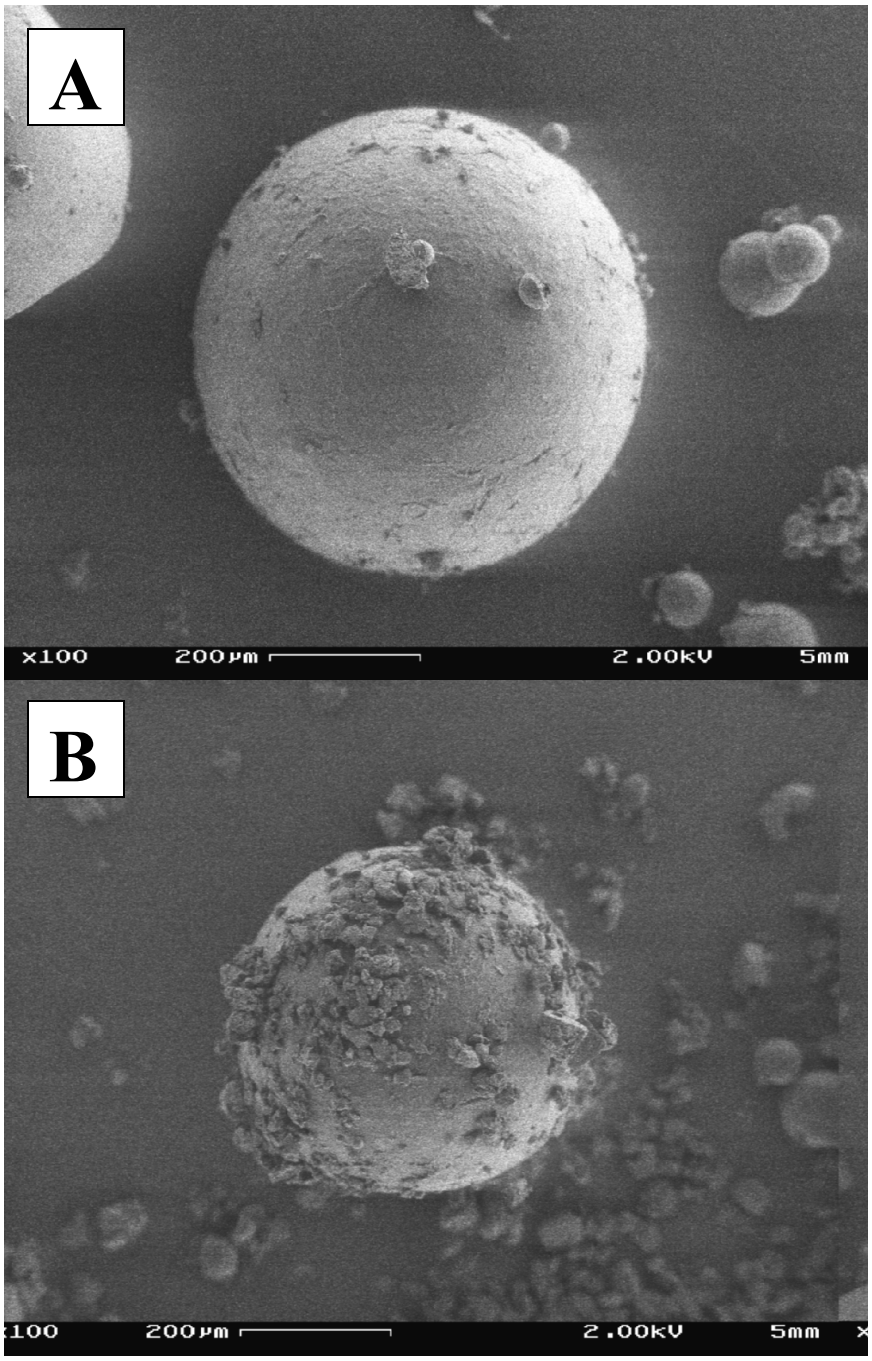

Figure 4.12. Microspheres of size fraction 600 µm prepared from 27 % Eudragit® polymer concentrations using light mineral oil as the external phase: (A) Eudragit® RS 100, (B) Eudragit® RL 100.

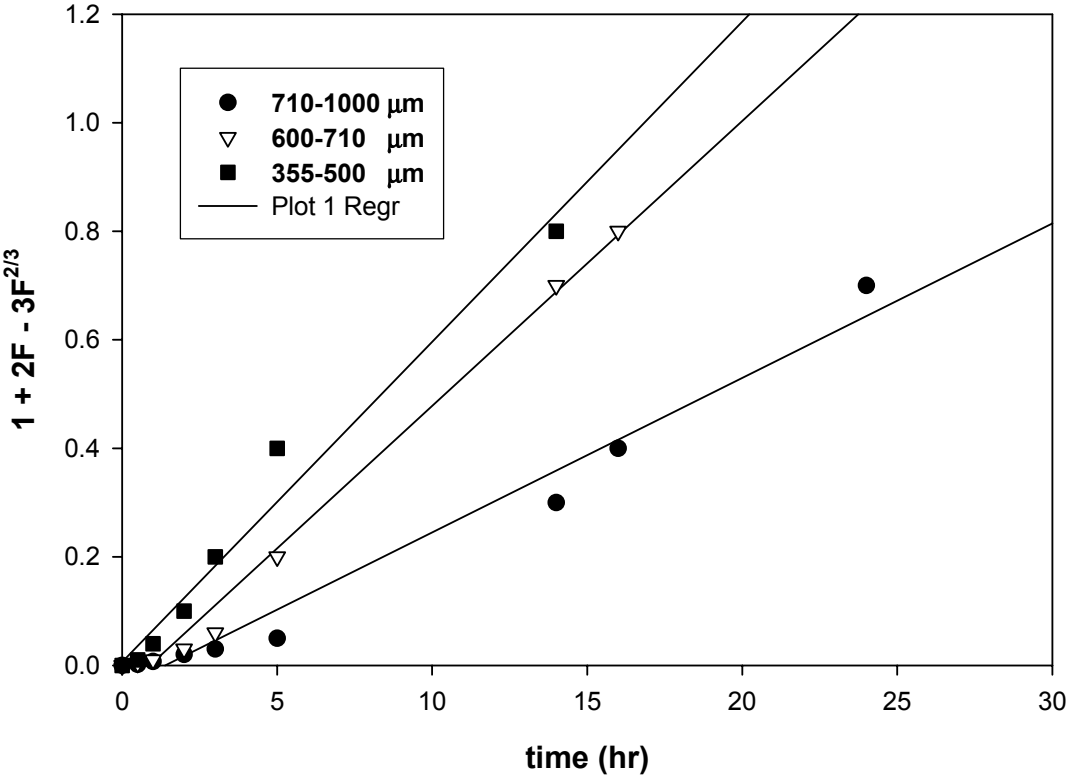

Figure 4.13. Higuchi plots for dissolution of different size fractions of theophylline microspheres prepared from 27 % Eudragit® RS 100 in acetone (light mineral oil).

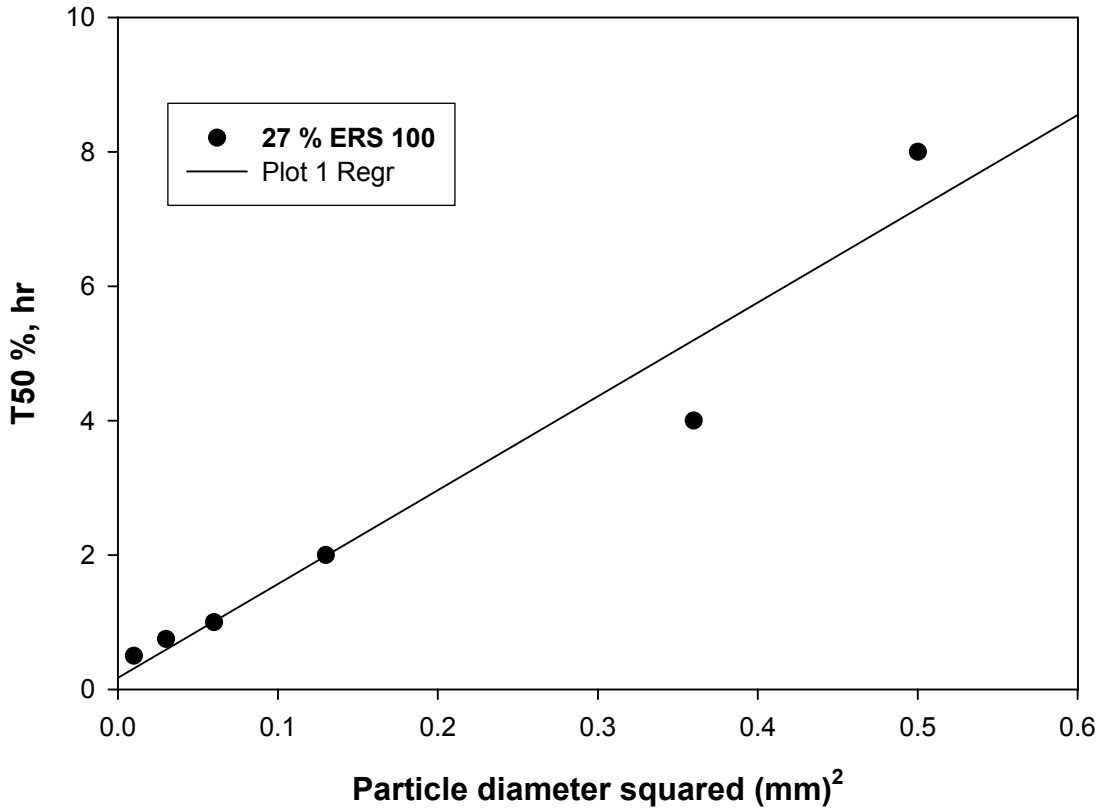

Figure 4.14. The relation between T50 % and the square of the microsphere diameter prepared from 27 % Eudragit® RS 100 polymer (light mineral oil).

Particle size distribution – The same method to control the particle size distribution of Eudragit® polymer microspheres prepared by emulsion-solvent evaporation was employed for microspheres prepared from Eudragit® RL 100/ ETHOCEL® 100 (altering the agitation intensity during the emulsification process). As the concentration of the polymer solution phase increased, the stirring speed was increased; these adjustments were made in both light and heavy mineral oil preparations (see Table 4.3). In light mineral oil preparations, altering the agitation yielded similar particle size distributions (45-1000 μm), while heavy mineral oil preparations did not. Instead, the increase in agitation intensity with increase in polymer concentration resulted in a wider range of particle sizes (45-710 μm at 14 %). Concentrations of 8 % and 10 % Eudragit® RL 100/ ETHOCEL®100 in acetone had relatively small particle size ranges (45-180 μm), but at concentrations of 12 % and higher, the particle size range increased. In the Eudragit® polymer study, heavy mineral oil preparations generally yielded smaller particle size ranges due to the aggregation of small particles during the emulsification process that were not recovered. However, these results suggest that larger particle sizes, as well as a wider particle size range can be achieved under the proper conditions using a (1:1) combination of Eudragit® RL 100/ ETHOCEL® 100; the proper conditions being a high viscosity polymer phase stirred at high rpm. The increase in particle size range in heavy mineral oil preparations of Eudragit® RL 100/ ETHOCEL® 100 is probably attributed to the high apparent viscosities of the polymer phase and the high speed at which agitation occurs. Thus, it is believed that combination of relatively high polymer phase viscosity and high agitation intensity contributed to a good mixing between the polymer phase and the continuous oil phase resulting in an extensive range of particle sizes. The increase in particle size distribution of microspheres prepared from 8 %, 10 %, 12 %, and 14 % concentrations of Eudragit® RL 100/ ETHOCEL® 100 polymers in acetone

using heavy mineral oil as the external phase is clearly shown in Figures 4.16-4.19 (log probability plots); the typical log-probability plot of the particle size distribution of microspheres prepared from 8 %, 10 %, 12 %, and 14 % concentrations of Eudragit® RL 100/ ETHOCEL®100 polymers in acetone using light mineral oil as the external phase is depicted in Figure 4.20. Geometric mean and geometric standard deviations are given in Table 4.10. The size distributions of the microspheres, in light or heavy mineral oil preparations, were generally narrow as indicated by the geometric standard deviations calculated from 50 % oversize/ 84 % oversize (see Table 4.10).

Larger particle sizes and a wider particle size range were generally favored in microsphere formulations using light mineral oil as the external phase. This is attributed to light mineral oil being more soluble in acetone than in heavy mineral oil, causing the acetone in the emulsion globules to go into the light mineral oil rapidly and the quick formation of a gelled-matrices resulting in a wide range of particle sizes. However, at the highest concentration of 14 % using heavy mineral oil, the particle size distribution was comparable to the 14 % concentration prepared with light mineral oil, in that larger particle sizes were produced as well as an extensive range of microspheres of various sizes (see Figures 4.21-4.22). Nevertheless, as indicated in Table 4.10, using light mineral oil as the external phase usually results in larger microsphere sizes.

Drug loading – Tables 4.11 and 4.12 show the drug content of microspheres with a theoretical drug loading of 33.3 % calculated from the weight of drug and polymers (the ratio of weights of theophylline: Eudragit® RL 100/ ETHOCEL® 100 was 1:2) in light and heavy mineral oil preparations. Drug content was determined for only the 8 % and 10 % Eudragit® RL

100/ ETHOCEL® 100 concentrations. For each concentration, there was not much variability in drug loading, especially in the light mineral oil preparations.

Dissolution characteristics - Dissolution profiles of different size fractions of theophylline microspheres prepared from 8 % and 10 % concentrations of Eudragit® RL 100/ ETHOCEL® 100 are shown in Figures 4.23-4.26 (light and heavy mineral oil preparations). In the 8 % and 10 % concentrations prepared using light mineral oil as the external phase, the fastest release from microspheres was observed at the smaller particle sizes (see Figures 4.24 and 4.26). However, this wasn't entirely true at the 8 % polymer phase concentration. At this concentration, the largest size fraction (600 μm) exhibited faster release than smaller particle sizes of 180 –355 μm. In contrast, the largest size fractions (600 μm and 710 μm) prepared from 10 % polymer phase concentration had the slowest release among the size fractions. Furthermore, at a fraction size of 600 μm, the release from the 10 % concentration was significantly slower than the 8 % concentration (see Figure 4.27). This may be attributed to the higher polymer phase viscosity of the 10 % concentration (see Table 4.9) potentially holding drug more firmly within the microsphere and inhibiting the migration of drug particles to the microsphere surface, which would essentially slow the diffusion of drug and lower the initial release. In addition, the release was faster for 600 μm size fractions from the 8 % concentration because of the presence of aggregates of small particles and hollow shell-like particles; at the 10 % concentration, little or no aggregation was detected (see Figure 4.28). However, at particle sizes less than 600 μm, the release was substantially higher from the 10 % polymer phase concentration in comparison to the 8 % polymer phase concentration; this is shown in Figures 4.29-4.31. Typically, an increase in the polymer (organic) phase viscosity tends to promote the slower drug release; but in this particular situation, the effect of the viscosity was negated by the presence of thin rod-like

structures that consisted mostly of drug and very little polymer to act as a barrier to retard the release. These drug filaments were probably formed from polymer phase droplets with suspended drug that became elongated and the solvent completely evaporated before it regained its original shape. They were readily accessible to the dissolution and the release was faster due to the increase in surface area. Although there were some aggregates of small particles in the 8 % polymer phase concentration, these rod-like filaments were not detected in this same concentration (see Figure 4.32). Release from the larger particle sizes of the 10 % polymer phase concentration was probably not affected by these rod-like structures because during the sieving process they fell down to the bottommost sieves. Nevertheless, dissolution rates of smaller size fractions of 8 % Eudragit® RL 100/ ETHOCEL® 100 microspheres (< 600 μm), and larger size fractions of 10 % Eudragit® RL 100/ ETHOCEL® 100 microspheres (≥ 600 μm,) could be described by the Higuchi spherical matrix model as displayed in Figures 4.33-4.36.

In the dissolution profiles of 8 % and 10 % Eudragit® RL 100/ ETHOCEL® 100 concentrations using heavy mineral oil as the external phase, 8 % polymer phase concentration exhibited the slower release rates for size fractions 106-180 μm (see Figure 4.37). However, in a similar manner to 8 % polymer phase concentration prepared with light mineral oil, the largest particle size did not have the slowest release (due to aggregates of small particles and hollow shell-like particles). Nonetheless, the release behavior of the other particles was as expected (the smallest size had the fastest release). For 10 % polymer phase concentration, the release was not normal. As the particle size decreased, the rate of release decrease (this was definitely evident in the first three hours of dissolution). Despite the presence of some aggregates and hollow shell-like particles in the 8 % polymer phase concentration, they were more prevalent in the 10 % polymer phase concentration and therefore contributed to faster release at the larger particle sizes

(see Figure 4.38); as in the light mineral oil preparations, the effect of viscosity on drug release was insignificant. Release profiles from 8 % Eudragit® RL 100/ ETHOCEL® 100 microspheres could be described by the Higuchi spherical matrix model as shown in Figure 4.39 (R^2 values .97 and higher). For 10 % Eudragit® RL 100/ ETHOCEL® 100 microspheres, release profiles of 63 μm size fractions were best described by this model (see Figure 4.40).

The dissolution profiles of size fractions of 63 μm, 106 μm, 150 μm, and 180 μm microspheres prepared from 8 % and 10 % Eudragit® RL 100/ ETHOCEL® 100 polymer concentrations using light mineral oil, were compared to release profiles of similar size fractions of microspheres prepared with heavy mineral oil. For the 10 % polymer phase concentration, release was slower in the heavy mineral oil preparations (see Figure 4.41). The faster release in the light mineral oil preparations is probably a result of the rod-like structures depicted in Figure 4.32. In the 8 % polymer phase concentration, release was only slower at the largest particle size (180 μm) for light mineral oil preparations as shown in Figure 4.42; from 63-150 μm, the release was slower for heavy mineral oil preparations (see Figure 4.43). The faster release that is exhibited in both preparations (light and heavy mineral oil) could be attributed to the formation of aggregates of smaller particles, hollow shell-like particles, as well as some smaller particles attached to larger particles. Dissolution rates of the above mentioned size fractions of microspheres prepared from only 8 % Eudragit® RL 100/ ETHOCEL® 100 could be described by the Higuchi spherical matrix model for both heavy and light mineral oil preparations (see Figures 4.44 and 4.45).

Table 4.9. Apparent viscosities of different concentrations of Eudragit® RL 100 (ERL 100)/ETHOCEL® 100 (EC-100) (1:1) in acetone.

Formulation	**Concentration % w/w**	**Viscosity of polymer phase (cps) ± Std Dev**
M2 HM2	8 % ERL 100/EC-100	47.8 ± 0.00
M1 HM1	10 % ERL 100/ EC-100	113 ± 1.01
M3 HM3	12 % ERL 100/ EC-100	369 ± 4.51
M4 HM4	14 % ERL 100/ EC-100	630 ± 0.00

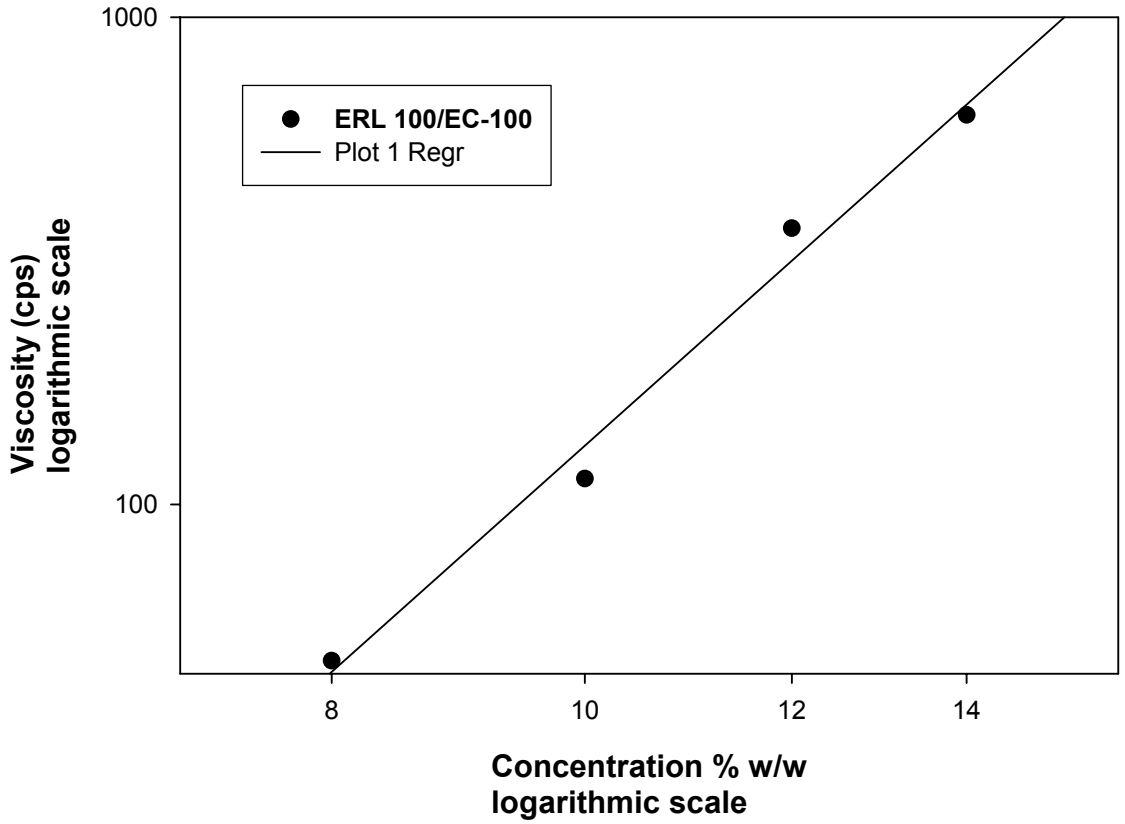

Figure 4.15. Apparent viscosities of different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) (1:1) in acetone.

Table 4.10. Particle size analysis of microspheres prepared using Eudragit® RL 100(ERL 100)/ ETHOCEL® 100 (EC-100) in acetone.

Polymer concentration in acetone (w/w)	**Geometric mean diameter (d_g) (µm)**	**Geometric standard deviation (σ_g)**	**External phase**
8 % ERL 100/EC-100	130	1.55	heavy mineral oil
8 % ERL 100/EC-100	240	1.60	light mineral oil
10 % ERL 100/EC-100	110	1.45	heavy mineral oil
10 % ERL 100/EC-100	270	1.69	light mineral oil
12 % ERL 100/EC-100	155	1.68	heavy mineral oil
12 % ERL 100/EC-100	260	1.73	light mineral oil
14 % ERL 100/EC-100	170	1.57	heavy mineral oil
14 % ERL 100/EC-100	245	1.63	light mineral oil

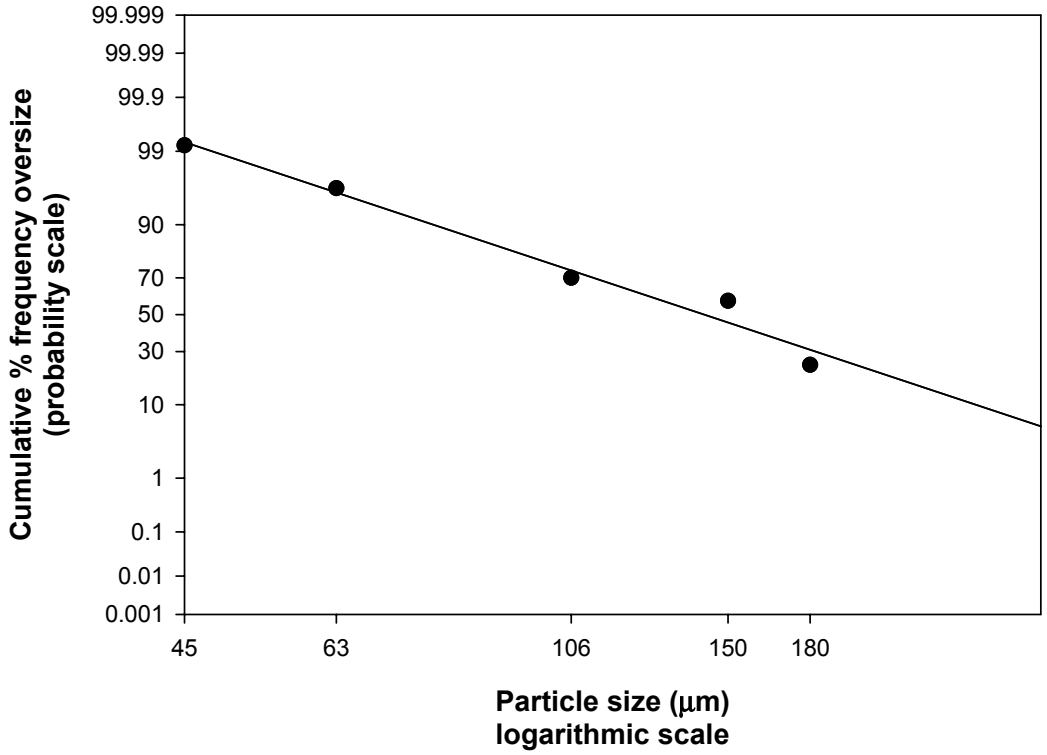

Figure 4.16. Log-normal particle size distribution of microspheres prepared from 8 % Eudragit® RL 100/ ETHOCEL® 100 (HM2/heavy mineral oil).

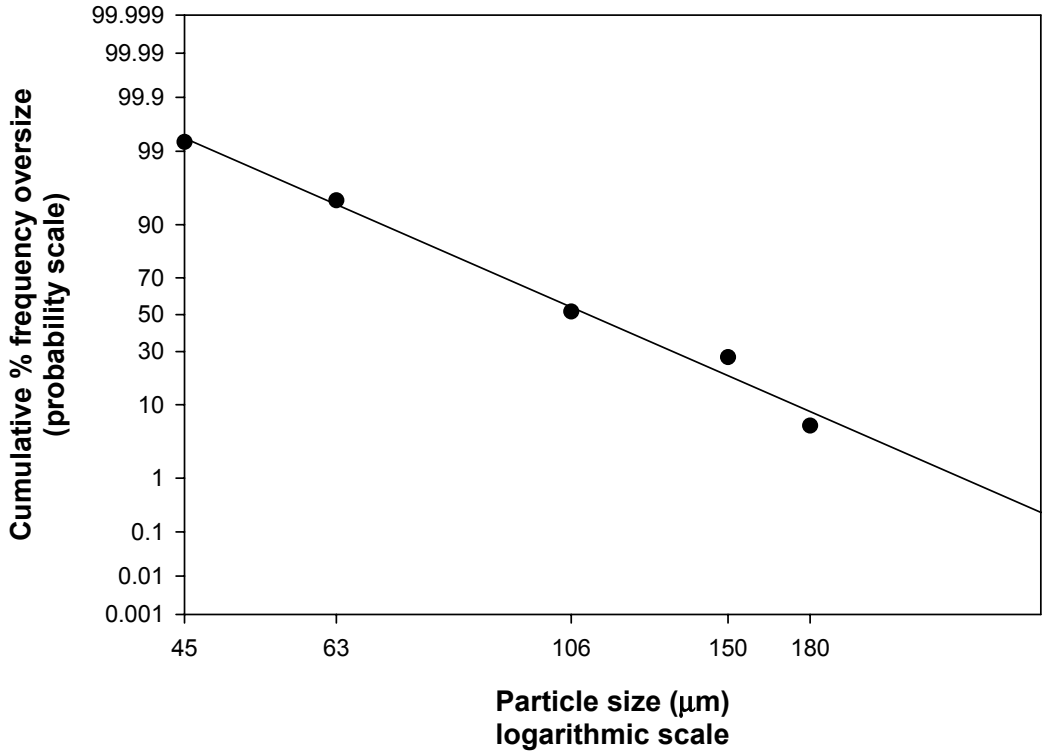

Figure 4.17. Log-normal particle size distribution of microspheres prepared from 10 % Eudragit® RL 100/ ETHOCEL® 100 (HM1/heavy mineral oil).

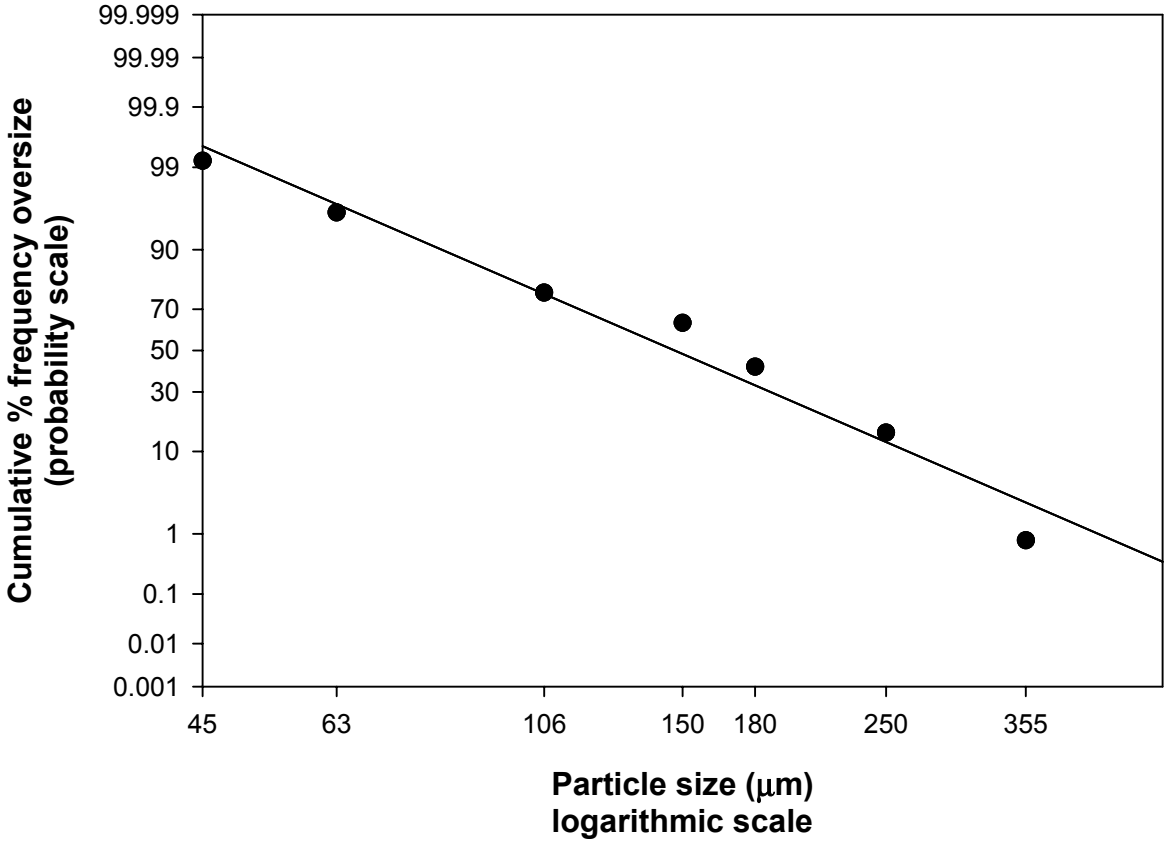

Figure 4.18. Log-normal particle size distribution of microspheres prepared from 12 % Eudragit® RL 100/ ETHOCEL® 100 (HM3/heavy mineral oil).

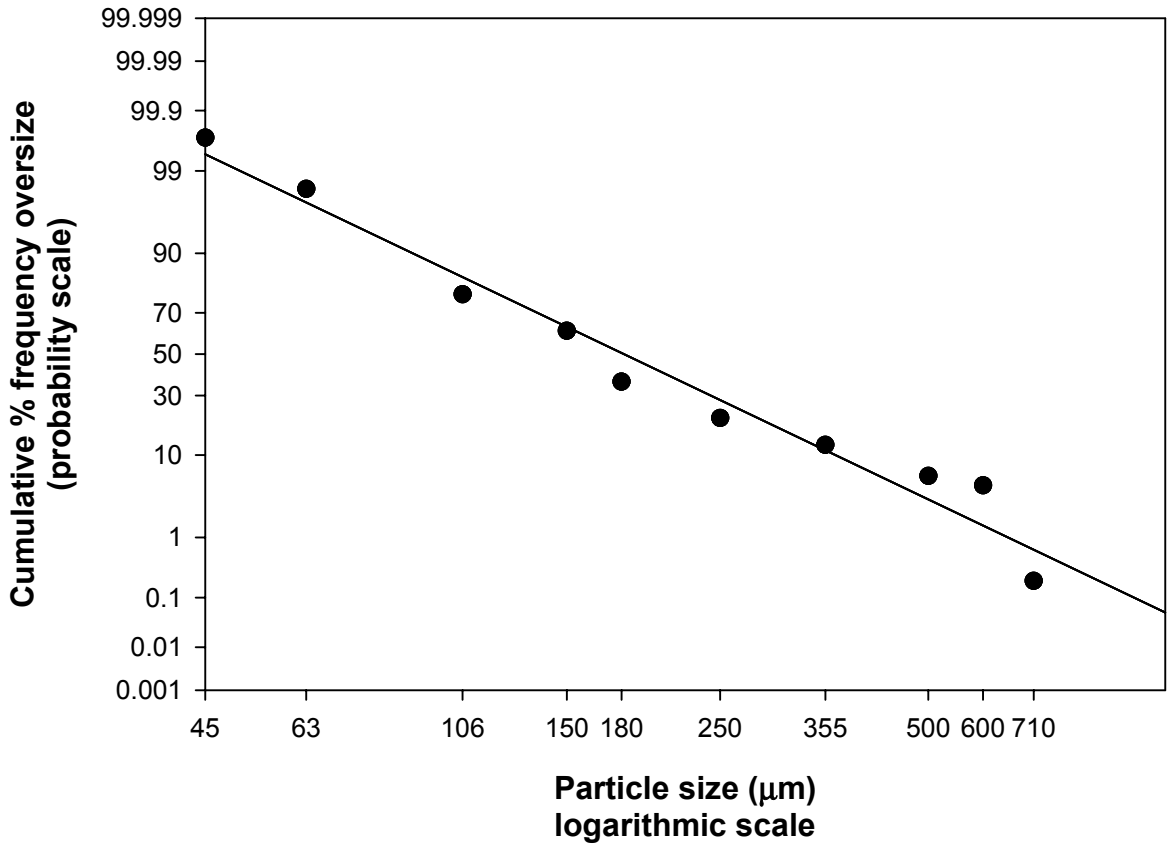

Figure 4.19. Log-normal particle size distribution of microspheres prepared from 14 % Eudragit® RL 100/ ETHOCEL® 100 (HM4/heavy mineral oil).

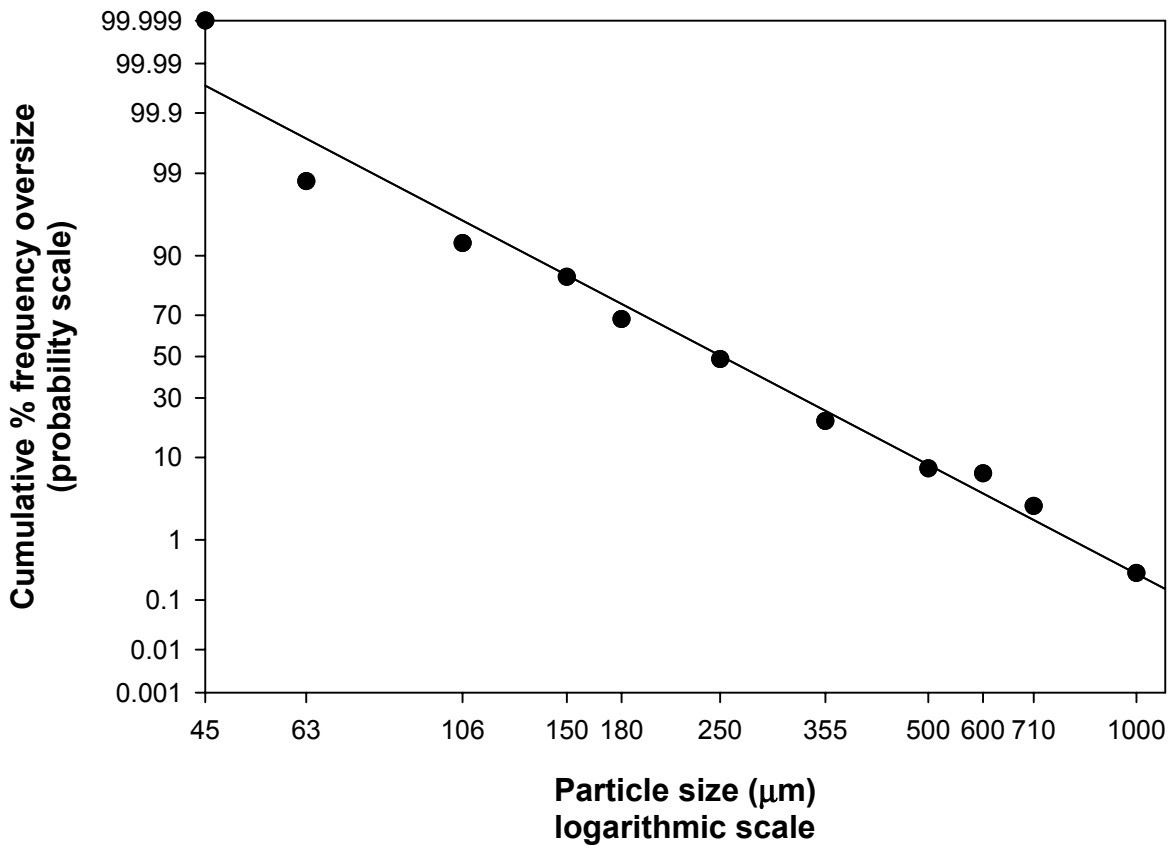

Figure 4.20. Log-normal particle size distribution of microspheres prepared from 14 % Eudragit® RL 100/ ETHOCEL® 100 (M4/light mineral oil).

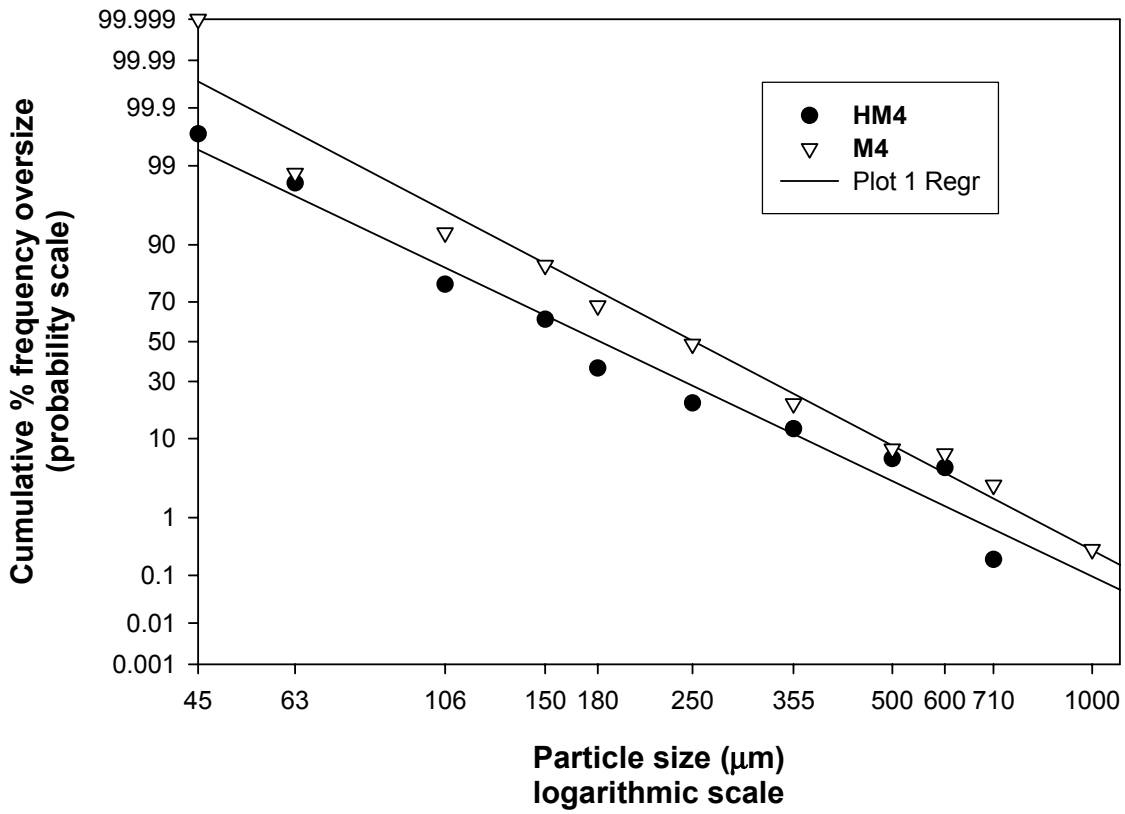

Figure 4.21. Log-normal particle size distribution of microspheres prepared from 14 % Eudragit® RL 100/ ETHOCEL® 100 (M4/light mineral oil, HM4/heavy mineral oil).

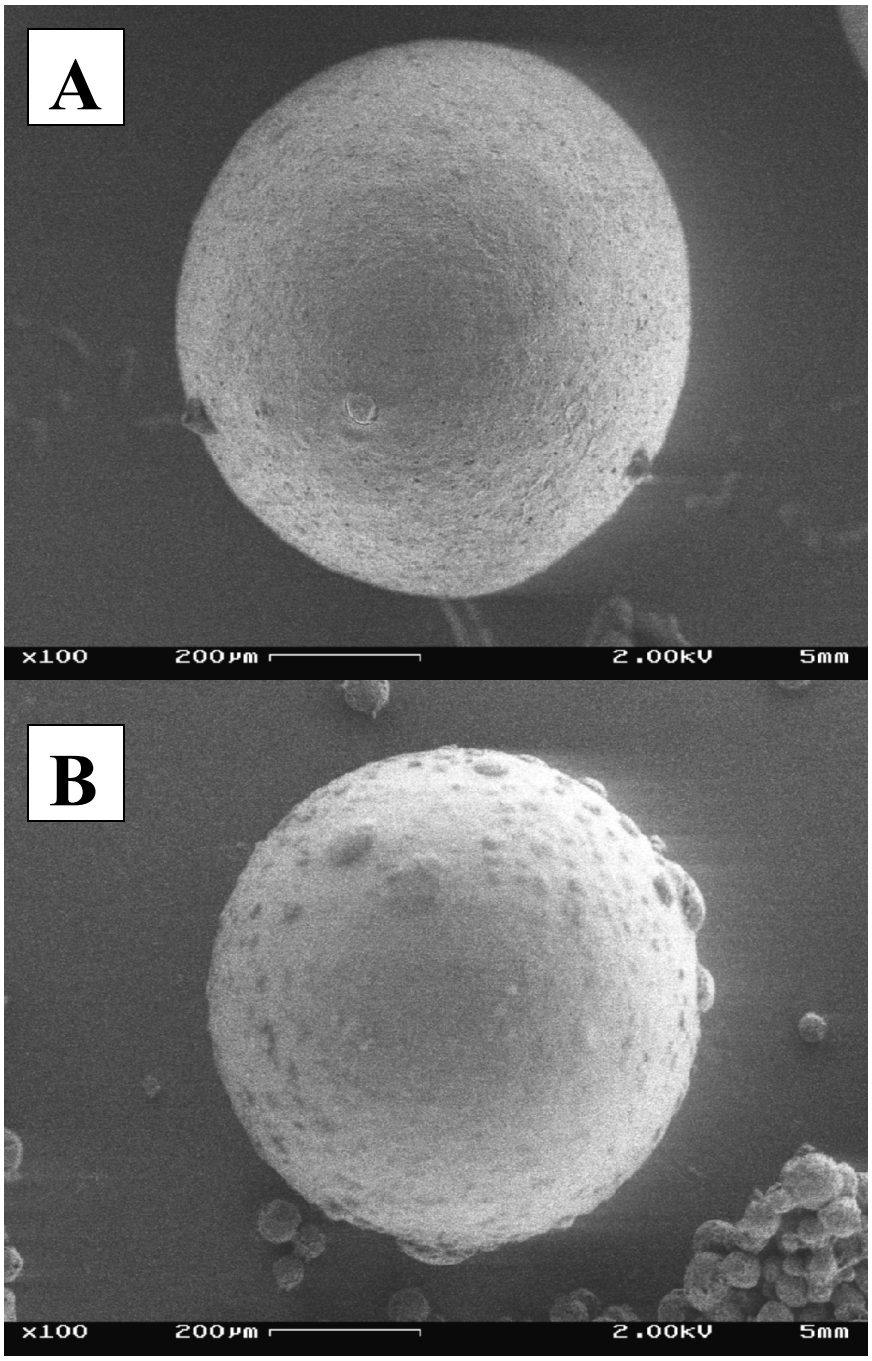

Figure 4.22. Microspheres prepared from 14 % Eudragit® RL 100/ ETHOCEL®100 polymer concentrations in acetone: (A) 600-710 µm (light mineral oil), (B) 600-710 µm (heavy mineral oil).

Table 4.11. Drug contents of different size fractions of theophylline microspheres prepared using Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (heavy mineral oil: theoretical drug loading = 33.3 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (μm)**	**Drug content (%) ± Std Dev**
8 % ERL 100/EC-100	180-250	24 ± 1.15
	150-180	25 ± 1.15
	106-150	23 ± 4.58
	63-106	21 ± 1.15
10 % ERL 100/EC-100	180-250	25 ± 1.15
	150-180	24 ± 0.58
	106-150	28 ± 0.00
	63-106	25 ± 3.06
	≤ 63	26 ± 2.08

Table 4.12. Drug contents of different size fractions of theophylline microspheres prepared using Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (light mineral oil: theoretical drug loading = 33.3 %).

Polymer concentration in acetone (w/w)	**Microsphere size range (μm)**	**Drug content (%) ± Std Dev**
8 % ERL 100/EC-100	600-710	28 ± 1.15
	500-600	29 ± 0.58
	355-500	28 ± 1.53
	250-355	27 ± 1.00
	180-250	27 ± 1.53
	150-180	27 ± 1.00
	106-150	29 ± 1.53
	63-106	28 ± 2.31
10 % ERL 100/EC-100	710-1000	26 ± 1.53
	600-710	27 ± 0.58
	355-500	26 ± 0.58
	250-355	26 ± 1.73
	180-250	28 ± 1.53
	150-180	28 ± 1.15
	106-150	27 ± 1.15
	63-106	26 ± 0.58

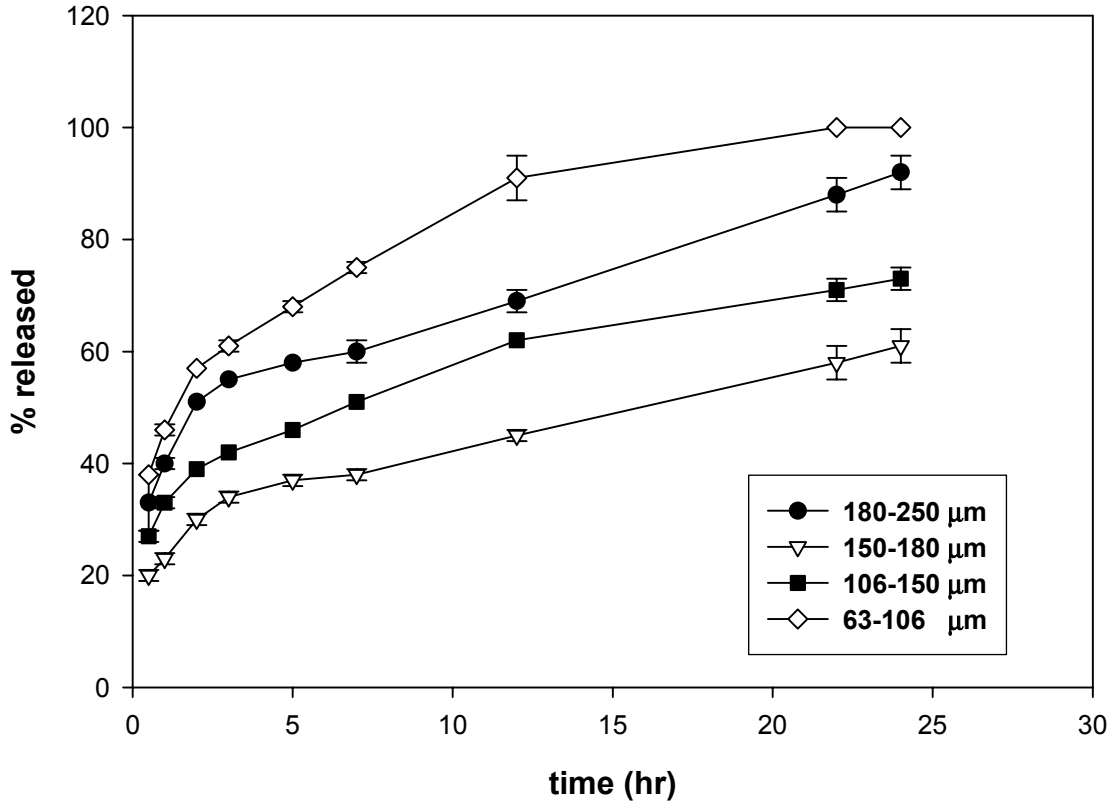

Figure 4.23. Release profiles of size fractions of theophylline microspheres prepared using 8 % Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM2/heavy mineral oil).

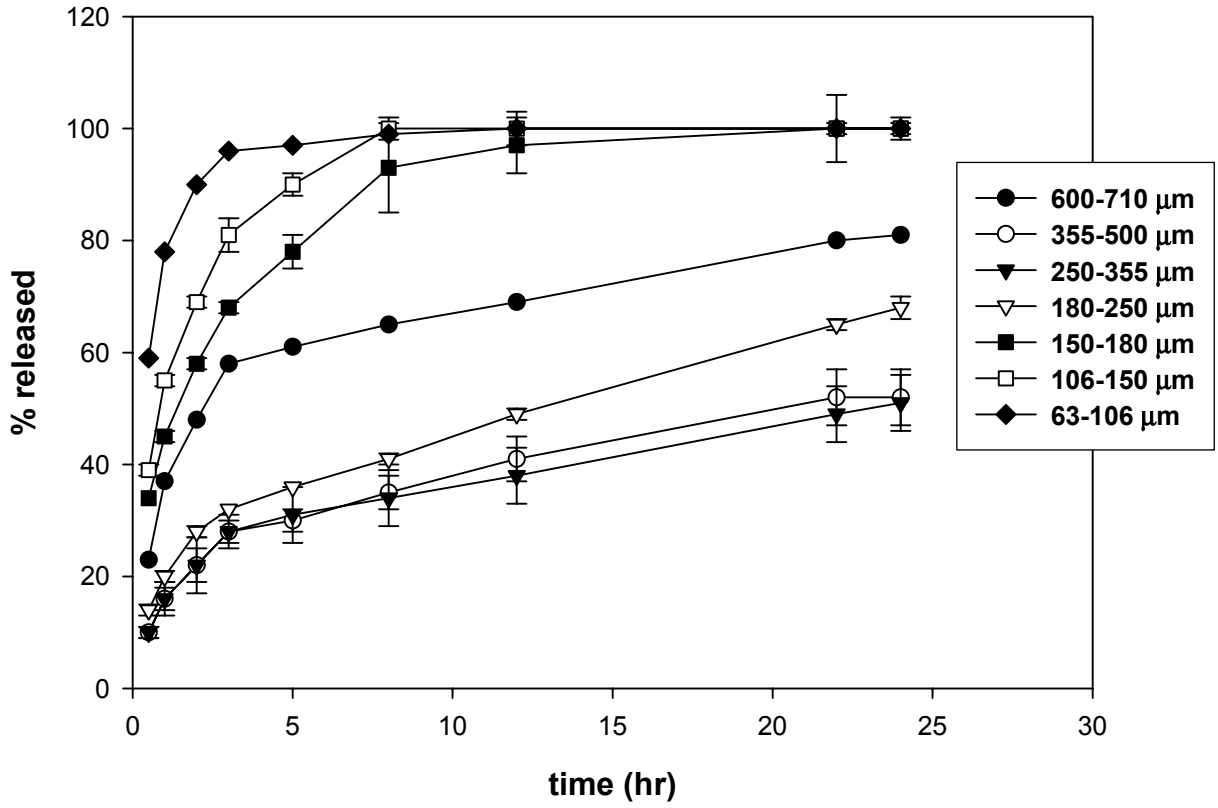

Figure 4.24. Release profiles of size fractions of theophylline microspheres prepared using 8 % Eudragit® RL 100/ ETHOCEL® 100 in acetone (M2/light mineral oil).

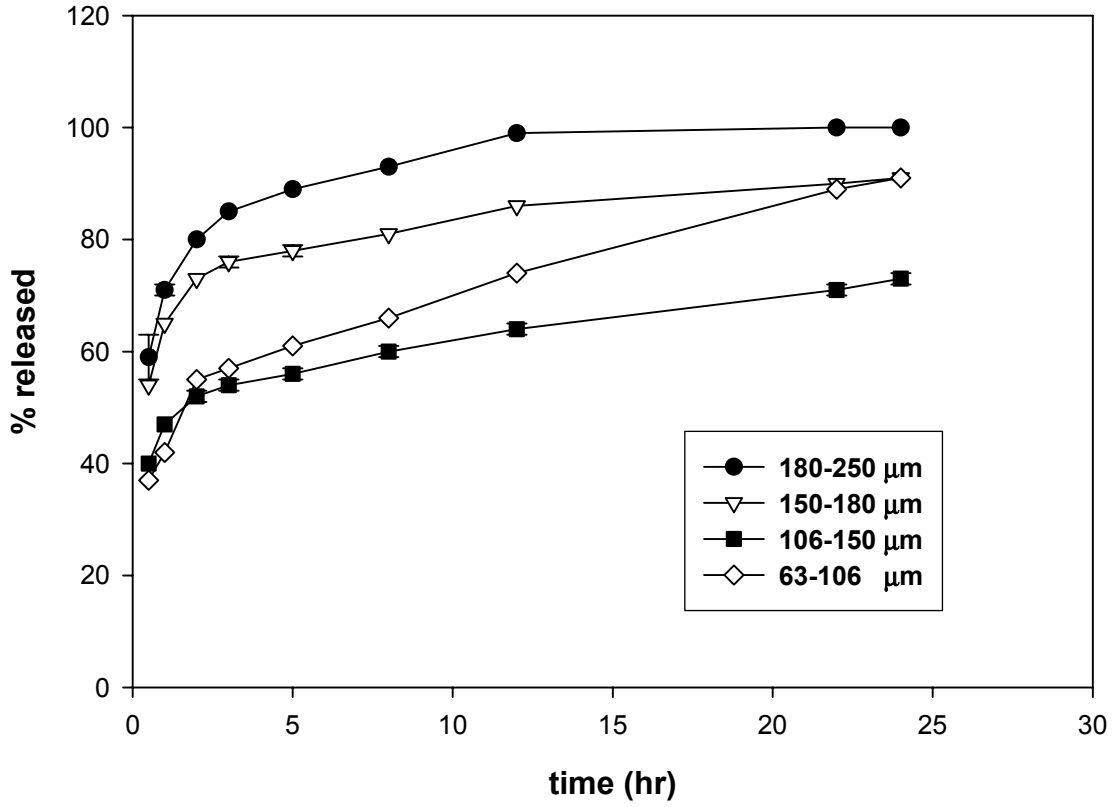

Figure 4.25. Release profiles of size fractions of theophylline microspheres prepared using 10 % Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM1/heavy mineral oil).

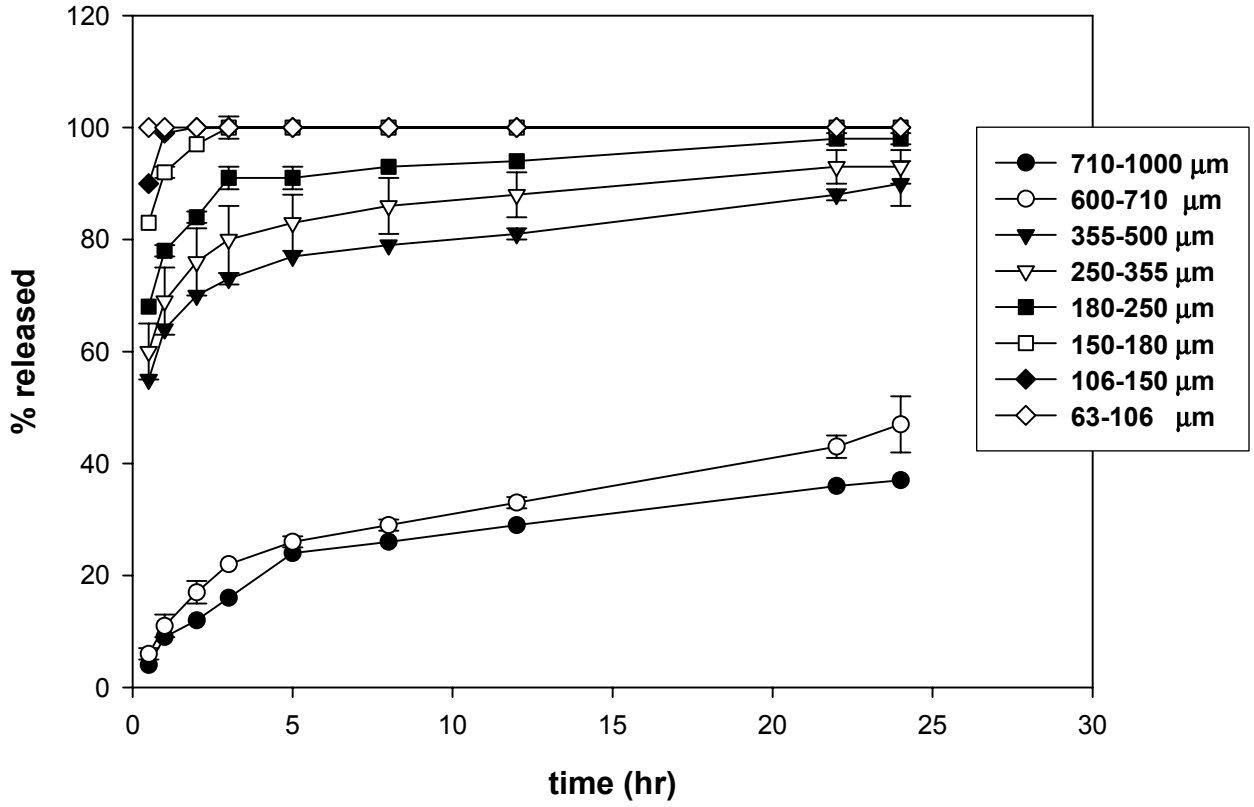

Figure 4.26. Release profiles of size fractions of theophylline microspheres prepared using 10 % Eudragit® RL 100/ ETHOCEL®100 in acetone (M1/light mineral oil).

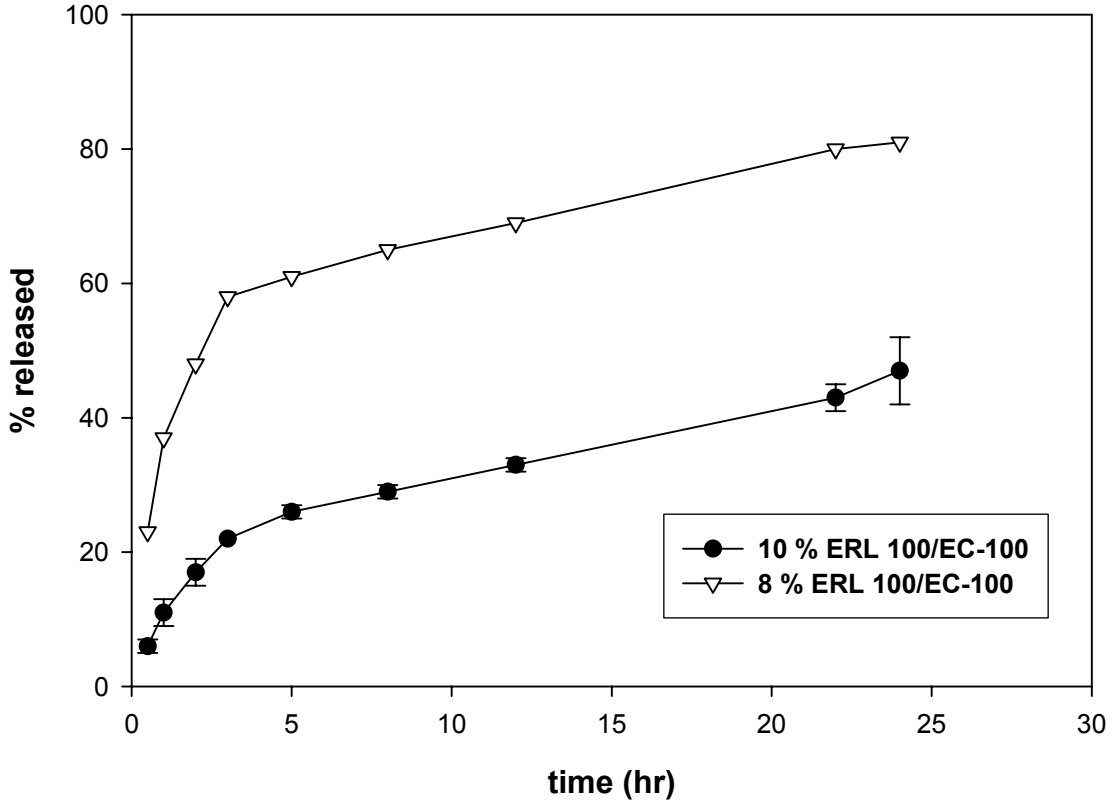

Figure 4.27. Release profiles of 600-710 μm theophylline microspheres prepared from different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

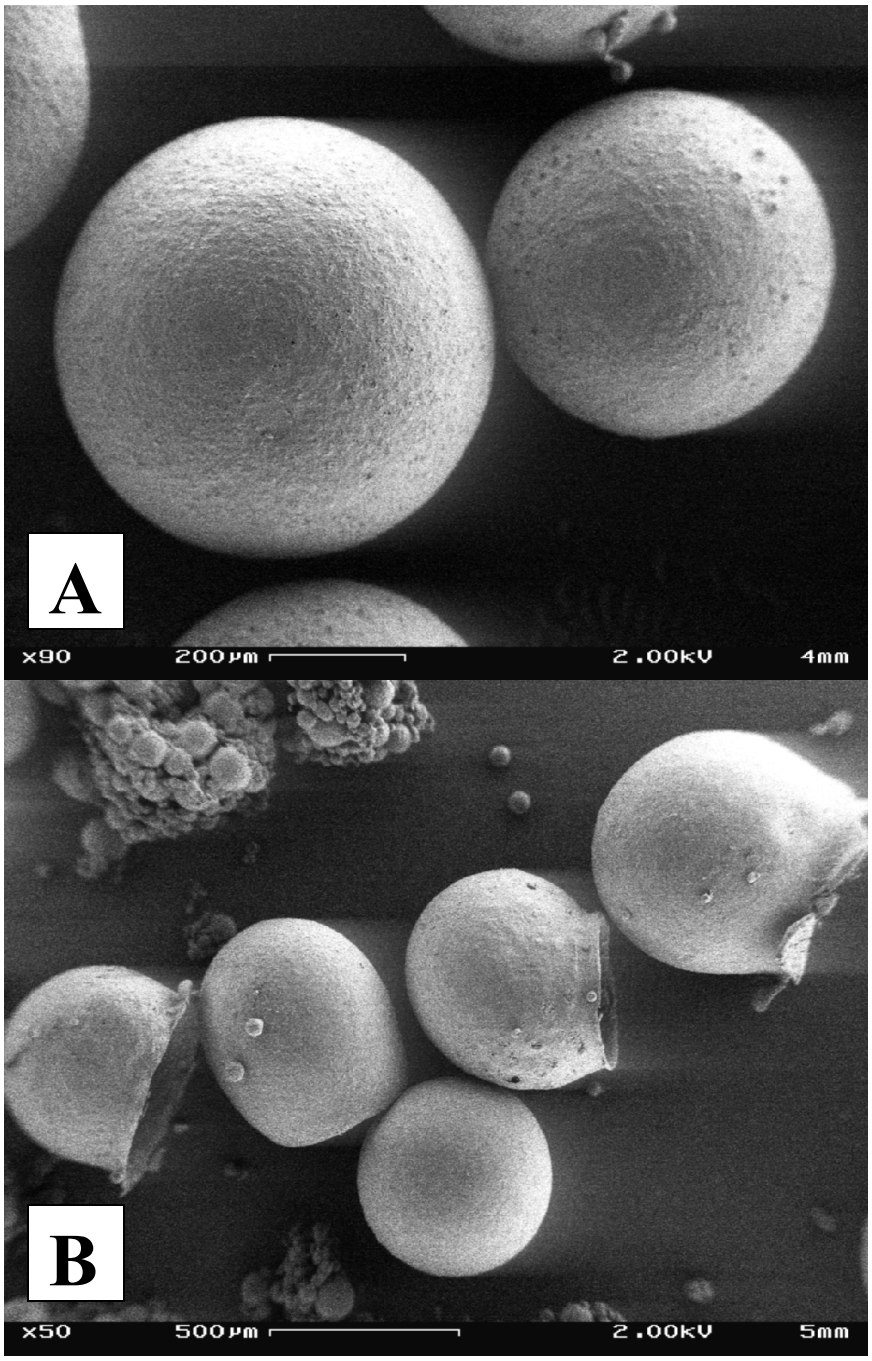

Figure 4.28. Microspheres prepared from Eudragit® RL 100/ ETHOCEL® 100 polymer concentrations in acetone (light mineral oil): (A) 600-710 µm (10 %), (B) 600-710 µm (8 %).

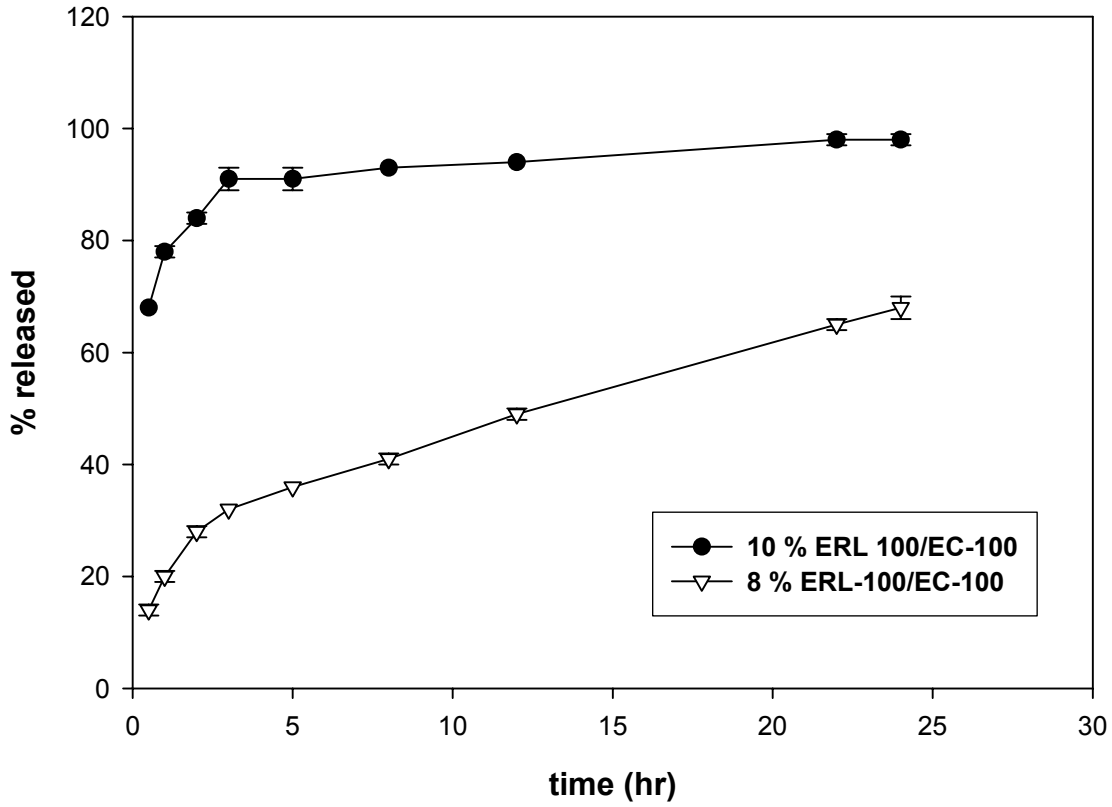

Figure 4.29. Release profiles of 180-250 μm theophylline microspheres prepared from different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL®100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

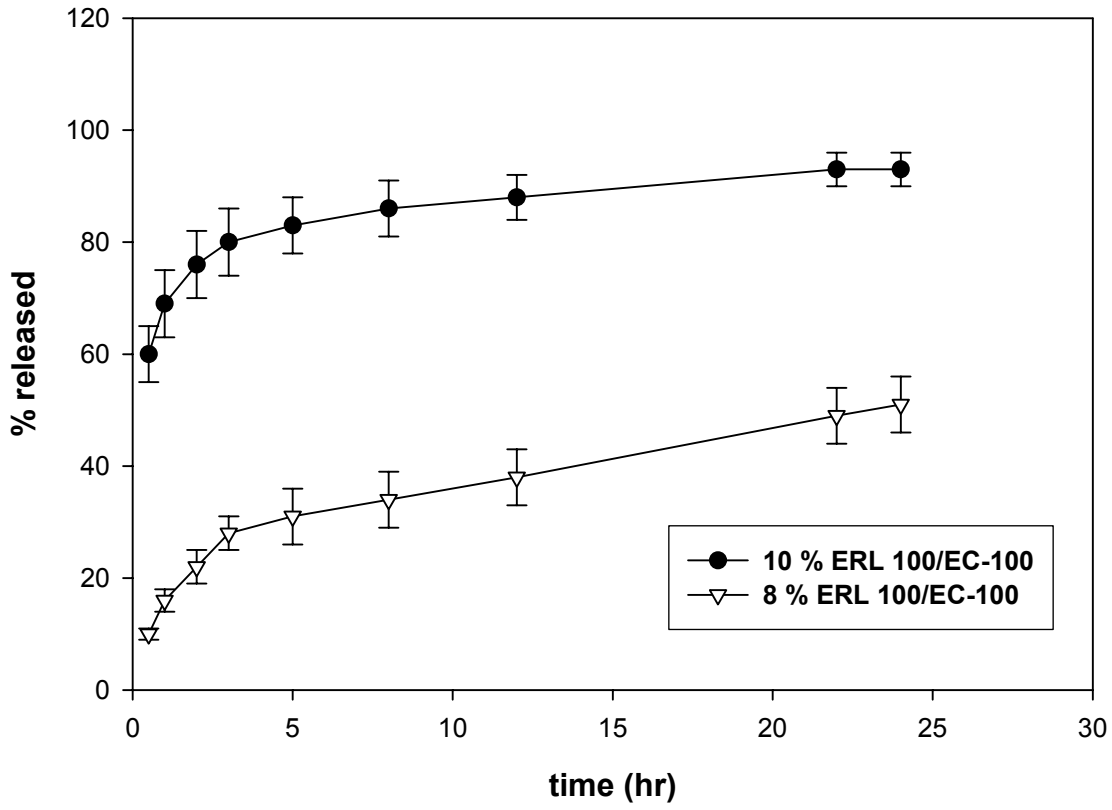

Figure 4.30. Release profiles of 250-355 μm theophylline microspheres prepared from different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) (8 %, 10 %) in acetone, with respective viscosities (47.8, 113) (light mineral oil).

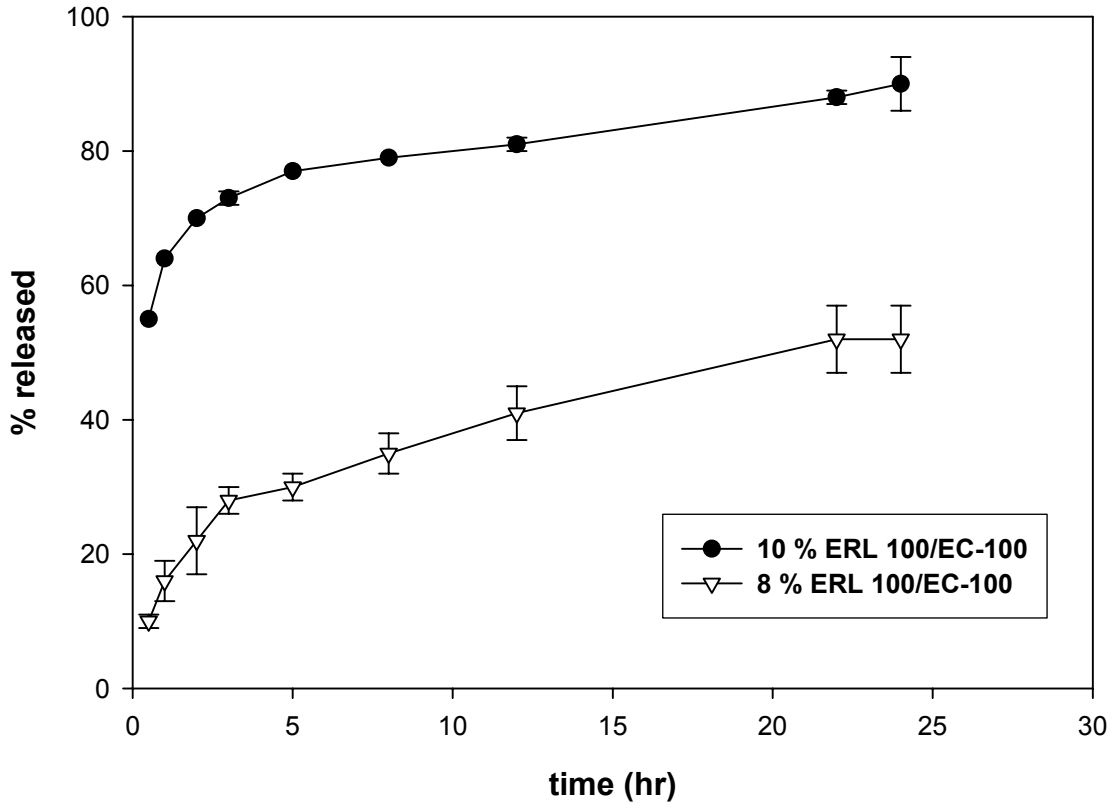

Figure 4.31. Release profiles of 355-500 μm theophylline microspheres prepared from different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

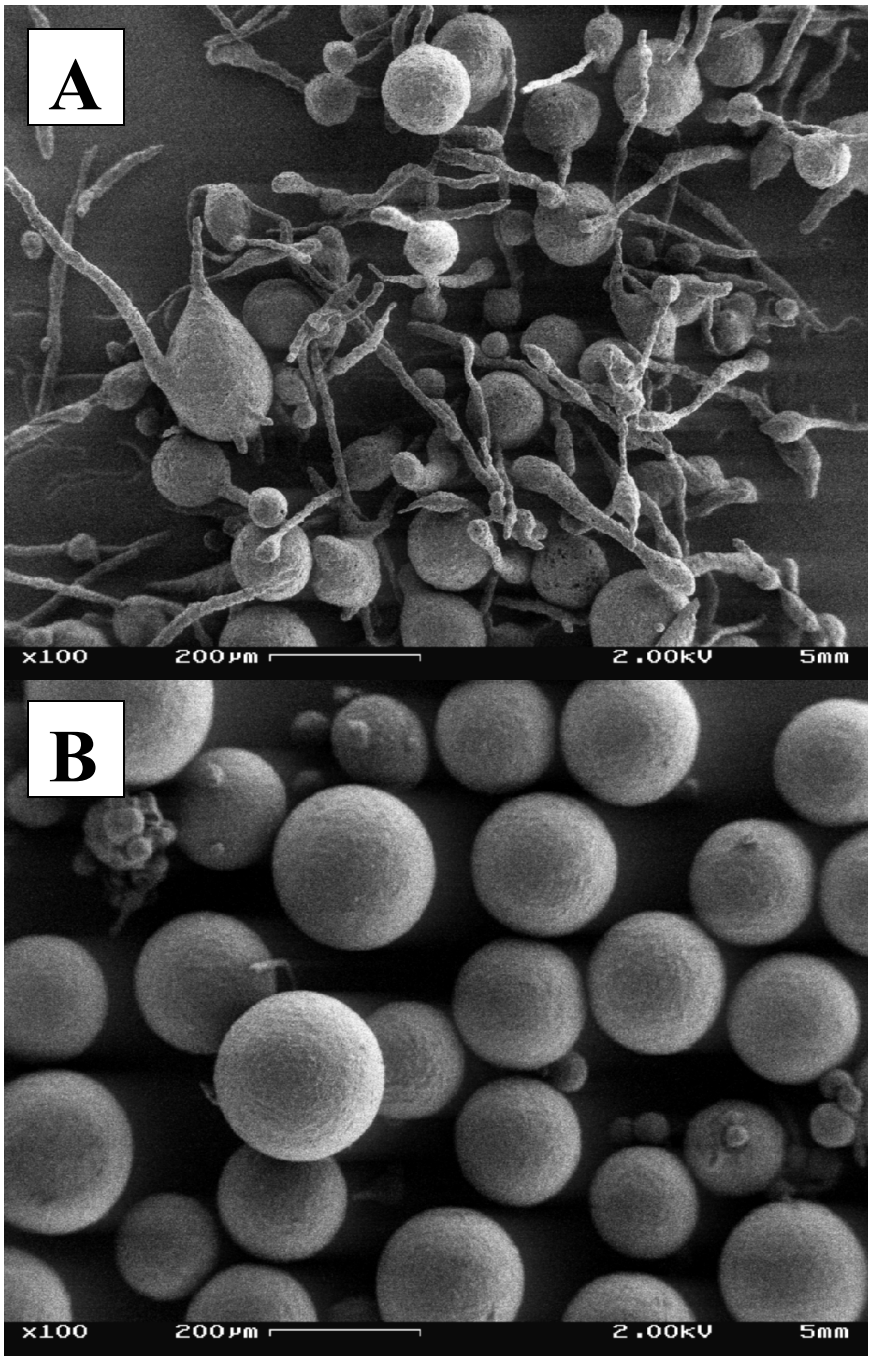

Figure 4.32. Microspheres prepared from Eudragit® RL 100/ ETHOCEL® 100 polymer concentrations in acetone (light mineral oil): (A) 180-250 µm (10 %), (B) 180-250 µm (8 %).

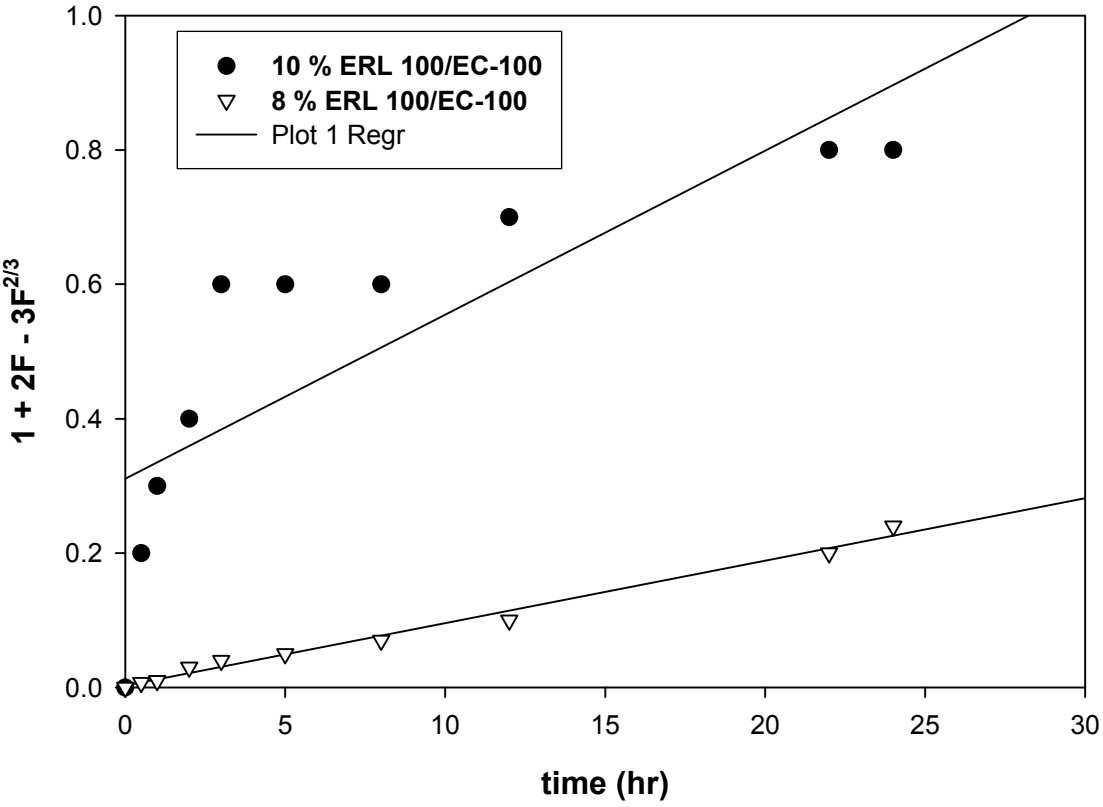

Figure 4.33. Higuchi plots for dissolution of 180-250 μm theophylline microspheres prepared using different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

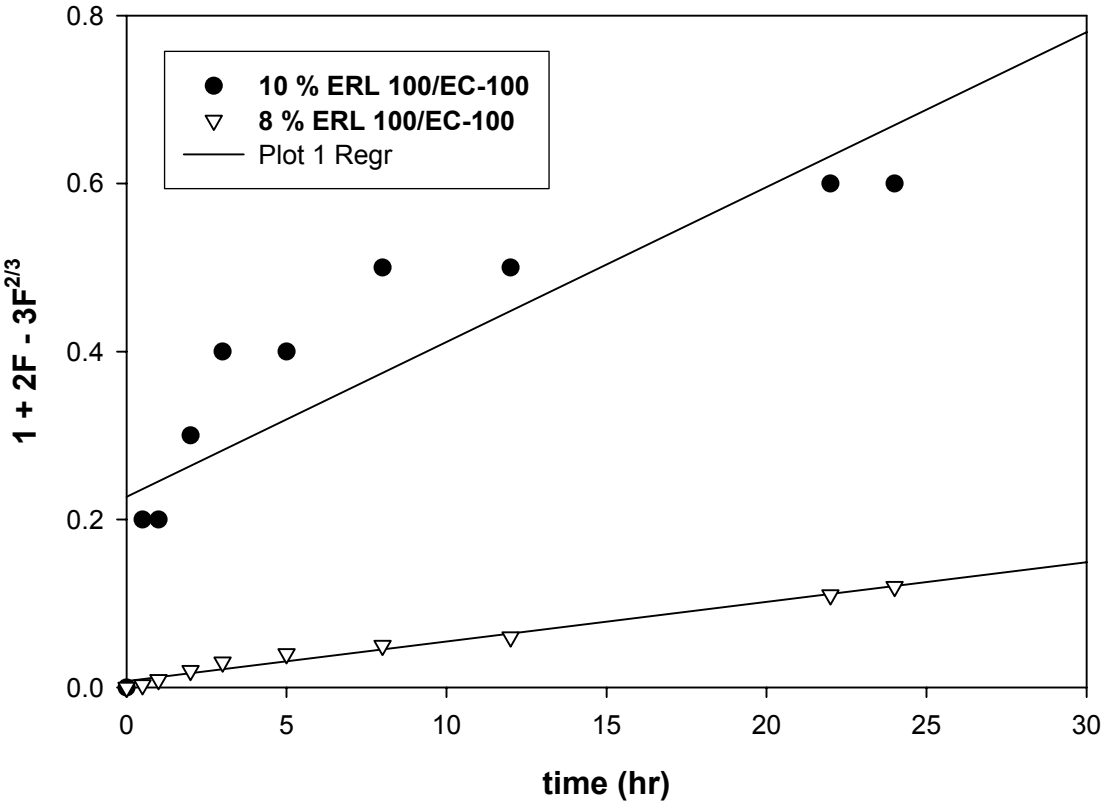

Figure 4.34. Higuchi plots for dissolution of 250-355 μm theophylline microspheres prepared using different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

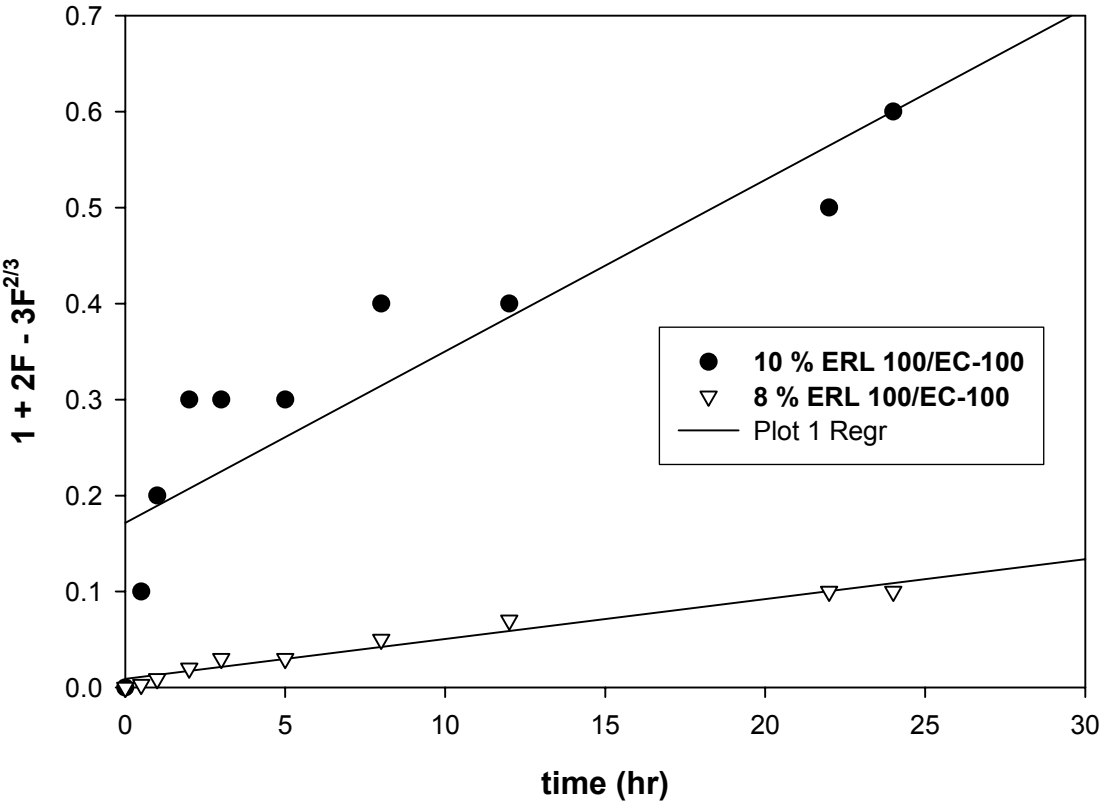

Figure 4.35. Higuchi plots for dissolution of 355-500 μm theophylline microspheres prepared using different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

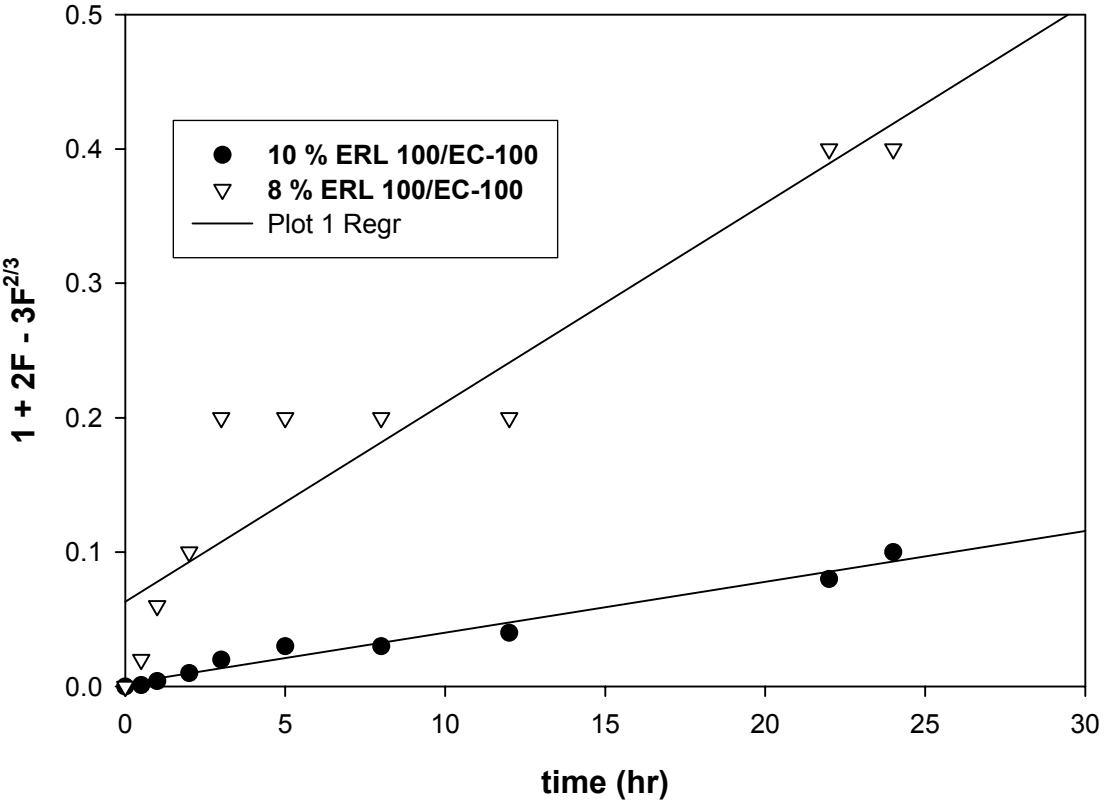

Figure 4.36. Higuchi plots for dissolution of 600-710 μm theophylline microspheres prepared using different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (light mineral oil).

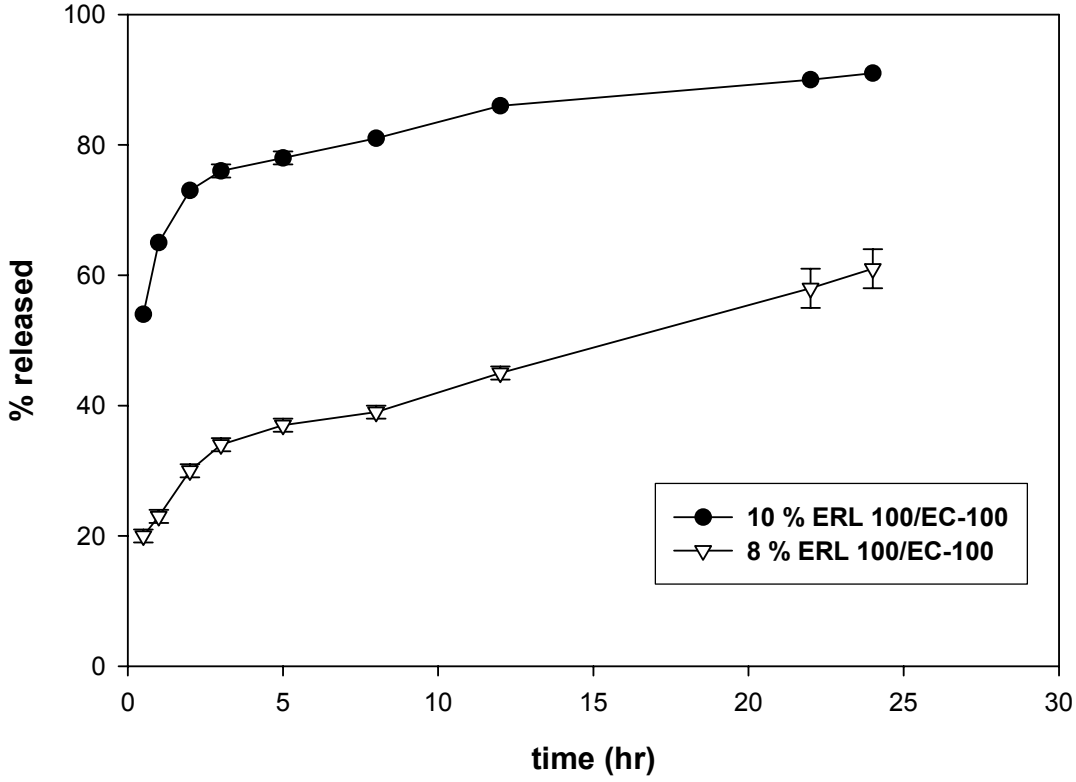

Figure 4.37. Release profiles of theophylline from 150-180 μm theophylline microspheres in different concentrations of Eudragit® RL 100 (ERL 100)/ ETHOCEL® 100 (EC-100) in acetone (8 %, 10 %), with respective viscosities (47.8, 113) (heavy mineral oil).

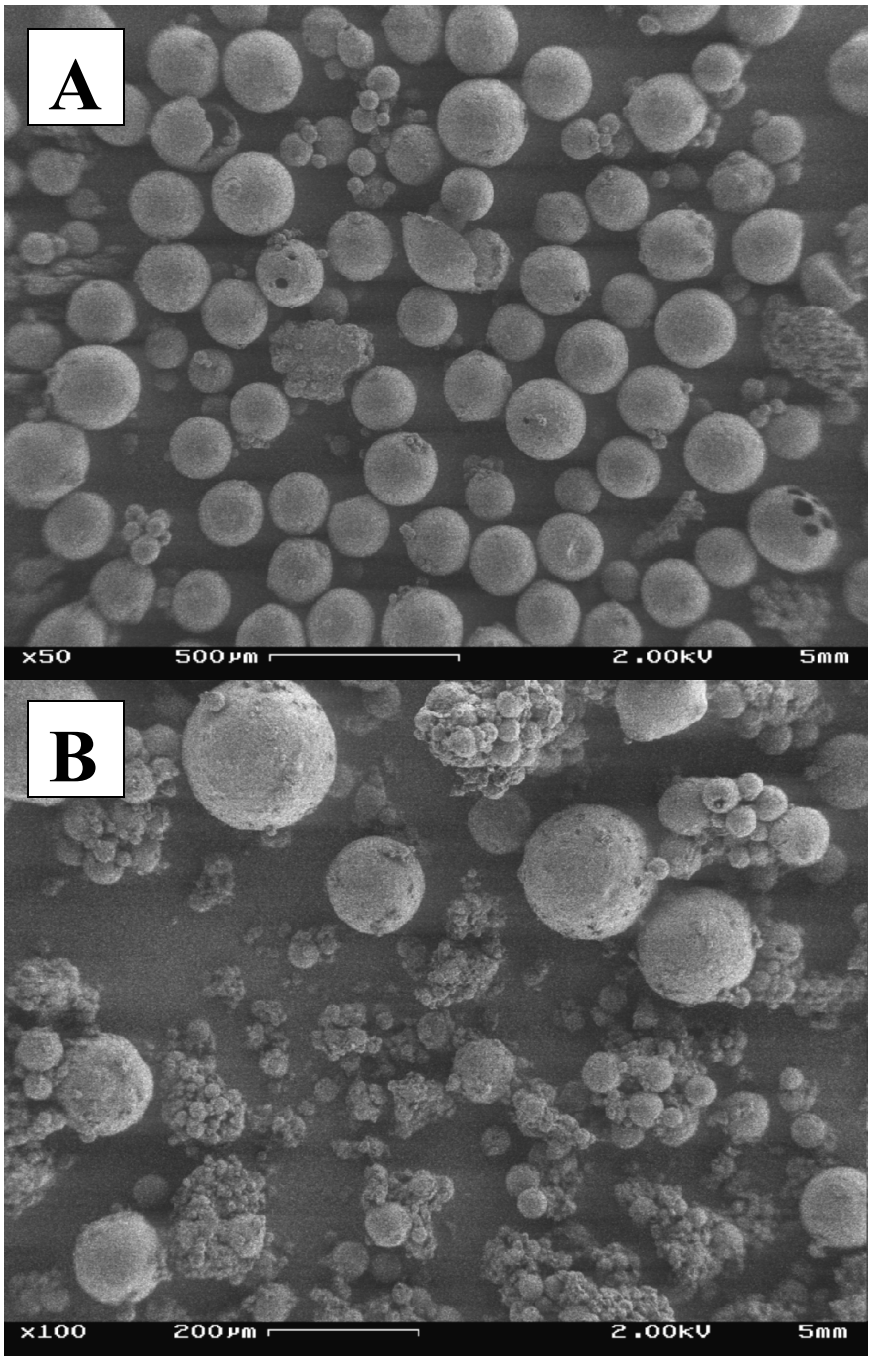

Figure 4.38. Microspheres prepared from Eudragit® RL 100/ ETHOCEL®100 polymer concentrations in acetone (heavy mineral oil): (A) 180-250 µm (8 %), (B) 180-250 µm (10 %).

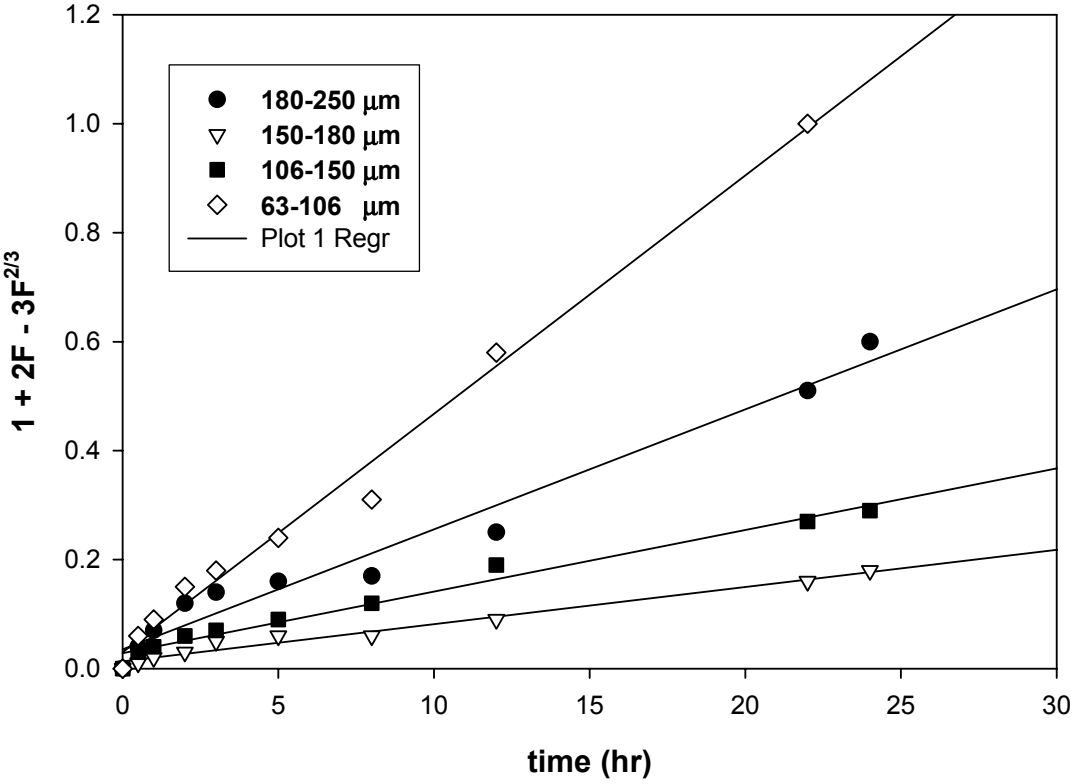

Figure 4.39. Higuchi plots for dissolution of different size fractions of theophylline microspheres prepared from 8 % Eudragit® RL 100/ ETHOCEL® 100 in acetone (heavy mineral oil).

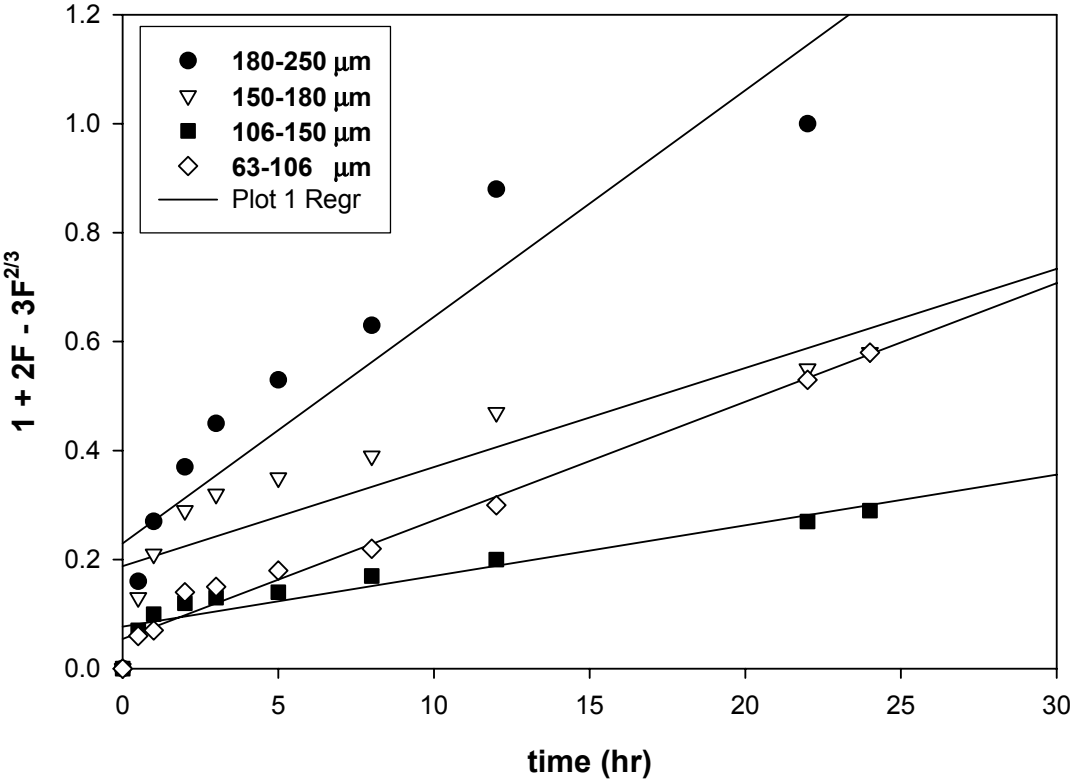

Figure 4.40. Higuchi plots for dissolution of different size fractions of theophylline microspheres prepared from 10 % Eudragit® RL 100/ ETHOCEL® 100 in acetone (heavy mineral oil).

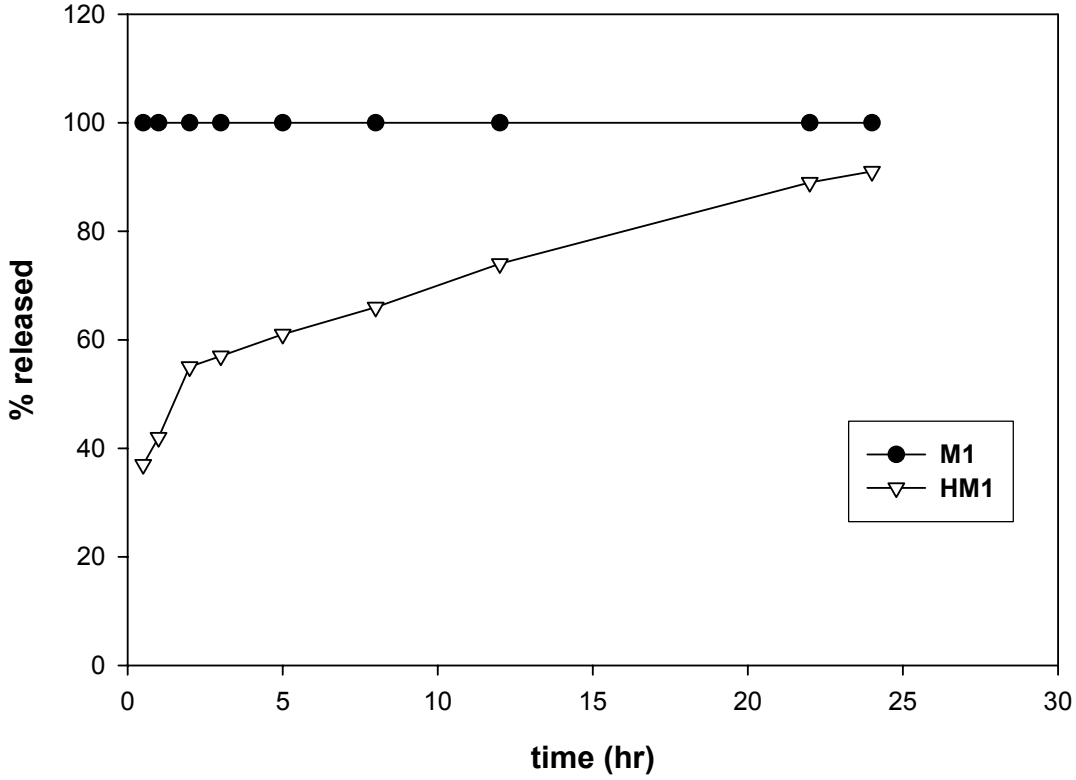

Figure 4.41. Release profiles of 63-106 μm theophylline microspheres prepared from 10 % concentration of Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM1/heavy mineral oil, M1/light mineral oil).

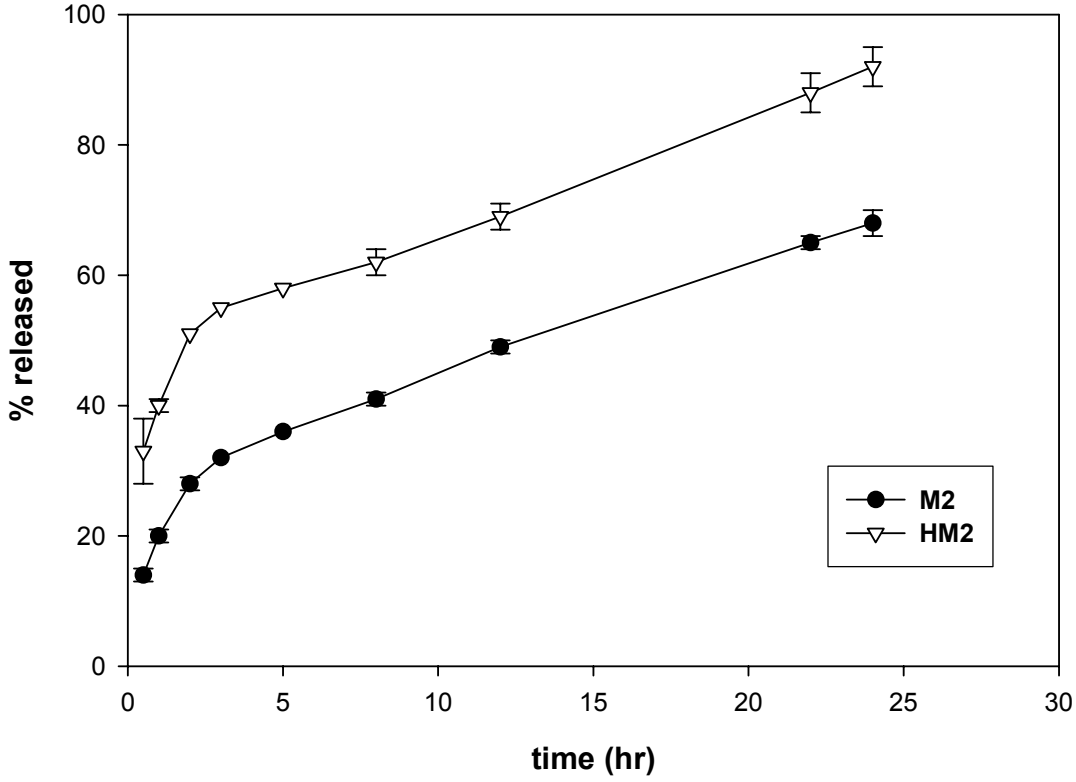

Figure 4.42. Release profiles of 180-250 μm theophylline microspheres prepared from 8 % concentration of Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM2/heavy mineral oil, M2/light mineral oil).

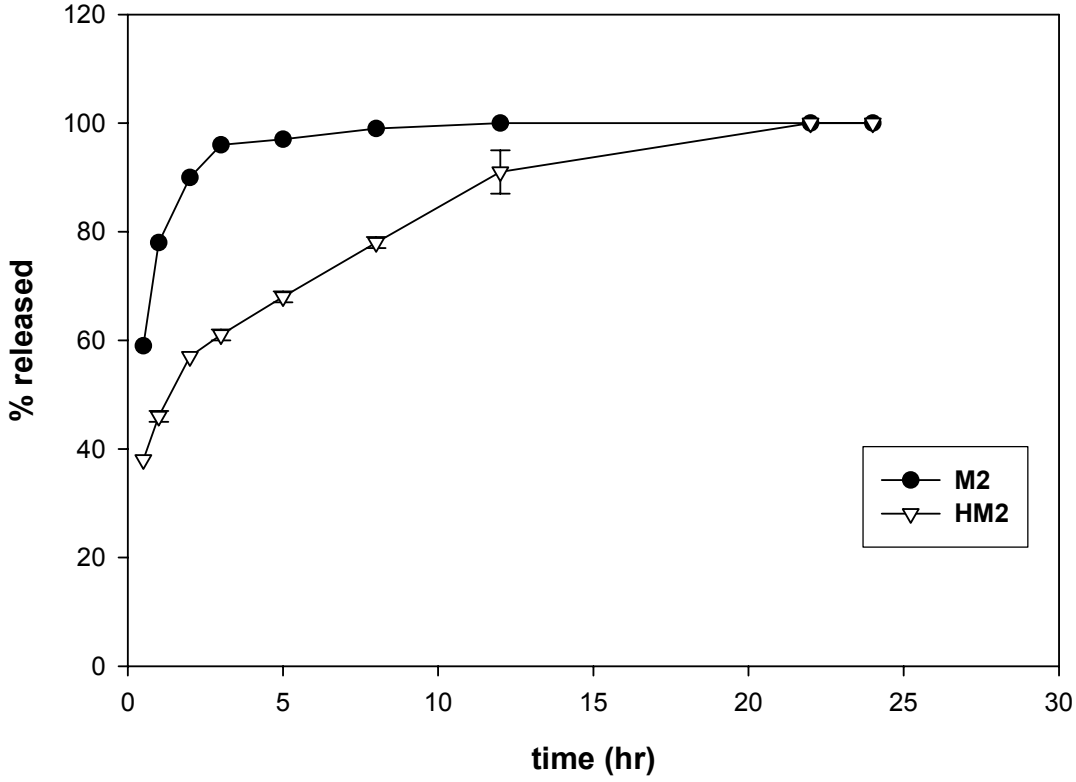

Figure 4.43. Release profiles of 63-106 μm theophylline microspheres prepared from 8 % concentration of Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM2/heavy mineral oil, M2/light mineral oil).

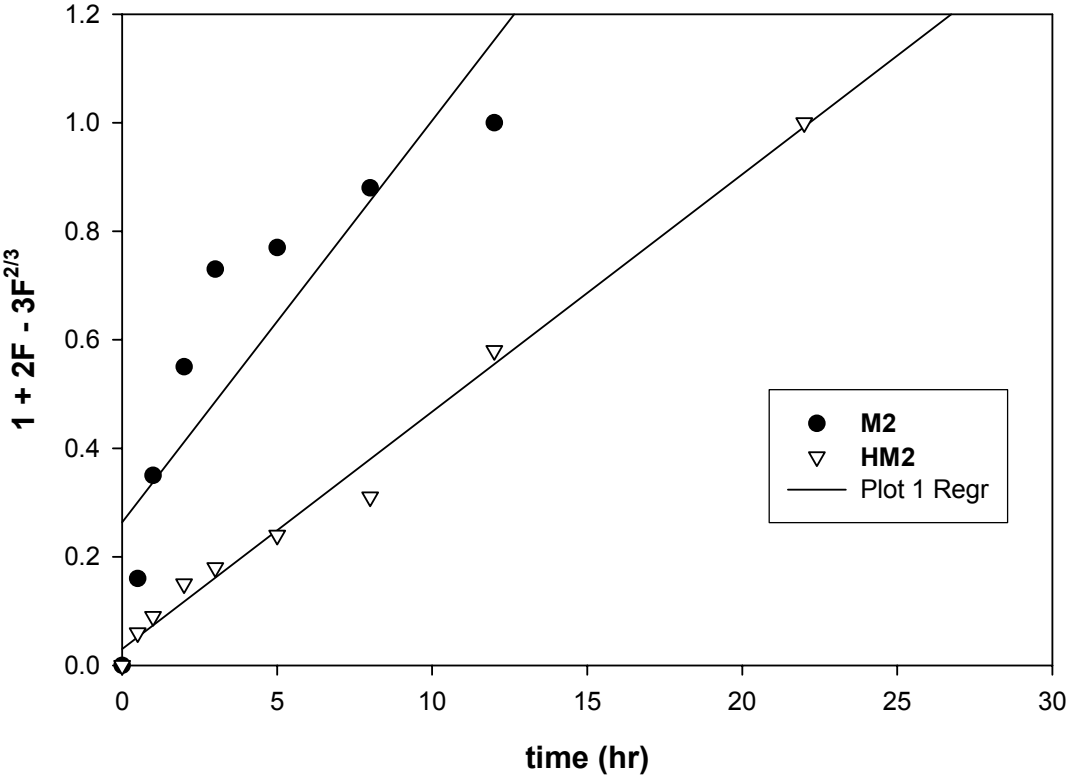

Figure 4.44. Higuchi plots for dissolution of 63-106 μm theophylline microspheres prepared from 8 % concentration of Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM2/heavy mineral oil, M2/light mineral oil).

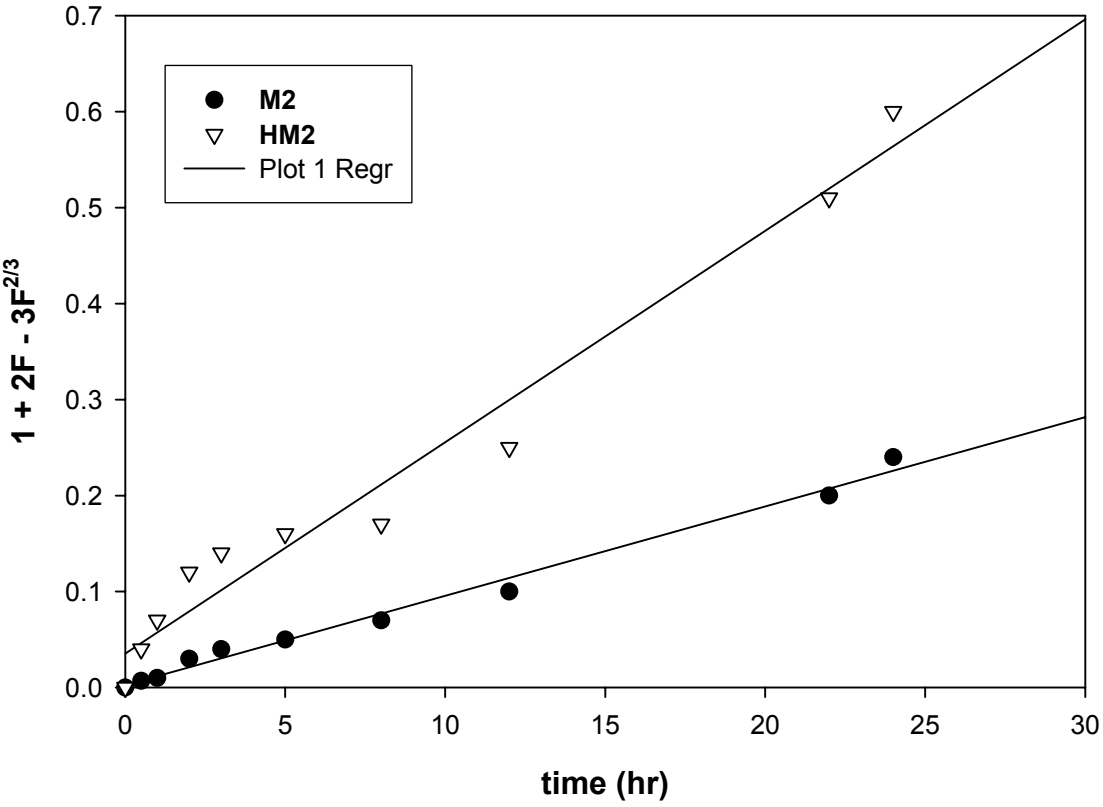

Figure 4.45. Higuchi plots for dissolution of 180-250 μm theophylline microspheres prepared from 8 % concentration of Eudragit® RL 100/ ETHOCEL® 100 in acetone (HM2/heavy mineral oil, M2/light mineral oil).

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CHAPTER 5

CONCLUSIONS

When considering oral drug delivery, multiple-unit dosage forms are generally favored because of their many advantages over single unit preparations such as reduced systemic toxicity and minimal side effects without appreciably lowering the drug bioavailability. Monolithic (matrix) microspheres is a specific type that is commonly employed. In addition to the ruggedness, matrix microspheres are advantageous because they can be easily prepared and various types of drugs can be encapsulated within the matrix structure. However when preparing matrix microspheres, processing and formulation factors must be understood as well as controlled to ensure that quality microspheres are produced. In this study, the continuous phase viscosity, polymer phase viscosity, and stirring speed were some of formulation variables that were evaluated in the optimization of the matrix microsphere formulation.

There was a considerable difference in microsphere size and the range of particle sizes between ETHOCEL® polymer concentrations using heavy mineral oil, and ETHOCEL® polymer concentrations using light mineral oil. Light mineral oil preparations had the tendency to favor larger particle sizes and a wider range of microsphere sizes. Calculated geometric mean diameters in light and heavy mineral oil indicated that average microsphere size was at least three times higher in light mineral oil preparations. In addition, the drug release rates from microspheres prepared with a higher molecular weight polymer of ETHOCEL® 100 were uncharacteristically faster than release from microspheres prepared from lower molecular weight

ETHOCEL® 20. It was expected that with a higher molecular weight polymer, the release would be slower due to the higher apparent viscosities that tend to slow release by holding drug firm within the microspheres and away from the surface to avoid immediate dissolution; however, this was not the case. It is believed that aggregation was prevalent enough in the higher polymer molecular weight microsphere preparations, to offset the effect of the polymer phase viscosity. The use of light mineral oil as the external phase presents an opportunity to increase the particle size as well as the particle size range. Nevertheless, further studies should be done on the effect of external phase (heavy mineral oil, light mineral oil) on microsphere particle sizes for other polymer classes.

Small particle sizes and low viscosities are typically associated with Eudragit® polymer concentrations of 25 % or less. In addition, the particle size range is also limited at these concentrations. These findings were true for preparations using heavy or light mineral oil as the external phase. At these concentrations, regardless of what external phase was used, the emulsion had a to break up and a lot of settling was observed. Furthermore, there was a pronounced, immediate release of drug from the microspheres due to a large number of aggregates of small particles, crowding of particles, and small particle sizes attached to larger particles. Nonetheless it was discovered that at Eudragit® polymer concentrations of 27 % in acetone, with light mineral oil as the external phase, produced larger particle sizes and wider range of particle sizes. In addition, the microspheres that were formulated did not have immediate release, especially at the larger particle sizes (slower release). This was in contrast to Eudragit® polymer concentrations of 27 % in acetone, that used heavy mineral oil as the external phase, where smaller particle sizes and immediate release was common. However, it was demonstrated that larger particle sizes could be attained in heavy mineral oil by increasing the

polymer concentration and thereby increasing the polymer phase viscosity through the incorporation of two polymers in acetone and mixing them at a substantially higher rpm. Also, the release kinetics from larger sized microspheres prepared from 27 % Eudragit® RS 100 with light mineral oil could be described by the Higuchi spherical matrix model. This was also true for larger sized particles prepared from a 1:1 mixture of 10 % Eudragit® RL 100/ ETHOCEL® 100 using light mineral oil as the external phase. Typically, dissolution from larger sized microspheres from light mineral oil preparations was more predictable and slower over time. Thus, it can be said that the combination of light mineral oil external phase with high polymer phase viscosities using emulsion-solvent evaporation could produce substantially larger microspheres that could potentially optimize release rates of matrix microspheres because larger sizes tend to promote slower release of the drug; especially if the larger sized microspheres are prepared using high polymer phase viscosity solutions. However, it must be noted that excessive amounts of aggregates and other extraneous material could interfere with release profiles and cause significant disparities in the dissolution kinetics, regardless of how large the microsphere is and/or how high the polymer phase viscosity. Nevertheless, further investigation should be attempted for other polymer classes.