UNIVERSITÉ DE MONTRÉAL

EFFECT OF DRUG LOADING AND PLASTICIZER ON DRUG RELEASE FROM POLY LACTIC ACID FILM

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TO MY FATHER AND MOTHER

TO MY BROTHERS AND SISTERS

WITH

ADMIRATION AND APPRECIATION

FOR THEIR SUPPORT

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Sommaire

L'objectif de cette étude est d'évaluer l'effet de la charge en médicament et du niveau d'agent plastifiant sur la cinétique de libération à partir d'un film polymérique d'acide polylactique (PLA). Premièrement, des films polymériques d'acide polylactique composé de 50 % basse (Mw 64800) et de 50% haute (Mw 252000) masse moléculaire avec différentes charges en médicament (20, 25 et 30%) ont été préparé sans agent plastifiant dibutyl sebacate (DBS) afin d'évaluer la libération de pentoxifylline des matrices polymériques. Deuxièmement, l'agent plastifiant (DBS) à différents niveaux (10, 20 et 30%) a été ajouté à la formulation afin d'évaluer la libération de pentoxifylline des matrices polymériques. Le Differential Scanning Calorimetry (DSC) (Mettler TC II TA processor) a été employé pour caractériser et étudier le comportement thermique des films et du médicament. Le GPC (Gel Permeation Chromatography) (model ALC-202 liquid chromatographs Waters associates Inc) a été employé pour caractériser le poids moléculaire des échantillons d'acide polylactique. Le Scanning Electron Microscopy (SEM, Jeol Inc. Peabody.MA JSM-5900LV) a été employé pour caractériser la surface des films à différentes charges de médicament. La diffraction au rayon X (Scintag XDS-2000, Si (Li) Peltier-cooled solid state detector) a été utilisée (source de CuKalpha à une puissance de générateur de 45 kilovolts et d'ampérage de 40 mA) pour détecter les pics du médicament à l'état cristallin et de l'acide polylactique. On a observé un effet significatif des niveaux de chargement de drogue sur le taux de libération du médicament. L'effet de l'agent plastifiant sur le taux de libération du médicament dépend des

niveaux de charge. À basse charge (10 et 20%), à mesure que le niveau de plastifiant augmente le taux de libération augmente, alors qu'à charge élevée (60%) le taux de libération diminue.

Mot-Clé : Acide polylactique, Charges en médicament, Plastifiant, Libération du médicament.

Summary

The objective of this study was to evaluate the effect of drug loading and plasticizer level on the release kinetic from films composed of polylactic acid (PLA). First, the polymeric film of polylactic acid of 50 % low and 50% high molecular weights with different drug loadings (20, 25 and 30%) was prepared without the plasticizer (DBS) to evaluate the drug (pentoxifylline) release from the polymeric matrix. Secondly, the plasticizer (DBS) with different levels (10, 20 and 30 %) was added to the formulation and the drug release from the polymeric film was evaluated. Differential Scanning Calorimetry (Mettler TC II TA processor) was used to characterize and study thermal behavior of the film and the drug. Gel Permeation Chromatography GPC (model ALC-202 liquid chromatographs Waters associates Inc) was used to characterize the molecular weight of the polylactic acid. Scanning Electron Microscopy, (Jeol Inc. Peabody.MA JSM-5900LV) was used to characterize the film surface at different drug loadings. X-ray powder diffraction using Scintag XDS-2000, Si (Li) Peltier-cooled solid state detector (CuKalpha source at a generator power of 45 kV and amperage of 40 mA) was used to measure crystals peaks of the drug and the polylactic acid. The study was done to evaluate the effect of the drug loading levels and plasticizer levels on the drug release rate from the polymeric film. A significant effect of the drug loading levels on the drug release rate was observed. The effect of plasticizer on the drug

release rate has a different effect based on the drug loading levels, at low drug loading level (10 and 20%), as plasticizer level increases the drug release rate , while at high drug loading (60%) the drug release rate decreases as the plasticizer level increases.

Key Words: polylactic acid, drug loading, plasticizer, drug release.

Table of contents

Pages

List of Figures X

List of Tables XIII

List of Abbreviations XIV

I. Theoretical 1

A. Introduction 1

1. Drug delivery systems 2

a) Definition and introduction 2

i Conventional release 2

(a) Definition 2

(b) Advantages 3

(c) Disadvantages 3

ii Long-acting dosage forms 4

(a) Definition 4

(i) Sustained action dosage 4

(ii) Prolonged action dosage forms 4

(iii) Repeat action 4

(b) Advantages 5

(c) Disadvantages 5

iii Controlled release 6
(a) Definition 6
(b) Rate control 8
(c) Location control 8
(d) Advantages 8
(e) Disadvantages 9
b) Classification of controlled drug delivery systems 9
i Mechanical pumps 9
ii Osmotic pumps 10
iii Chemically controlled systems (biodegradable) 10
(a) Drug encapsulated with a polymer 11
(b) Drug coupled to polymer pro-drug 12
(c) Drug dispersed in polymer matrix 12
iv Diffusion-controlled devices 13
(a) Reservoir devices 13
(b) Monolithic devices 14
(i) Monolithic solid solution (dissolved drug) 14
(ii) Monolithic dispersion (dispersed drug) 15
(a) Simple monolithic dispersion 15
(b) Complex monolithic dispersion 15
(c) Monolithic matrix systems 16
2. Polymer matrices for the controlled release of drugs 16
a) Classification of polymeric matrices 16

i Water-soluble polymers 17
ii Non-biodegradable polymers 18
iii Biodegradable polymers 18
3. Polylactic acid as drug carrier 21
a) Physical and chemical properties 21
b) Poly (L-Lactic acid) 22
c) Poly (DL-lactic acid) 22
d) Preparation 23
i Direct polymerization 23
ii Polymerization via cyclic monomers 24
e) Biomedical applications 25
i Utilization as sutures 26
ii Use as prostheses 26
iii Using the polymer as a carrier system in implantation 26
(a) Fibers 27
(b) Tablets 27
(c) Extruded implants 27
(d) Films 28
f) Some factors that affect drug release rate from polymeric matrices . 28
i Drug loading 28
ii Porosity 28
iii Particle size 29
iv Effect of plasticizer on drug release from polymeric matrix 29

(a) The effect on the polymer 29

(b) The effect on drug release 30

4. Microspheres 30

a) Introduction 30

b) Methods of preparation 31

i Spray-drying technique 31

ii Solvent evaporation 31

iii Solvent extraction 32

5. The drug model pentoxifylline 33

B. Objective 34

II. Materials and methods 35

A. Materials 35

1. Chemicals 35

2. Equipment 36

B. Methods 37

1. Characterization of PLA 37

a) Purification 37

b) Molecular weight determination by gel permeation chromatography 37

2. Preparation of the polymeric solution and plate-coating process 39

a) Polymeric solution preparation 39

b) Plate coating process 39

3. In vitro release study 40

4. Polymeric film characterization 40

a) DSC scanning 40
b) Scanning-electron microscopy and Fracture technique 41
c) Powder X-ray diffraction 41
III. Results and discussion 43
A. Characterization of PLA 43
1. Gel permeation chromatography results 43
2. Powder X-ray diffraction 44
B. Drug release studies 46
1. Drug release from unplasticized polymeric film 47
2. Release from polymeric film plasticized with dibutyl sebacate 50
C. Characterization of the film 58
1. Differential scanning calorimetry 58
2. Scanning-electron microscopy 64
IV. Conclusion 70
References: 72

List of Figures

Figure 1: Calibration curve of polystyrene standards for the PLA molecular weight determination.....38

Figure 2: Molecular weight distribution of low- and high-molecular-weight PLA. 44

Figure 3: Percentage of drug released as function of time(hrs) for films containing 20 % pentoxifylline without plasticizer 48

Figure 4: Percentage of drug released as function of time(hrs) for films containing 25 % pentoxifylline without plasticizer 49

Figure 5: Percentage of drug released as function of time (hrs) for films containing 30 % pentoxifylline without plasticizer 50

Figure 6: Percentage of drug released as function of time (hrs) for films containing 10 % pentoxifylline and 10 %, 20 %, and 30 % DBS.....51

Figure 7: Percentage of drug released as function of time (hrs) for films containing 20 % pentoxifylline and 10 %, 20 %, and 30 % DBS.....52

Figure 8 : Percentage of drug released as function of time (hrs) for films containing 60 % pentoxifylline and 10 % and 30 % DBS.....53

Figure 9: Percentage of drug released as function of time (hrs) for films containing 10 %, 20 %, and 60 % of pentoxifylline at a constant DBS level of 10 % 54

Figure 10: Percentage of drug released as function of time (hrs) for films containing 10 %, 20 %, and 60 % of pentoxifylline at a constant DBS level of 30 %(part-a).....55

Figure 11: Percentage of drug released as function of time (hrs) for films containing 10 %, 20 %, and 60 % of pentoxifylline at a constant DBS level of 30 %(part-b)..... 56

Figure 12: DSC scan of a mixture of low- and high-molecular-weight PLA dissolved in the solvent dichloromethane (DCM) without DBS after a second run showing the Tg..... 59

Figure 13: Second run of a mixture of low- and high-molecular-weight with plasticizer DBS dissolved in the solvent dichloromethane (DCM). 60

Figure 14: DSC scan of pure drug (pentoxifylline) at a theoretical 10%..... 61

Figure 15: DSC scans of 60% pentoxifylline and 30% DBS after the first run showing pentoxifylline peak..... 62

Figure 16: DSC scan of 20% pentoxifylline and 30% DBS after the first run showing a pentoxifylline peak..... 63

Figure 17: DSC scans of 10% Pentoxifylline and 30% DBS after the first run showing a plasticizer peak and the absent of the drug (pentoxifylline) peak. 63

Figure 18: SEM photo of 10% pentoxifylline and 10% DBS film before dissolution showing drug crystals on the film surface..... 64

Figure 19: SEM photo of 20% pentoxifylline and 10% DBS film before dissolution showing more drug crystals on the film surface..... 65

Figure 20: SEM photo of 60% pentoxifylline film before dissolution, showing drug crystals covering the film surface..... 66

Figure 21: SEM photo of 20% pentoxifylline and 10% DBS film after 48 hours dissolution, showing pores after pentoxifylline particles were dissolved..... 67

Figure 22: SEM photo of 60% pentoxifylline film after 3 hours dissolution, showing the pores after the dissolution of the pentoxifylline particles..... 68

Figure 23 : SEM photo of freeze fracture of 60% pentoxifylline film after 3 hours dissolution, showing the pores after the dissolution of the pentoxifylline particles. 69

List of Tables

Table 1: Molecular weights data of 3 selected lots of PLA for blending and purification. 37

Table 2: Data of low- and high-molecular-weight PLA characterized by Gel Permeation Chromatography 43

Table 3: Crystallography data from the X-ray powder diffraction pattern of pure pentoxifylline. 45

Table 4: Crystallography data of pentoxifylline from the X-ray powder diffraction pattern of films with different pentoxifylline loading samples (10%, 20%, and 60%) at a constant plasticizer level (DBS 10%) 46

Table 5: Crystallography data of PLA from the X-ray powder diffraction pattern of films with different pentoxifylline loading samples (10%,20%, and 60%) at a constant plasticizer level (DBS 10%). 46

Table 6: The effect of drug loading at constant plasticizer (10% DBS) on the release kinetics, $T60_{\%}$. 57

Table 7: The effect of drug loading at constant plasticizer (30% DBS) on the kinetics release, $T_{80\%}$. 57

Table 8: The effect of residual solvent on m.p. and Tg of PLA with and without plasticizer 58

Table 9: DSC data of films with different pentoxifylline loadings and different DBS levels 61

List of Abbreviations

PLA.....Poly Lactic Acid

DBS.....Dibutyl Sebacate

DSC.....Differential Scanning Calorimetry

DCM.....Dichloromethane

GPC.....Gel Permeation Chromatography

SEM.....Scanning Electron Microscopy

I. Theoretical

A. Introduction

A number of factors have prompted the recent focus in pharmaceutical research on the development of new drug delivery systems. First, the extension of patent protection for existing drugs coming off patent is well suited to the concepts and techniques of controlled release drug delivery systems. Second, new drug delivery systems are often the only conceivable approach to delivering genetically engineered pharmaceuticals such as peptides and proteins to their site of action without causing significant immunogenicity or biological inactivation. Third, targeting specific sites of action improves the treatment of enzyme-deficient diseases and cancer. Finally, reducing the size and number of doses helps prevent the side effects arising from conventional methods.[1]

While the search for new drugs remains the prime objective of pharmaceutical research, recent decades have marked a shift in the focus of pharmaceutical research to the conception and creation of new drug delivery systems. Different methods are used to prolong drug action, drug availability, and duration of effect. Combining drugs with substances that decrease their solubility, coating drugs with materials that do not dissolve in the stomach acid or that are either insoluble or slowly soluble, compressing drugs in dense tablets, or putting drugs into suspension or emulsion are all techniques to improve drug efficacy and bioavailability. [2, 3]

1. Drug delivery systems

a) Definition and introduction

An ideal drug delivery system can be achieved through one of two mechanisms. First, the drug should be delivered at a rate dictated by the needs of the body over the period of treatment. A clear relationship between steady state plasma levels and the resultant therapeutic response requires a constant rate for drug delivery. Second, the drug should be delivered to ;specific receptors, such as H_1 and H_2 antagonists' to specific targets, such as tumor cells; or to a specific area of the body, such as the joints for the treatment of arthritis or gout.[1]

Controlled release drug delivery systems can deliver a drug, either systemically or locally, at a predetermined rate for a specific period; however, such systems have no control over the fate of the drug once it enters the body. Even though targeted drug delivery systems can achieve site-specific delivery, they are as of yet incapable of controlling the release kinetics of drugs in a predicable manner.[1, 4]

i *Conventional release*

(a) Definition

Most active agents are administered orally, according to a specific administration schedule for immediate release into and rapid absorption by the circulation system. The drug/blood levels necessary for obtaining a

therapeutic response require an initially high release rate. The drug concentration in the blood decreases over time; therefore, further doses must be administered at specific time intervals to maintain a therapeutic level of the drug. These conventional drug administration techniques (intravenous injection and oral tablets) normally provide poor control of plasma drug concentrations, thus requiring large amounts of drug to maintain therapeutic levels. This renders such delivery systems costly and inefficient.[4-6]

(b) Advantages

Despite certain limitations, conventional dosage forms can yield the desired therapeutic levels using proper dose and dosing intervals.[6]

(c) Disadvantages

Because of the wide distribution in blood levels, conventional dosage forms are not suitable for the oral administration of drugs that have narrow therapeutic ranges. The treatment success of these classic drug delivery systems is highly dependent on patient compliance. Drugs with short half-lives will produce large valley and peak blood level profiles, thus rendering them unsuitable for the treatment of some diseases. For glaucoma, for example, Ocusert® Pilocarpine is used to decrease intraocular pressure, rather than a conventional pilocarpine that must be used every six hours, because accumulation following multiple doses could reach a toxic level. The large amount of drug that is necessary for achieving the required therapeutic response leads to local and systemic toxicity.[6, 7]

ii ***Long-acting dosage forms***

(a) Definition

Based on their release kinetics, long-acting dosage forms can be categorized into three major types: sustained action, prolonged action, and repeat action dosage forms. The many techniques that can be used to obtain the desired drug release characteristics depend on many factors, such as drug properties, route of administration, and physiological and pathological factors.[6, 8]

(i) Sustained action dosage

Sustained release dosage forms are designed to release a loading dose of the drug, that is, the amount of drug required to provide an initial therapeutic response followed by a maintenance dose to achieve an optimum and consistent therapeutic response for a desired period of time.[6]

(ii) Prolonged action dosage forms

Prolonged action dosage forms are formulated to deliver enough drug to provide a therapeutic response over a longer period of time than conventional dosage forms.[6]

(iii) Repeat action

Repeat action dosage forms are designed to provide a dosing system that releases an initial dose of drug followed by another single dose at a later time.[6]

(b) Advantages

Sustained release systems are used to minimize the problem of patient compliance by decreasing the number of doses that a patient must take and by minimizing the side effects and toxicity of drugs by eliminating or reducing the blood level fluctuations associated with rapid release dose forms. Drug activity can be prolonged over a number of hours to enable patients to sleep through the night, an effect that is particularly desirable with psychiatric patients. Patients accept long-acting dosage products compared to conventional dosage form products. As in the case of Aminophylline, patient acceptance of a drug product can be very important.[6]

(c) Disadvantages

Cost differences between two formulations might have important bearing on product selection when the clinical responses of the long-acting dosage form and those of the conventional dosage form do not differ substantially, as with Meprobamate. The slow clearance of some drugs might be a problem that leads to toxic levels. The variability of absorption among patients may reduce the predictability of the therapeutic response. A drug such as riboflavin is absorbed high in the intestinal tract, thus rendering a prolonged dosage form of it unnecessary. Accidental or intentional poisoning with long-acting dosage form requires special treatment that conventional dosage forms do not often require.[6]

iii ***Controlled release***

(a) Definition

Prolonged action duration may be a major consideration in designing a controlled delivery system for high dose, low toxicity drugs with relatively long biological half-lives. In order to obtain optimal therapeutic efficacy with minimal side effects, however, some drugs may require that the release kinetic from the dosage form be predictable and reproducible, particularly drugs with a narrow therapeutic index.

Controlled release systems offer three different release rates. In zero-order release, the release remains constant until the system is depleted. In first-order release, the release is proportional to the amount of drug remaining in the system. In the third type of release, the rate of release is proportional to the square root of time, a system in which a large amount of drug is released followed by the release of substantially smaller and decreasing amounts during the last half-life of the system.

Controlled release is a technique or method used to deliver the drug to the site at a predetermined rate over a desired period of time.[4, 9] In general, the controlled release of a drug to a specific site can occur through one of the following methods: diffusion through a rate-controlling membrane; the use of osmotically regulated flow; or the chemical degradation or erosion of a matrix in which the drug is incorporated.

Each of these methods has unique characteristics that must be considered in system design. Therefore, these methods are used to achieve a number of goals:

1. The design of a drug delivery device that uses zero-order kinetics, through which the rate of delivery can be modified by changing membrane thickness and/or area or composition.
2. The design of a device where such a mechanism not only releases the content by zero-order kinetics but can also sustains high delivery rates that cannot be achieved using membrane-moderated devices.
3. The design of a drug delivery device with a predetermined life that would preclude the need to remove the device after completion of its drug delivery role [9, 10]

There are a number of assumptions to be considered in explaining the dissolution and diffusion of a highly water-soluble drug from a porous planar surface composed of a hydrophobic polymeric matrix. The assumptions are the following: the initial drug loading exceeds drug solubility in the polymer; molecular diffusion is the only mass transport mechanism; water-filled pores are the only path by which the drug diffuses through the matrix; the diffusion coefficient of the solute is represented by the integral diffusion coefficient; sink conditions exist in the release environment; all of the dispersed drug is accessible for diffusion; and drug particles are homogenously dispersed in the matrix and are small compared to the diffusional distance. [11]

(b) Rate control

The rate of delivery can be controlled with various techniques to improve drug bioavailability, safety, compliance, and efficacy, some of which include the following. First, rate preprogrammed drug delivery systems preprogrammed the release of the drug from the delivery systems at a specific rate, such as polymeric matrix. Second, activation-modulated drug delivery systems activate the release of drug from this system through some physical, chemical, or biochemical process and/ or facilitate its release through an external energy supply, such as osmotic pump, magnetic and ultrasound energy. Third, feedback-regulated drug delivery systems use a triggering agent, such as a biochemical substance in the body, to control the release of the drug. This system also regulates the release of the drug through biochemical substance concentration via some feedback mechanism. [12, 13]

(c) Location control

Many drug delivery systems aim to control release at a specific site of action in the body. A targeting drug is one of location control applications. Gene and protein delivery therapy is a potential application of a localized delivery system to improve treatment and decrease the side effects. [12, 14, 15]

(d) Advantages

Controlled release drug delivery systems offer many advantages over conventional drug regimes, such as optimized drug input rates into

systematic circulation in order to achieve the optimum therapeutic goal, a lower drug level through local drug delivery, reduced side effects, less frequent administration, no need for follow-up, and improved patient compliance and comfort. Novel drug delivery systems can be formulated that can provide delivery systems with greater safety and efficacy than conventional delivery systems. [16]

(e) Disadvantages

For particular formulations, the cost of fabrication due to expensive ingredients and/or equipment is relatively high. Dose dumping, which is the sudden release of a high amount of drug due to delivery system failure can lead to systemic toxicity.[1, 6]

b) Classification of controlled drug delivery systems

A number of designs of controlled release systems have been developed to offer distinctive release profiles. Each requires a unique method for its fabrication.[4, 7]

i *Mechanical pumps*

Mechanical pumps have been used for a number of pharmaceutical applications. Mechanical pumps can be used to deliver drugs at a constant rate over prolonged periods. They were developed for drug infusion, but recently miniaturization has enabled the design and manufacture of implantable pumps to deliver Insulin and Heparin.[7, 17]

ii ***Osmotic pumps***

Osmosis is one of the different approaches that can be used to control drug delivery. Osmotic devices can deliver any drug, regardless of molecular weight and chemical composition. Osmotic mechanisms provide the opportunity to produce generic systems that operate independent of drug properties. Osmotic devices offer constant delivery rates much higher than diffusional devices. The Alza Corporation manufactures two types of osmotic devices. In the first device, the drug is placed in an inner and impermeable flexible reservoir surrounded by osmotic agents, and the reservoir is surrounded and sealed inside a rigid cellulose acetate semi-permeable membrane. In the other device, the drug and the osmotic agent are compressed into a core tablet, film coated with a rigid semi-permeable membrane containing a delivery orifice.[1, 4]

iii ***Chemically controlled systems (biodegradable)***

In this system, a chemical reaction is used to control the rate of drug release from the polymer. Chemical reaction includes enzymatic, hydrolytic, and ionization or protonation. Biodegradable devices do not require surgical removal, thus rendering them useful as implantable dosage forms. The transformation of water-insoluble materials into water-soluble materials leads to bioerosion, which can be divided into three types. In the first type, erosion occurs through the cleavage of cross-links or the water-soluble backbone. During bond cleavage, the matrix will begin to swell and eventually dissolve. However, the excessive swelling of polymer limits its applications. In the

second type, protonation or ionization and hydrolysis are involved in changing water-insoluble macromolecules into water-soluble macromolecules, such as polyethylene glycol, polyethyleneimine and polyacrylic acid. Because no backbone cleavage takes place, the solubilization does not result in any significant change in molecular weight. However, unless the backbone is also degradable, polymers in this class are only useful in topical applications that have no difficulty eliminating high molecular weight and water-soluble macromolecules. In the third type, the hydrolysis of labile bonds in the polymer backbone occurs in high molecular weight polymers. Because the polymers in this class converted to small, water-soluble molecules, the principle application of these polymers is for the systemic administration of drugs from subcutaneous, intramuscular, or intraperitoneal implantation sites. [1, 18]

(a) Drug encapsulated with a polymer

Polymer-surrounded drugs in the core have been under development. Simple polymer hydrolysis takes place without enzymatic hydrolysis. The fabrication of a polymer with different molecular weights can adjust the degradation time of the polymer to obtain a wide range of delivering times. Such a delivery system has been developed for use in a variety of pharmaceutical applications, such as the delivery of a sub-dermal contraceptive steroid.[1]

(b) Drug coupled to polymer pro-drug

The polymer containing the bound drug can act either as a depot or as a carrier. In depot mode, the polymer is localized at a certain body site, and the drug is released slowly through the cleavage of its attachment to the polymeric backbone. The backbone of the polymer must undergo a cleavage reaction to prevent high molecular weight residues in the body after drug release. Carriers can offer a unique mode to deliver the drug to specific body sites. In this case, the water-soluble polymer carries a homing group in addition to the bound drug. [1]

(c) Drug dispersed in polymer matrix

When the solubility of drug molecules in the polymer is very slow, the drug is uniformly dispersed throughout the polymer, exhibiting a release that is controlled by the diffusion of the drug through the polymer matrix and/or the dissolution of the polymer. The dispersed molecules are in equilibrium with dissolved molecules. Properties of polymer and drug are determined through the diffusion of drug within the matrix. As the drug is removed from the surface of the device, more drug molecules diffuse from the interior to the surface in response to the decreased concentration gradient leading to the surface. The selection of a drug-polymer combination depends on numerous factors, such as drug concentration, drug solubility in the polymer, polymer-water coefficient, diffusion coefficient, and geometry of the system. This system is used to deliver drugs with low doses that exhibit short half-lives.

Dispersed systems has been used, such as methamphetamine hydrochloride in sustained release tablet, vaginal implantation of contraceptive agents, and Norgestrel attached to intrauterine device.[4, 19]

iv ***Diffusion-controlled devices***

These devices are characterized by their primary release mechanism, the diffusion of the drug through the polymer into the surrounding medium.

Diffusion-controlled release can be found in two basic designs; monolithic devices and reservoir devices.[1]

(a) Reservoir devices

In the reservoir device, a core containing a drug is surrounded by a polymeric film that acts as a rate-controlling permeable membrane. A reservoir device offers a constant release over a considerable period of time, only if an excess amount of undissolved drug is available.[1, 19] A reservoir device can be used to prepare a delivery system with high drug loading levels. Different release rates can be obtained by controlling the thickness and thickness and permeability of the membrane. Based on drug concentration in the device, two types of reservoir release rates can be obtained. First, in the case of zero-order release or constant release, the concentration gradient is the driving force for drug diffusion. The release rate depends on maintaining drug concentration in the reservoir at the saturation level. The preparation of a saturated solution of drug with an excess amount of undissolved solid drug to maintain the saturated level yields a reservoir device with zero-order release behavior. Secondly, the gradual decrease of

the concentration gradient over time leads to non-zero-order release behavior. A reservoir device is habitually more expensive than other systems because of the parameters that need to be controlled, such as membrane thickness, area, and permeability of membrane.[1, 7]

(b) Monolithic devices

In a monolithic device, the drug is mixed thoroughly in a rate-controlling polymer. The drug is then incorporated into a polymer matrix, through which passage to the surface occurs either by diffusion through pores within the matrix structure or by diffusion though the polymeric phase itself.[7, 19] Simplicity of fabrication is one advantage of using the monolithic device. Furthermore, it avoids massive drug release due to rupture of the polymeric coat.[7]

(i) Monolithic solid solution (dissolved drug)

Monolithic solid solution is a delivery system in which the drug dissolved in the polymer must be below drug solubility level in the polymer. It can take the form of a sphere, cylinder, or slab. Penetration of the solvent into the polymeric matrix controls the dissolution rate.[19] The drug release rate from a monolithic device can be calculated according to the kinetic release of this system in two steps. Early time release is used to calculate the first 60% of the release, after which the late time release occurs. For the early part, the release is proportional to time square root. If the initial drug concentration is increased, the system could change from a dissolved system into a dispersed system. [7]

(ii) Monolithic dispersion (dispersed drug)

A monolithic dispersion device is a delivery system in which the drug is dispersed as a solid particle within the polymeric matrix.[7] Low drug solubility in the polymer causes the dissolution of a small amount of the drug and the homogenous dispersion of a large amount of the drug within the polymeric matrix. Monolithic dispersion systems are classified in three types, based on the drug loading level.[7, 19]

(a) Simple monolithic dispersion

For non-biodegradable polymers, drug loading levels, the volume of which can range from 0% to 5%, can have a significant effect on release kinetics. The drug is dissolved from the polymeric medium and is then diffused to the surface of the device. [7]

(b) Complex monolithic dispersion

Drug loading level volumes range from 5% to 10%, and the drug release mechanism is more complex. Drug particles form cavities near the surface of the device, which are filled with fluid imbibed from the dissolution medium. The cavities offer favored pathways for drug particles that remain within the device. In a complex monolithic dispersion device, cavities are not connected to form continuous pathways to the surface; rather, they may increase the overall apparent permeability of the drug in the device.[7]

(c) Monolithic matrix systems

With drug loading volumes of approximately 15% to 20%, drug particles dispersed in the polymeric matrix come in contact with one another. When the volume of dispersed drug concentration exceeds 20%, the cavities formed by drug particles during the dissolution are sufficiently numerous to form a continuous channel to the matrix surface. In the monolithic system, the majority of dispersed drug particles are released by diffusion through these channels. The solubility and diffusivity of drug particles in dissolution mediums filling the channels determine the drug release rate.[7]

2. Polymer matrices for the controlled release of drugs

Polymer matrices for controlled release are classified into three groups, water-soluble, biodegradable, and non-biodegradable polymers.[18]

Polymeric materials used in a polymeric matrix must provide the desirable release rate, be compatible with the drug and the body, and be biodegradable.

a) Classification of polymeric matrices

Polymeric matrices used as drug delivery systems are classified in three basic types.

i ***Water-soluble polymers***

Ethyleneoxy, amine, and carboxylic acid, the polymers that contain hydroxyl, are frequently used as drug delivery matrices. In the body, polymers with hydroxyl or ethyleneoxy groups are dissolved as a result of hydration, and polymers with amine or carboxylic acid groups are dissolved as a result of ionization or protonation. Water-soluble polymers dissolve in water as a result of protonation or ionization; they can be used for controlled drug delivery in gastrointestinal tract. Polyethylene glycol, polyethyleneimine, and polyacrylic acid are examples of such polymers. Since water-soluble polymers dissolve quickly in biological fluids, water-soluble polymers are usually used for short-term (several hours to several days) drug delivery. [18]

Many drugs are either poorly absorbed in the stomach or destroyed by acidic fluid; to increase efficacy, these drugs can be formulated as tablets or capsules with polymers of half esters of maleic anhydride.

Water-soluble polymers are used as aqueous solutions for drug delivery. After polymer dissolution, the polymer increases the viscosity of the drug, which leads to longer drug retention in the desired application. This technique is commonly used with the ocular, nasal, and oral application of drug solutions. [20, 21]

ii ***Non-biodegradable polymers***

Because these polymers are basically inert in the body and do not undergo any chemical reactions therein, non-biodegradable polymers can be used for extended drug delivery. Due to their biocompatibility and higher permeability of many drugs, silicones are excellent materials for drug delivery. Silicone has also been used in various drug deliveries, which has lead to the commercialization of silicone for such items as transdermal devices for nitroglycerine and contraceptive steroids. The drug release rate from drug delivery systems made of silicone matrices or reservoirs can be modulated according to the Fickian theory. [18]

iii ***Biodegradable polymers***

Bioerodiblity is the ability of the polymer to degrade to control drug release rate. In this context, the term "biodegradable polymers" refers to water-insoluble polymers that are gradually converted in the body into water-soluble materials by chemical reactions. Since degradation involves chemical reactions that usually occur over a long period of time, these polymers can be used for long-term drug delivery. Different methods can be used to change water-insoluble polymer into water-soluble materials in the body.[18, 22]

In the first method, a side chain that undergoes hydrolysis in the body to produce hydroxyl, carboxyl, or other hydrating groups can be added to a

polymer chain. Therefore, these groups act to make the entire polymer water-soluble. The second method is to crosslink a water-soluble polymer with a hydrolysable cross-linking agent. The polymer becomes water-soluble once it is placed in the body. In the third and most frequently used method, water-soluble polymers house hydrolysable functional groups directly in the polymer chain. Upon hydrolyzation of such groups, the polymer chain is slowly reduced to increasingly shorter segments that finally become water-soluble. In this case, an extremely high-molecular-weight polymer with good mechanical properties can be used. In this case, the polymer is eliminated from the body when the polymer chain is reduced into water-soluble fragments.[18]

Even though many examples of the first two categories have been evaluated for drug delivery, problems, such as controlling the hydrolysis rate of the side chain groups and preventing the reaction of side chain groups with the drug itself have occurred. Moreover, it is very difficult to provide enough cross-linking to make the polymer insoluble but also degradable within a reasonable period of time. In the other biodegradable polymers, the polymer chain of the water-soluble segment must be less than (50,000) Daltons in order to achieve proper elimination from the body. Because of the disadvantages of the first two categories, the third category of biodegradable polymers has received more attention for drug delivery applications.[18]

Aliphatic polyesters prepared from lactic and glycolic acids are widely used in various applications as synthetic biodegradable polymers.

Homopolymers and copolymers of lactic and glycolic acids have been studied. Those polymers have Food and Drug Administration approval to be used for drug delivery matrices. The commercial availability of polylactic acid and polyglycolic acid as well as the ability to accurately control their biodegradation rates make these polymers the first choice for biodegradable polymers.[18]

Different degradation times of biodegradable polymers afford a wide range of applications for those polymers as drug delivery matrices. The degradation time of aliphatic polyester homopolymers in vivo normally ranges from one to two years, depending on crystallinity and hydrophobicity. Polyanhydrides and polyorthoesters are other series of biodegradable polymers which depend upon chain degradation.[18]

Polyanhydrides and polyorthoester polymers contain hydrophobic units that join along polymer chains by functional groups and are subjected to hydrolysis. Because of the nature of those polymers, water only breaks through the outer layers when the polymers are implanted in the body. The outer layers' contact with water causes quick hydrolysis of the water-labile linkage, followed by the degradation and loss of the outer layer of the polymer. After the loss of the outer layer of polymer, another layer comes in contact with water and the process continues until the polymer is gradually eroded from the surface.[18]

The rate of hydrolytic degradation at the surface of polyanhydrides and polyorthoester polymers is much faster than the permeation rate of water into

the matrices of those polymers. The pH solution increases as the degradation rates of the copolymer and homopolymers increases. In many examples of drug release from these polymers, the drug release rate has a good correlation with polymer degradation or erosion. In some examples of compression-molded release, drug release has been faster than polymer erosion, probably because of inhomogeneous drug dispersion or a microporous structure. These polymers protect drugs susceptible to degradation in the body and deliver the drug at a constant rate in an active. This maintains the polymers' usability in different applications.[18, 20-25]

3. Polylactic acid as drug carrier

a) Physical and chemical properties

The presence of a methyl group on the alpha carbon of polylactic acid differentiates the polylactic acid chemically, physically, and mechanically from polyglycolic acid, even though the two are structurally very similar. There are many factors such as the ester linkage due to presence of the methyl group; the molecular weight; degree of crystallinity, and the physio-chemical environment, which make the polylactic acid more hydrotically stable than polyglycolic acid. The chirality at alpha carbon of polylactic acid makes it possible for the polymer to exist as L, D, or DL isomers. A racemic mixture of L (-) lactide and D (+) lactide isomers is used to prepare DL-PLA, while L-PLA is made from L-lactide and D +PLA is made from D+ lactide.[26, 27]

b) Poly (L-Lactic acid)

L- Polylactic acid has a melting point (T_m) of approximately 175°C and a glass transition (Tg) of approximately 65°C. It is a biodegradable, crystalline polymer. Its tensile strength is (10,000-15,000 psi) and its modulus of elasticity is (500,000 psi), which results in a more crystalline polymer. The crystallinity of L-PLA is reported in the range of 35%, which makes it less than that of PLG. L-polylactic acid is soluble in organic solvents, such as chloroform, and has a specific gravity of approximately 1.2-1.3.[24, 28, 29]

Solid-state polymerization is used to prepare poly (L-lactic acid) with a very high-molecular-weight polymer (1,000,000). When polymerization temperatures are lower than the melting point of the polymer, solid-state polymerization is obtained as a result of the crystallization of the polymerizing polymer.

Stannous octoate or stannic chloride dehydrate are used as catalyzers in the polymerization of L-polylactic acid.[26, 27, 30]

c) Poly (DL-lactic acid)

On the other hand, DL polylactic acid has a Tg of approximately of 57°C. It is a completely amorphous polymer with a specific gravity of approximately 1.2-1.3, which is similar to that of L-PLA. L-polylactic acid is less accessible to hydrolytic attack than DL-polylactic acid, which makes the DL-polylactic acid polymer degrade faster than L-polylactic acid polymer. DL-polylactic acid has a much lower tensile strength (5,000 psi) than L-PLA and PLG and

a modulus of elasticity of (250,000 psi), probably due to the lack of polymer crystallinity. Temperature ranges of 135-155°C are typically used in DL-PLA polymerization. Because it is an amorphous polymer, solid-state polymerization cannot be achieved with L-polylactic acid. The reaction can be catalyzed by stannous octoate or stannic chloride dehydrates. Chain-control agents, such as water, primary alcohols, amines, or other active hydrogen compounds are used to control the molecular weights of PLA. Tri- or poly-functional chain-control agents are used to prepare branched polymers. Alcohols, such as 1-dodecanol or 1- or 6-hexanediol, which have functionalities of less than two, are used to prepare linear polymers.[24, 26, 27, 30]

d) Preparation

Direct polymerization from linear monomers or oligomers of lactic acid might be used, but this yields a polymer with a limited molecular weight. For most applications, using cyclic dimers as starting materials is the optimal method for polymer and copolymers. The two methods are explained below. [26, 27, 30]

i *Direct polymerization*

Low molecular weight polylactic acid can be prepared through the direct polyesterification of lactic acid. Because water can effect the condensation of α-hydroxycarboxylic acids, water is removed from the reaction mixture by

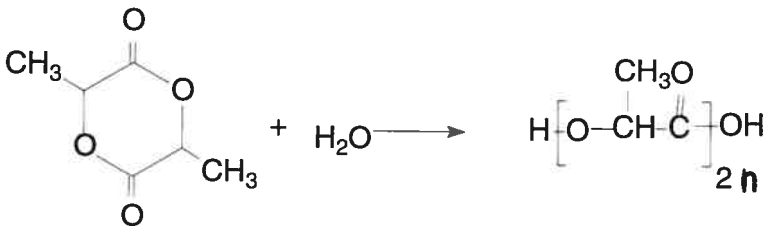
boiling the water or by performing azeotropic distillation with an aromatic hydrocarbon solvent.[26, 31]

Adding an acid catalyst at a temperature below 120°C increases the reaction rate; however, above 120°C, water removal is a rate-limiting step, so there is no benefit of adding a catalyst. Reactants with known purity and stability are necessary for an efficient reaction. The presence of monofunctional impurities in the reactants can terminate the polymer chain. In order to prepare a chain with 100 mer units, the impurities must be less than 1%. To prepare a lactic acid polymer with high molecular weight of (10,000) or higher, it is necessary to use the cyclic monomer of lactide rather than the direct condensation method. [26]

ii ***Polymerization via cyclic monomers***

When high-molecular-weight polymers are required, polymerization via cyclic monomers has many advantages over the direct method. Contrary to direct polymerization, this method does not require a high degree of dehydration. Cyclized or linear forms of the polymer can be differentiated by their physical properties. Moreover, monofunctional impurities can be reduced and stoichiometry, assured. Acid catalysts and certain organometallic compounds are the most useful catalysts. [26]

The formation of polylactic acid from lactide can be written as follows:



Equation 1 : Preparation of polylactic acid from lactide

In the polylactic acid preparation illustrated in Equation 1, one mole of polymer is formed for each mole of water added to the reaction mixture. Because each mole of catalyst contains one mole of water, the number of moles of polymer produced at equilibrium equals the number of moles of catalyst added. It is useful to use organometallic catalysts, such as dialkyl zinc, trialkyl aluminum or tetralkyl tin complexes, to prepare polymer with an average molecular weight of 40,000 or greater.[26]

e) Biomedical applications

Polylactic and polyglycolic acids and their copolymers have recently, been used as matrices of drug delivery and as excipients for the sustained release of drugs. The formation of surgical mesh, sutures, woven or knitted tubular or vascular grafts comprised of copolymer fibers, absorbable staples, solid prostheses used as cylindrical pins and screws, and reinforcing plates are further applications of polylactic and polyglycolic acids and their copolymers.[26, 30, 32-35]

i ***Utilization as sutures***

This application has generated the most valuable information about biocompatibility and biodegradability. Polylactic acid and polyglycolic acid polymers have a little or no residual effects on tissues. Very slow shrinkage when it is combined with PLG might cause lactic acid with optical isomers of pure L(+) or D(-) to be chosen over D,L-lactic acid.[26, 30, 34, 35]

ii ***Use as prostheses***

Based on the purpose of those preparations, different proportion of PLA and PLG or pure forms of one or the other are used to achieve the desired implant degradation time. Faster polymer degradation is obtained using DL-PLA rather than L (+)-PLA.

When polylactic acid and polyglycolic acid polymer are used in implantation, there is no toxic, inflammatory, or tissue reaction reported. Moreover, this method renders surgical removal unnecessary. The degradation products of those polymers have none of complications that occur with conventional implants such as corrosion, foreign body reaction, and migration after being left for a long time in the body.[26, 30, 32, 33, 35]

iii ***Using the polymer as a carrier system in implantation***

Implants prepared from polylactic acid and polyglycolic acid polymers in forms such as fibers, pressed tablets, extruded forms, or films are used in controlled drug delivery.[36]

(a) Fibers

Biodegradable fibers are prepared from polylactic acid, and can take the form of solid fibers or hollow ones. These fibers are given subcutaneously, using special needles. The drug delivery rate of the hollow fiber depends strongly on the structure membrane of the wall. Hollow fiber systems can be used with any drug that can be made in an aqueous solution. Such systems are interesting because of their ease of use and their ability to release the drug in a controlled manner; however, such reservoir systems always carry the risk of "dose dumping" as a result of membrane failure.[36]

(b) Tablets

A direct compression method, at either ambient or elevated temperatures and with or without added solvent, is common for preparing polylactic and glycolic acid tablets for implantation. Most compression methods are based on traditional pharmaceutical techniques, which are limited to low-molecular-weight polymer with glass transitions at approximately 30°C. Unless a solvent is used, this allows for the fusion of individual particles and the integration of polymer and drug upon compression.[36]

(c) Extruded implants

Extruded matrix delivery systems disperse a drug in a polymeric matrix. These devices usually take the form of cylinders. They can be used as monolithic matrix release systems or be coated with polylactic acid to limit degradation and subsequent drug release.[36]

(d) Films

Films are prepared simply by dissolving the polylactic acid polymer in a solvent, such as chloroform or acetone dichloromethane, and then adding the drug to obtain solution or suspension.[36]

f) Some factors that affect drug release rate from polymeric matrices

i *Drug loading*

Since sustained release and controlled drug release have been the focus of pharmaceutical research, the polymeric matrix has received most interest. After Higuchi's work (1963) on the release of drugs from polymeric matrices, more effort is being devoted to the study of the parameters that affect release from the polymeric matrix. Drug loading has a potential effect on release from the polymeric matrix. A drug loading level (high or low) within the polymeric matrix can be treated with either a porous matrix or a non-porous matrix system.[37, 38]

ii *Porosity*

Generally, porosity is the volume of void spaces in a given material. It is the inter- and intra-pore space. For a matrix device, porosity is defined as the part of the matrix that exists as pores and channels that liquid can penetrate. Different instruments can measure porosity based on the characteristic information of the sample to be measured, such as density, gas adsorption, water displacement, and porosimetry. Mercury intrusion permeability is used when the actual pore size distribution is needed. Helium pycnometry and

mercury porosimetry are other methods for porosity determination. Drug release can be modulated by controlling porosity through pore size and volume fraction.[39-43]

iii ***Particle size***

Unless the particle shape is defined, identifying the particle shape is very difficult. There is no unique diameter for particles. An equivalent spherical diameter that relates the size of a particle to the diameter of a sphere with the same surface area, volume, or diameter is used to calculate particle size. There are different methods for measuring particle size. Some of the most common methods are microscopy, screen (sieve) analysis, electronic counting (Coulter, Malvern), sedimentation (Andreasen apparatus), permeametry (sub-sieve sizer), and reflectance FTIR (Otsuka and Mastuda, 1996). [39, 40, 43]

iv ***Effect of plasticizer on drug release from polymeric matrix***

(a) The effect on the polymer

Polymers are used to coat tablets and beads. The plasticizer improves the physical properties of the polymer by reducing brittleness, improving flow, and increasing toughness, tear resistance, and strength. The glass transition of the polymer can be reduced by adding the plasticizer. The amount and type of plasticizer and the reaction between the polymer and plasticizer will determine the degree of plasticization. Increasing the flexibility of the polymer depends on the degree at which the plasticizer affects the intermolecular

attractions, thus increasing the mobility of the molecules. The plasticizer affects the rate of release by changing the water permeability of the polymer. It also decreases polymer-polymer interaction and can improve the mechanical properties of the polymeric matrix.[44-48]

(b) The effect on drug release

The type and amount of plasticizer have an important influence on the drug from the polymeric matrix. The plasticizer increases the drug release from the polymeric matrix by increasing the mobility of the polymeric chain. A plasticizer can also influence the physicochemical characteristic of the polymer, which, in turn, affects the permeability rate of some molecules. Permeation occurs because the plasticizer agents can weaken the intermolecular forces between the polymer chains. The presence of plasticizers reduces polymer-polymer interactions, thereby increasing the mobility of polymer chains and, consequently, drug permeation.[45, 48]

4. Microspheres

a) Introduction

Microspheres are polymeric entities that fall in the range of 1-1000 micrometers. They are porous microparticulate drug delivery systems that promote the controlled release of drugs. They represent a polymeric matrix system containing the drug uniformly distributed throughout the polymeric matrix. Microspheres are one method of representing the polymeric matrix systems with uniform drug distribution. Both natural and synthetic polymers

are used for microsphere preparation. Drug and polymer properties are crucial factors for choosing a suitable method of microsphere preparation.[49, 50]

A number of methods are used for microsphere preparation, each of which has its own advantages and disadvantages. Microsphere characteristics are influenced by the chosen preparation method.[51]

b) Methods of preparation

i *Spray-drying technique*

The spray-drying technique has been widely used in the pharmaceutical industry. The technique has recently been used to prepare microparticulate drug delivery systems. Spray drying is an attractive technique because the rapid, single-step method is suitable for sensitive drugs. It consists of spraying a suspension or a liquid through a nozzle in a drying chamber to obtain spherical solid particles. The structure of microparticles will be determined based on the polymeric solution that will be sprayed and on whether the drug is dispersed or dissolved in the polymeric solution. Microspheres are obtained by spraying a solution of the drug and the polymer, while microcapsules are obtained by spraying the polymeric solution in which the drug is suspended. [49]

ii *Solvent evaporation*

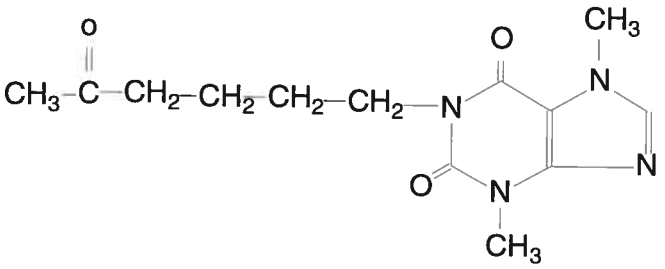
The evaporation of an organic solvent is another method for microsphere preparation for controlled drug release. Microspheres can be prepared by

dispersing oil droplets that contain the drug and the polymer. The organic solvent is chosen based on the physicochemical properties of drug. A double emulsion is frequently used. First, the aqueous phase is prepared by dissolving the drug in water for encapsulation. DCM (dichloromethane) is used as an organic solvent, and the aqueous phase is dispersed in the solvent, which contains a biodegradable polymer to prepare the first W/O emulsion. An aqueous stabilizer is used to prepare the second O/W emulsion. The microspheres are formed when the DCM is evaporated, and the hardening of the polymer causes the encapsulation of the drug.[52, 53]

iii ***Solvent extraction***

The preparation of microspheres by solvent extraction generally consists of dispersed or dissolved drug in an organic solvent that contains the polymer. The organic phase is then emulsified in another immiscible, often aqueous phase, followed by an extraction process to obtain microspheres from the droplets of the organic solvent. The organic solvent of the dispersed phase of the emulsion is eliminated by two stages. In the first stage, the solvent extraction is the diffusion of the solvent in the dispersing phase. In the second stage, solvent evaporation is the elimination of the solvent at the dispersing phase-air interface.[54]

5. The drug model pentoxifylline



Empirical formula $C_{13}H_{18}N_4O_3$ Molecular weight 278.31

Pentoxifylline has a melting point range from 105°C to 106°C and is very soluble in acetic acid; freely soluble in chloroform, methanol, and acetone; sparingly soluble in ethanol; slightly soluble in ether; and practically insoluble in hexane. Pentoxifylline decreases blood viscosity, thereby improving blood flow probably through its effect on erythrocyte deformability, platelet adhesion, and platelet aggregation. It is also thought to improve the oxygenation of ischemic tissues. Pentoxifylline is used mainly in the treatment of peripheral vascular disorders. It has also been used in cerebrovascular disorders. The reason for the choice of pentoxifylline as a drug model was to continue a previous project in the laboratory. The objective of the project is to design an oral modified release form (reservoir type) for the release of pentoxifylline over a period of at least for 48 hours to treat a Founder afoot. Founder foot is a horse disease characterized by a reduced microcirculation of the foot leading to lameness. The administration of pentoxifylline improves circulation, reducing the symptoms and prolongs the useful life of the animal. [55, 56]

B. Objective

The objective of this project is to develop and characterize plasticized film formulations containing mixtures of high and low molecular weights of polylactic acid with different drug loading levels.

The specific objectives are as follows:

1. To develop and optimize a plate-coating process technique that will yield a homogenous film.

2. To develop and characterize a formulation that could be transformed into a dosage form to be used in vivo.

3. To evaluate the effect of formulation process parameters, such as drug loading and plasticizers on in vitro release kinetics

II. Materials and methods

A. Materials

1. Chemicals

High-molecular-weight PLA 252000, lot number 516988, was brought from (Polysciences, Inc). Low-molecular-weight PLA 64800, lot number R-020510, was purified from previously synthesized PLA in the laboratory. Pentoxifylline with lot number 18P0334 was used as drug model. Dichloromethane (solvent grade) with lot number A04814 was brought from J.T. Baker and was used as a solvent for the polymeric solution. Chloroform lot number 001173, (HPLC) grade was brought from Laboratoire Mat and was used as a mobile phase of Gel Permeation Chromatography (GPC). Acetone (99.5% histological) grade, lot number 00648DB, was used in low-molecular-weight PLA purification. Polystyrene with different molecular weights were brought from Polysciences Inc and were used as standards for PLA molecular weights determination. The different molecular weights were as follows: molecular weight 20,000, lot number 430232; molecular weight 50,000, lot number 431655; molecular weight 90,000, lot number 432010; molecular weight 200,000, lot number 412702; molecular weight 400,000, lot number 431655; and molecular-weight 600,000, lot number 414884. Sodium phosphate dibasic A.C.S reagent, lot number 083K0120; sodium chloride crystal A.C.S reagent, lot number M35589; and potassium phosphate mono basic crystal A.C.S reagent, lot number M37148 were brought from J.T.Baker, Inc and were used for phosphate buffer preparation.

2. Equipment

Compressed air (80 psi) was used with a spray gun (Badger250-4) that was used to spray the polymeric solution onto stainless steel plates of approximately 2cm x 2cm of known surface area and 0.6mm thickness. An Ultrospec 2000 manufactured by Biocharm, Ltd. and a UV/visible spectrophotometer 8452A Diode Array spectrophotometer manufactured by Hewlett-Packard were used to measure drug release at wavelength 274nm. Water gel permeation chromatography GPC model ALC-202 liquid chromatographs manufactured by Waters Associates Inc were used to determine PLA molecular weights. A differential scanning calorimetry (DSC) Mettler TC II TA processor manufactured by Mettler was used to characterize low- and high-molecular-weight drugs as well as selected samples of films. An electron microscope MA JSM-5900LV, manufactured by Jeol Inc. Peabody was used to characterize the surface of selected film formulations before and after dissolution. Scintag XDS-2000, Si (Li) Peltier-cooled solid-state detector CuKalpha source at a generator power of 45 kV and amperage of 40 mA was used to measure crystal peaks of the drug and the polymer in selected film formulations.

B. Methods

1. Characterization of PLA

a) Purification

Polylactic acids of low molecular weight were purified with 38.26 g of PLA for the different molecular weights, as shown in Table 1. The PLA was dissolved in 382 ml of 10% acetone in water at room temperature and stirred for 30 minutes. The PLA solution was slowly poured into 4 liters of distilled water under constant mixing at room temperature in 50 ml increments of acetone in 500 ml of distilled water and then centrifuged at 3000 rpm for one hour. After the separation of the supernatant, sodium sulfate was mixed into the supernatant to precipitate the remaining PLA. The solid product was dried for 24 hours over phosphorous pentoxide under vacuum to remove residual solvents.

Weight	MW_w	MW_n	Polydispersity
17.77g	32700	12000	2.73
16.70g	36600	17900	2.04
3.79g	35000	12600	2.76

Table 1: Molecular weights data of 3 selected lots of PLA for blending and purification.

b) Molecular weight determination by gel permeation chromatography

Molecular weight and polydispersity of polylactic acid samples were determined by Waters Gel Permeation Chromatography (GPC) model ALC-202 liquid chromatographs (Waters Associates, Inc.). Gel permeation chromatography was performed with chloroform as a mobile phase using a Waters pump system connected to a differential refractive index detector and

a Waters 730 data module. Two Phenogel columns with nominal porosities ranging from 5um 10^3 to 5um 10^5 angstroms were used for all samples and polystyrene standards. A standard curve from five different polystyrene molecular weights was created as it is shown in Figure 1. In order to obtain the calibration coefficient, 5 mg of each standard was dissolved in 5 ml chloroform and 100 µl was injected. After the calibration coefficients were obtained, 50 mg of each sample was dissolved in 5 ml chloroform and 50 µl was injected to determine the molecular weight.

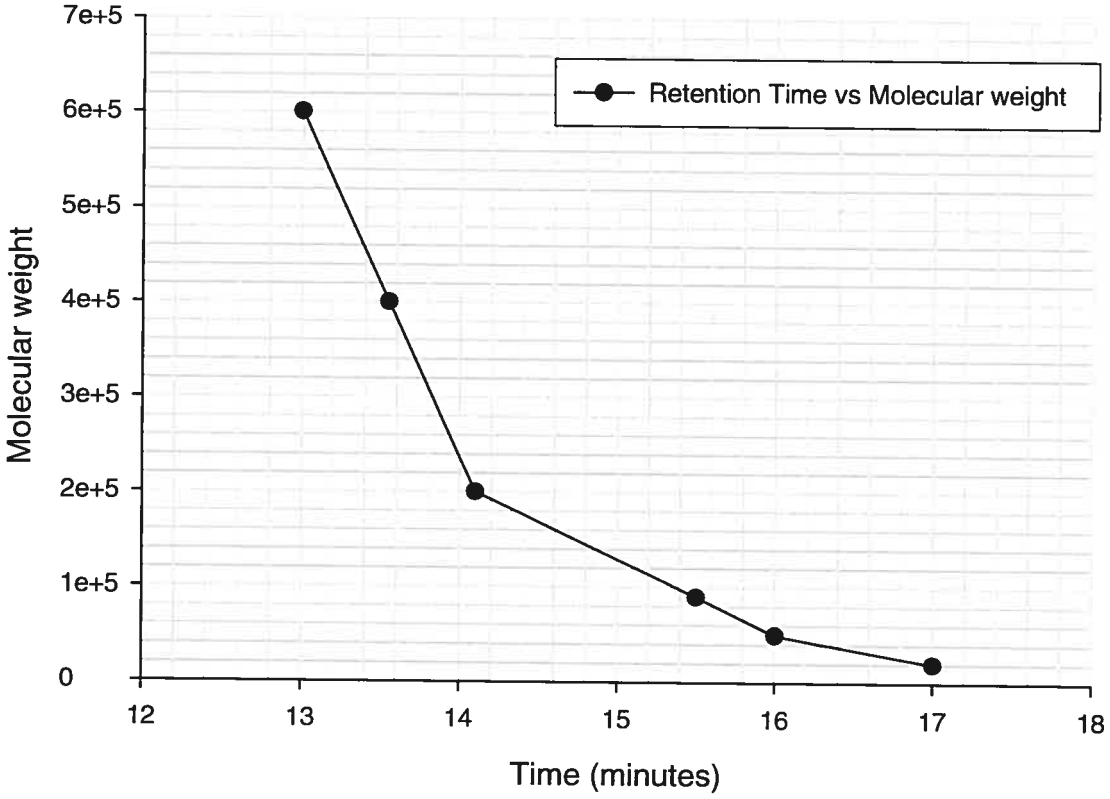


Figure 1: Calibration curve of polystyrene standards for the PLA molecular weight determination.

2. Preparation of the polymeric solution and plate-coating process

a) Polymeric solution preparation

The polymeric solution was prepared by measuring 75 ml of the dichloromethane (DCM) solvent and then weighing the amount of drug required to obtain the necessary drug loading. The drug was added to the solvent by stirring at room temperature until a clear solution was obtained, after which the polymer was added to the solution by stirring for 40 minutes until it was completely dissolved. Different drug loadings were prepared with and without plasticizers. In the cases where the plasticizer was needed, the right volume of plasticizer was added at beginning before the drug is added.

b) Plate coating process

Stainless steel plates 2cm x 2cm in size and 0.6mm in thickness were first cleaned once in 1N HCL hydrochloric acid for 20 minutes and then put in the solvent DCM for another 20 minutes. Four dried and cleaned plates were arranged over a clean sheet for the coating process. The polymeric solution that contained drug, the polymer, and the plasticizer was sprayed onto the first side of the plates. A spray gun, Badger 250-4, was used as a spraying system. A model 202 Oster air gun used as a source of hot air was directed onto the plates after each spray to evaporate the solvent, to avoid condensation of the moisture on the plates, and to produce a clear homogenous film. The plates were weighed before and after the spraying process to calculate weight gain and drug content of the film. Through

numerous trials of spraying the polymeric solution containing drug and DBS over the stainless plate and applying hot air to dry the film, the experimental conditions such as spray time, spray distance, and drying time were optimized. The quality of compressed air is critical and must be free of particulate matter, oil, and be anhydrous.

3. In vitro release study

A standard curve of the drug model with five different concentrations was prepared using dilutions from a stock solution. The plate containing polylactic acid film was hanging down in the flask filled with a phosphate buffer solution with a pH of 7.4. The flask was put in a thermostated water bath shaker at 37C°. Samples from the release solution were periodically removed from the flasks using syringes. The drug released into the medium buffer was assayed using a Hewlett-Packard 8452A Diode Array Spectrophotometer and Ultrospec 2000 UV/Visible Spectrophotometers (Pharmacia Biotech) at a wavelength of 274 nm. The percent and amount of drug release were used to evaluate the kinetics of release from the different batches.

4. Polymeric film characterization

a) DSC scanning

Thermal characterization was carried out using a Mettler TC II TA processor differential scanning calorimeter. Two heating runs up to 200C° and one cooling run at -40C° at 10 K/min were performed. The melting point (Tm) and the glass transition (Tg) of polylactic acid samples and films with

different levels of plasticizer and drug loadings were determined. The sample weights ranged from 4mg to 22mg. Aluminum sample pans were used. Different samples of low and high molecular weight of PLA with and without DBS were prepared by dissolving the materials in the solvent DCM (dichloromethane) and then evaporating the solvent.

b) Scanning-electron microscopy

The samples were mounted on aluminum stubs using carbon tape and then examined directly (without conductive coating) in an MA JSM-5900LV electron microscope (Jeol Inc. Peabody) using secondary electron imaging with an accelerating voltage of 5-7 kV.

c) Powder X-ray diffraction

X-ray diffraction patterns were measured with a Scintag XDS-2000, Si (Li) Peltier-cooled solid-state detector, CuKalpha source at a generator power of 45 kV and amperage of 40 mA. Divergent beam slits of 2 and 4 mm were used, as were receiving slits of 0.5 and 0.2 mm. Scan range was set from 2 to 40 degrees 2 θ using the step scan mode at a step size of 0.02 degrees 2 θ and a count time of 2 seconds. Samples were placed on the low background quartz disk. In order to obtain a good diffraction pattern, rather than grinding the samples, the films of different samples containing low molecular weight PLA, 10%, 20%, and 60% drug and 10% DBS were slightly broken up. A high molecular weight PLA sample was used without grinding

and a standard holder was used. The instrument alignment was verified weekly using a corundum disk (NIST SRM 1976).

III.Results and discussion

A. Characterization of PLA

1. Gel permeation chromatography results

As shown in Table 2 and Figure 2, GPC results of PLA characterization were obtained for the low- and high-molecular-weight PLA. The results confirm the expected significant differences in molecular weight required for this study.

Sample	Mn	Mw	Mz	D
Low molecular weight	25300	64800	445000	2.55
High molecular weight	146000	252000	222500	1.72

Table 2: Data of low- and high-molecular-weight PLA characterized by Gel Permeation Chromatography.

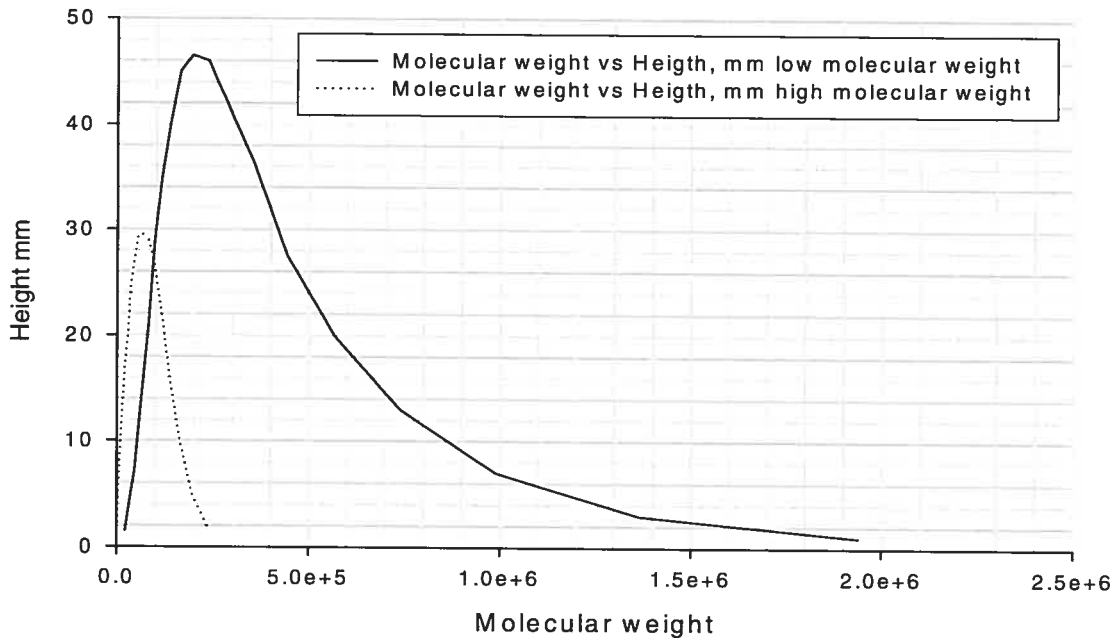


Figure 2: Molecular weight distribution of low- and high-molecular-weight PLA.

2. Powder X-ray diffraction

Table 3 shows the diffraction peaks of pure pentoxifylline. Table 4 reports an X-ray diffraction characteristic of selected peaks of samples at different drug loading levels (10%, 20%, and 60%) and a constant plasticizer level (DBS) (10%) based on the intensity of four specific different peaks. These peaks were selected on the basis of lack of interference from the PLA peaks. It shows that pentoxifylline sample peaks increase as drug loading levels increase. Diffraction peaks of the drug (pentoxifylline) confirmed the presence of the crystalline drug (pentoxifylline) dispersed in the matrix. Table 5 shows PLA diffraction peaks from the samples increasing as the drug loading decreases.

Scattering Angle (degree 2-θ)	d-spacing (A)	Relative Intensity I/I_o (%)
6.77	13.0452	14.99
7.57	11.6683	50.56
11.45	7.7216	12.70
12.65	6.9916	44.28
13.57	6.5196	47.56
15.13	5.8507	100.00
15.18	5.6006	9.14
20.41	4.3475	13.00
21.69	4.0938	14.91
22.41	3.9638	11.69
24.05	3.6971	27.61
24.93	3.5686	6.76
25.69	3.4647	8.12
26.53	3.3569	9.83
27.85	3.2007	22.23
28.61	3.1174	7.81
29.85	2.9906	8.01
31.65	2.8246	7.74
32.41	2.7600	6.43
34.45	2.6011	12.64
35.13	2.5523	10.16
42.05	2.1469	5.60
45.61	1.9873	5.00

Table 3: Crystallography data from the X-ray powder diffraction pattern of pure pentoxifylline.[55]

Scattering Angle (degree 2-θ)	Height of pentoxifylline Peaks		
	10% loading	20 % loading	60 % loading
13.57	-	0.35mm	0.65mm
15.13	-	0.25mm	0.35mm
24.05	-	0.45mm	0.75mm
28.61	0.20mm	0.40mm	0.60mm

Table 4: Crystallography data of pentoxifylline from the X-ray powder diffraction pattern of films with different pentoxifylline loading samples (10%, 20%, and 60%) at a constant plasticizer level (DBS 10%).

Scattering Angle (degree 2-θ)	Height of PLA Peaks		
	10% loading	20 % loading	60 % loading
16.50	6.20mm	2.60mm	0.60mm
19.00	1.60mm	0.70mm	-

Table 5: Crystallography data of PLA from the X-ray powder diffraction pattern of films with different pentoxifylline loading samples (10%,20%, and 60%) at a constant plasticizer level (DBS 10%).

B. Drug release studies

A USP dissolution system was used to evaluate the drug released from different formulations of polylactic acid polymeric film. The effect of drug loading with and without plasticizer on drug release was evaluated first. The plasticizer was used to modify the physical properties and release characteristics. Dibutyl sebacate was selected as the plasticizer on the basis of prior research.[44, 48]

1. Drug release from unplasticized polymeric film

Drug released from different formulations containing 50% low- and 50% high-molecular-weight PLA with different drug loadings (20%, 25%, and 30%) was evaluated from spray-coated stainless steel plates immersed in a dissolution fluid. Figures 3 to 5 show the dissolution results for the different loadings. The results of the 20% drug loading show extreme variability of drug release among coated plates of the same batch due to the eventual cracking of the film. Film cracking occurs at variable times and to different extents due to the film quality as shown in Figure 3 for different films containing 20 % drug loading without DBS. The film for the various plates cracked at 60 hrs (#1), 2 hrs (#2), at 48 hrs (#3), at 12 hrs (#4) and at 4 hrs (#5). The extreme variability in dissolution for film plates from the same batch makes the film without plasticizer makes this approach totally unreproducible and unreliable for drug delivery. The cracking of the film leads to the infiltration of dissolution media between the film and the plate, thereby increasing the effective surface area of dissolution leading to an increase in the rate of release. Because of film cracking, an accurate evaluation cannot be achieved for the drug release from the film without the plasticizer.

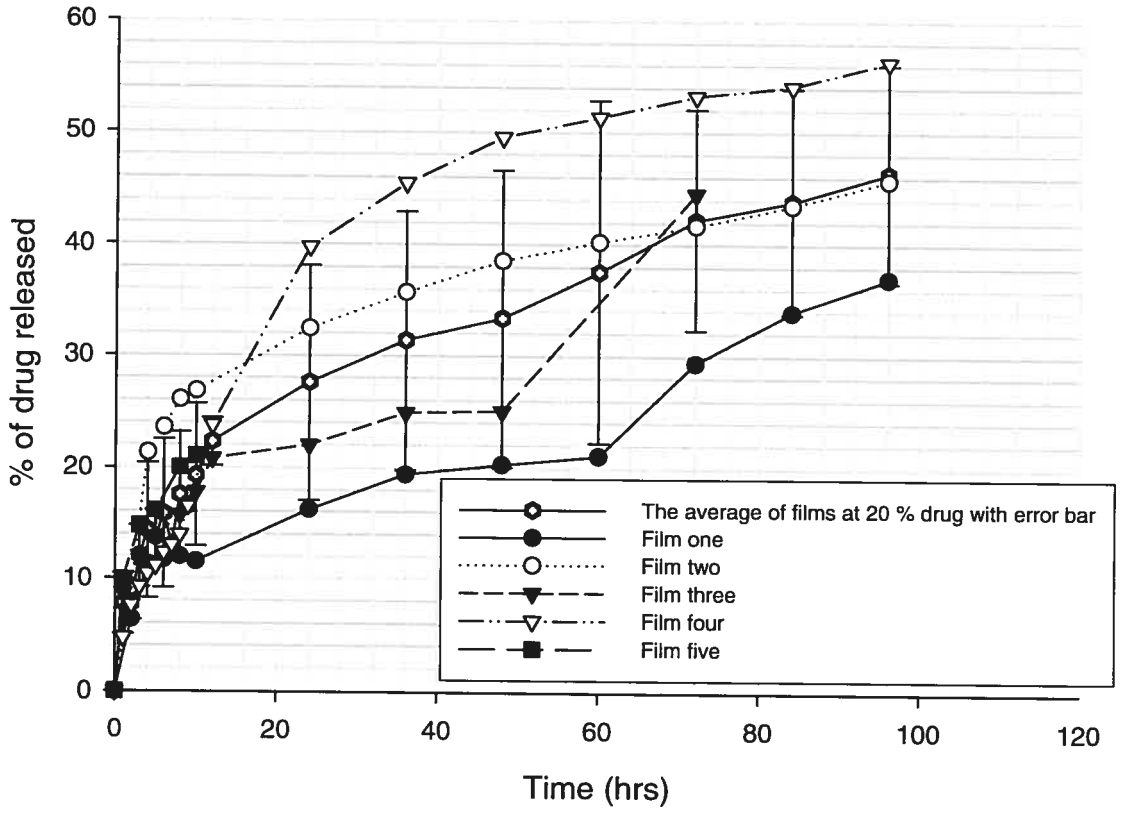


Figure 3: Percentage of drug released as function of time(hrs) for films containing 20 % pentoxifylline without plasticizer

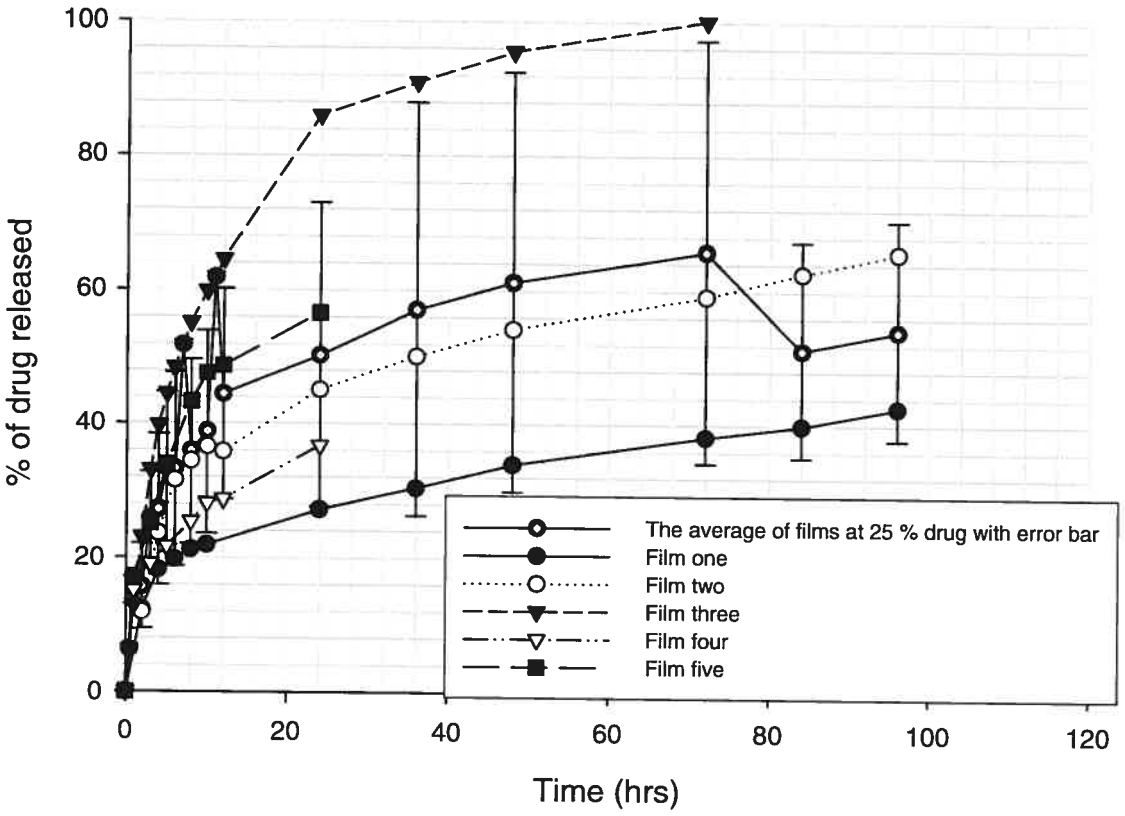


Figure 4: Percentage of drug released as function of time(hrs) for films containing 25 % pentoxifylline without plasticizer

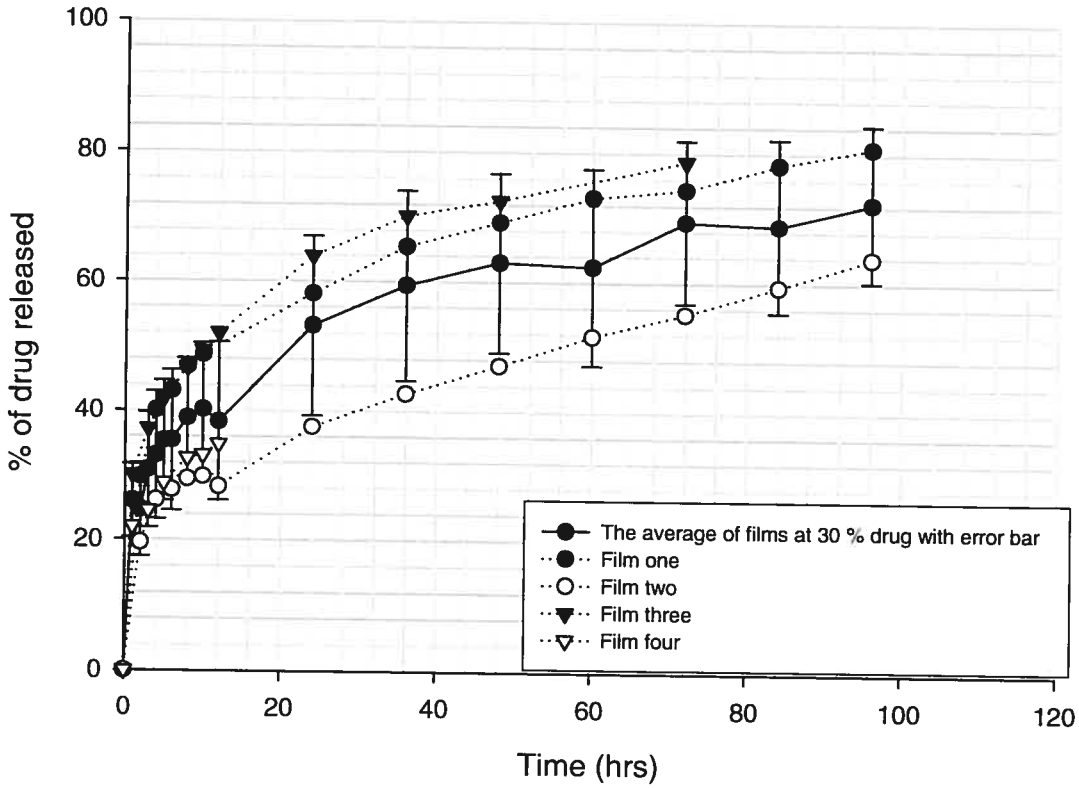


Figure 5: Percentage of drug released as function of time (hrs) for films containing 30 % pentoxifylline without plasticizer

2. Release from polymeric film plasticized with dibutyl sebacate

As a result of previous dissolution study data, dibutyl sebacate (DBS) was added to the film formulation at different levels, 10%, 20%, and 30%, and drug loading levels of 10%, 20%, and 60 %. The dissolution studies show that there was no sign of film cracking at any level of plasticizer. Figure 6 shows that, at a 10% drug loading, as the DBS level increases, the release rate increases due to a decrease in crystallinity of the polymer, which results in a higher diffusivity of the drug in the polymer.[57, 58]

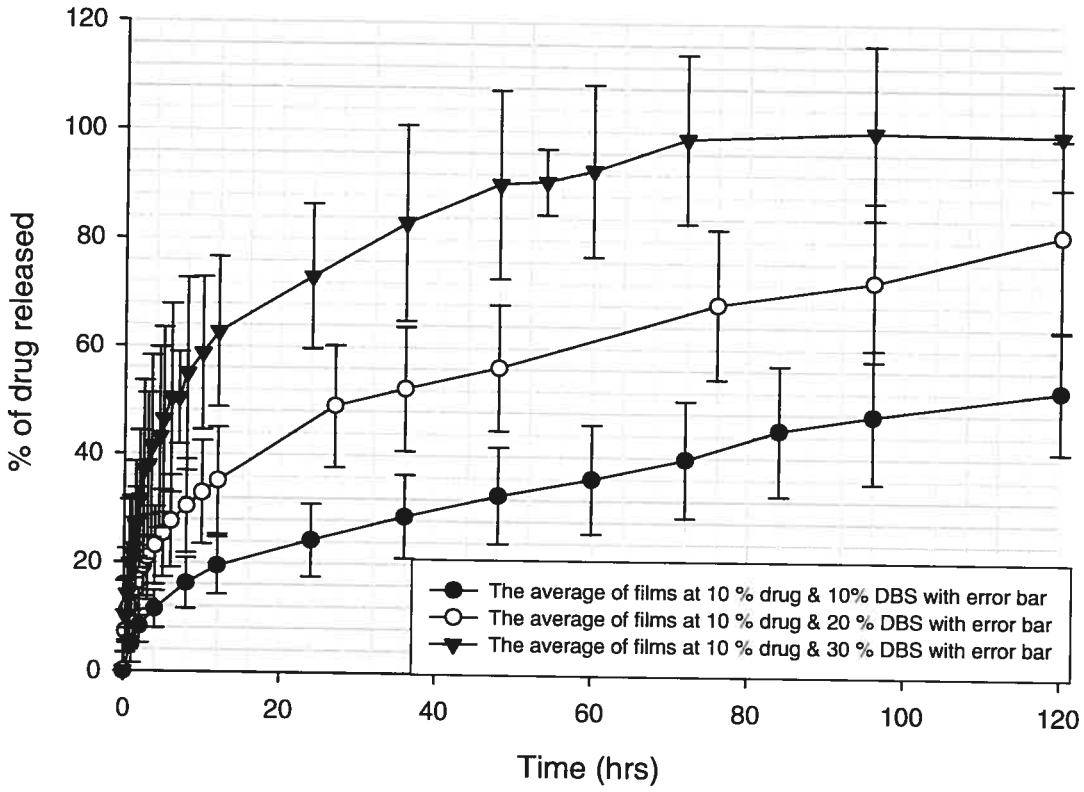


Figure 6: Percentage of drug released as function of time (hrs) for films containing 10 % pentoxifylline and 10 %, 20 %, and 30 % DBS

Figure 7 shows that increasing the level of plasticizer for the 20% drug loading increases the release rate. It also makes evident that the release rate is much higher than at a 10% drug loading, which is probably due to a mixed mode release mechanism of diffusion through polymer and porous diffusion from channels created as solid drug particles dissolve.

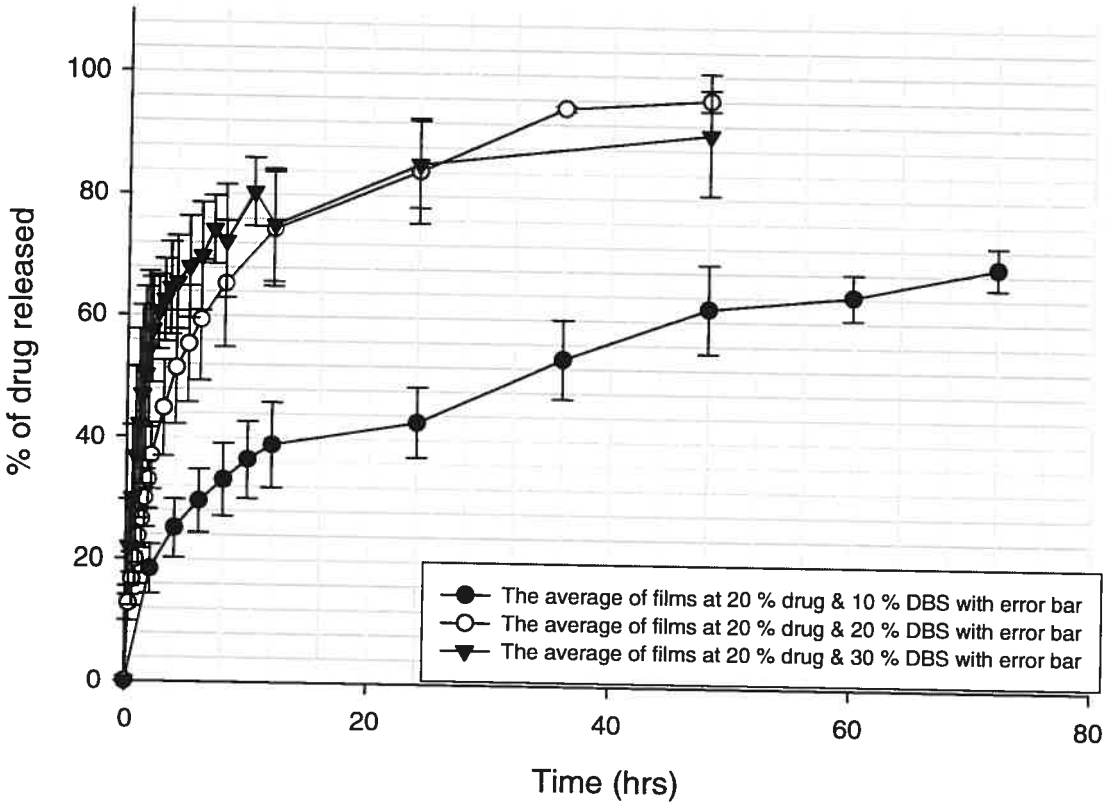


Figure 7: Percentage of drug released as function of time (hrs) for films containing 20 % pentoxifylline and 10 %, 20 %, and 30 % DBS

Figure 8 shows that there is no effect of the DBS on the drug release at 60% drug loading because the release occurs exclusively through the pores created from the dissolution of drug particles. Generally, drug release at both 10% and 20% drug loading occurs first from drug particles at the surface of the film in contact with dissolution liquid, then through a network of interconnected pores that were created as the drug particles dissolved.[57, 58]

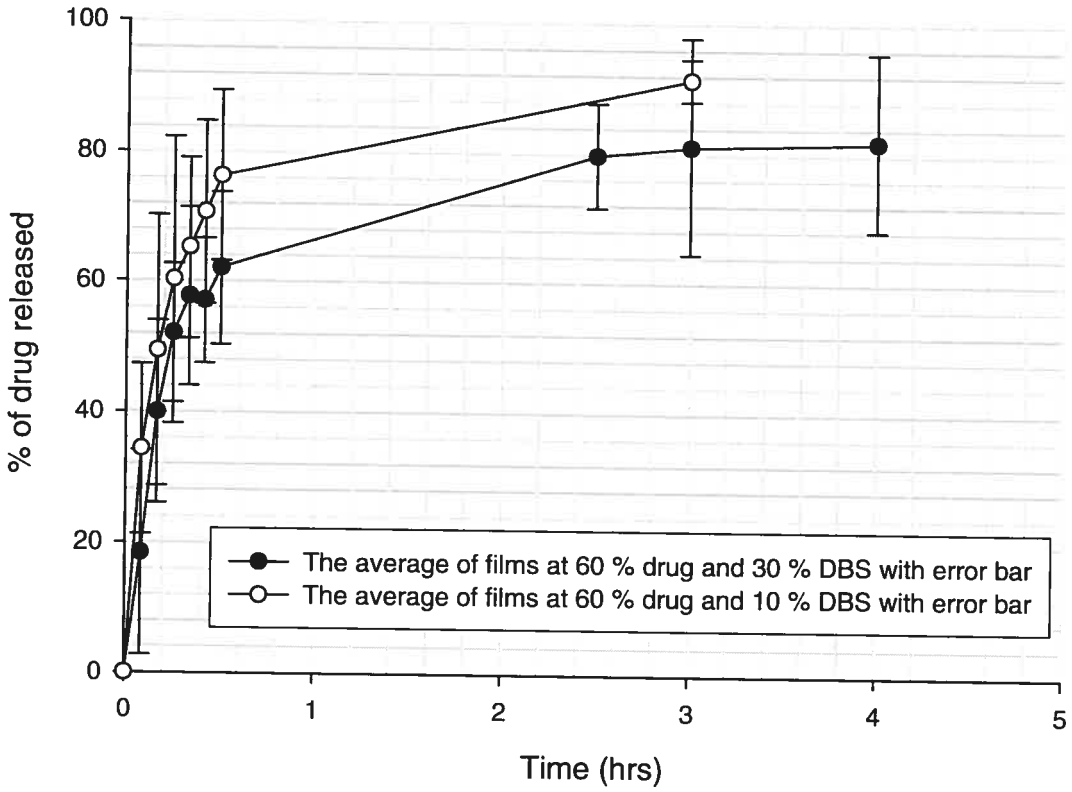


Figure 8 : Percentage of drug released as function of time (hrs) for films containing 60 % pentoxifylline and 10 % and 30 % DBS

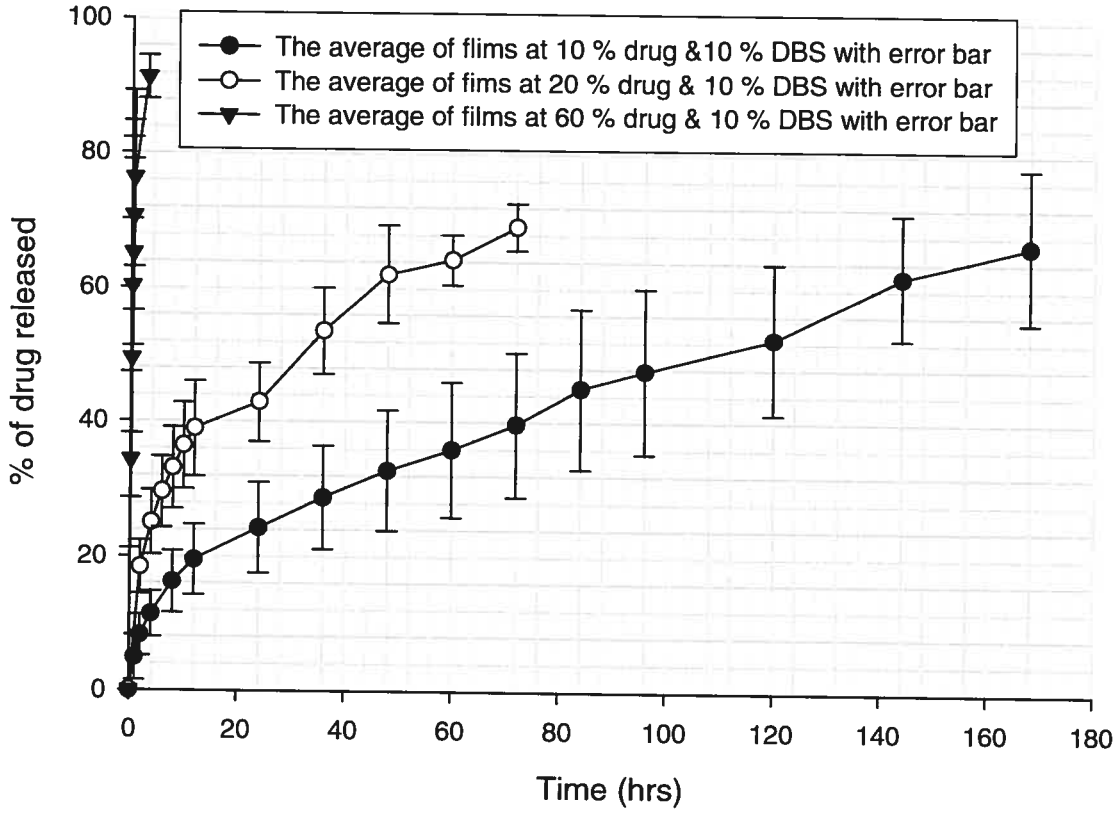


Figure 9: Percentage of drug released as function of time (hrs) for films containing 10 %, 20 %, and 60 % of pentoxifylline at a constant DBS level of 10 %

Figure 9 shows that the drug release from films at low levels (10%) of DBS plasticizer is highly dependent on drug loading (10%, 20%, and 60 %). As indicated by the slope of the curves, as the drug loading level increases, there is a marked increase in the drug rate from the film.

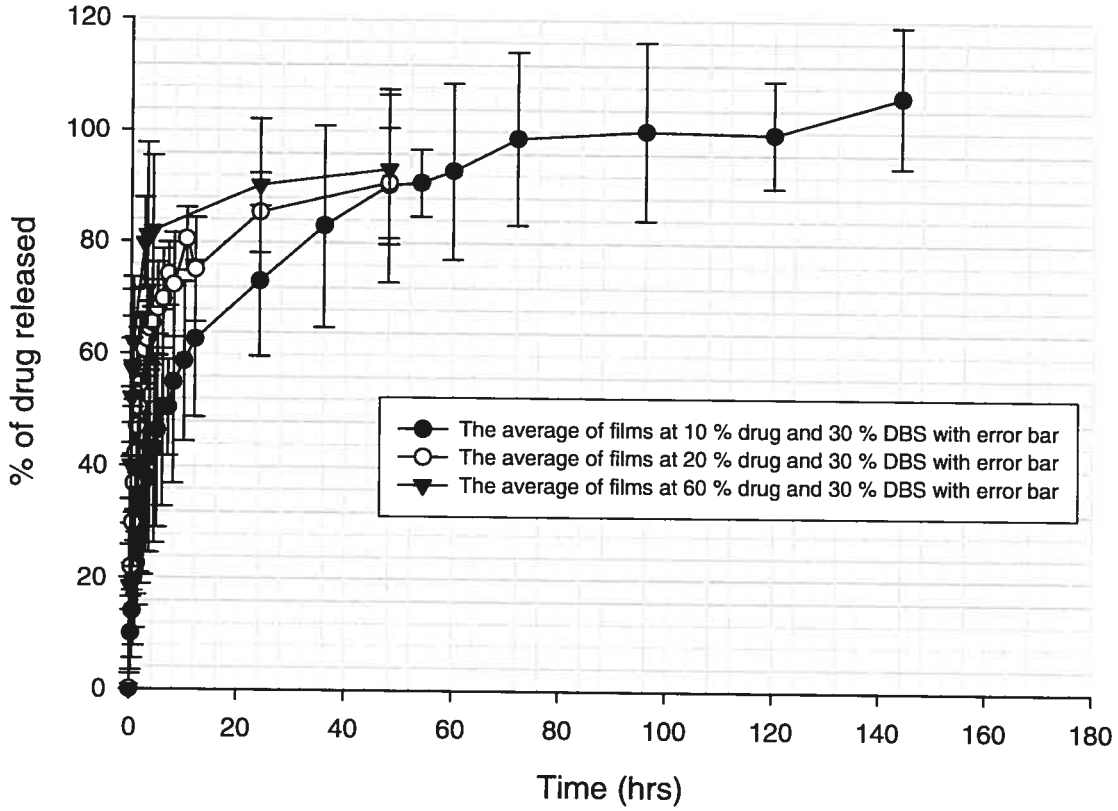


Figure 10: Percentage of drug released as function of time (hrs) for films containing 10 %, 20 %, and 60 % of pentoxifylline at a constant DBS level of 30 %(part-a)

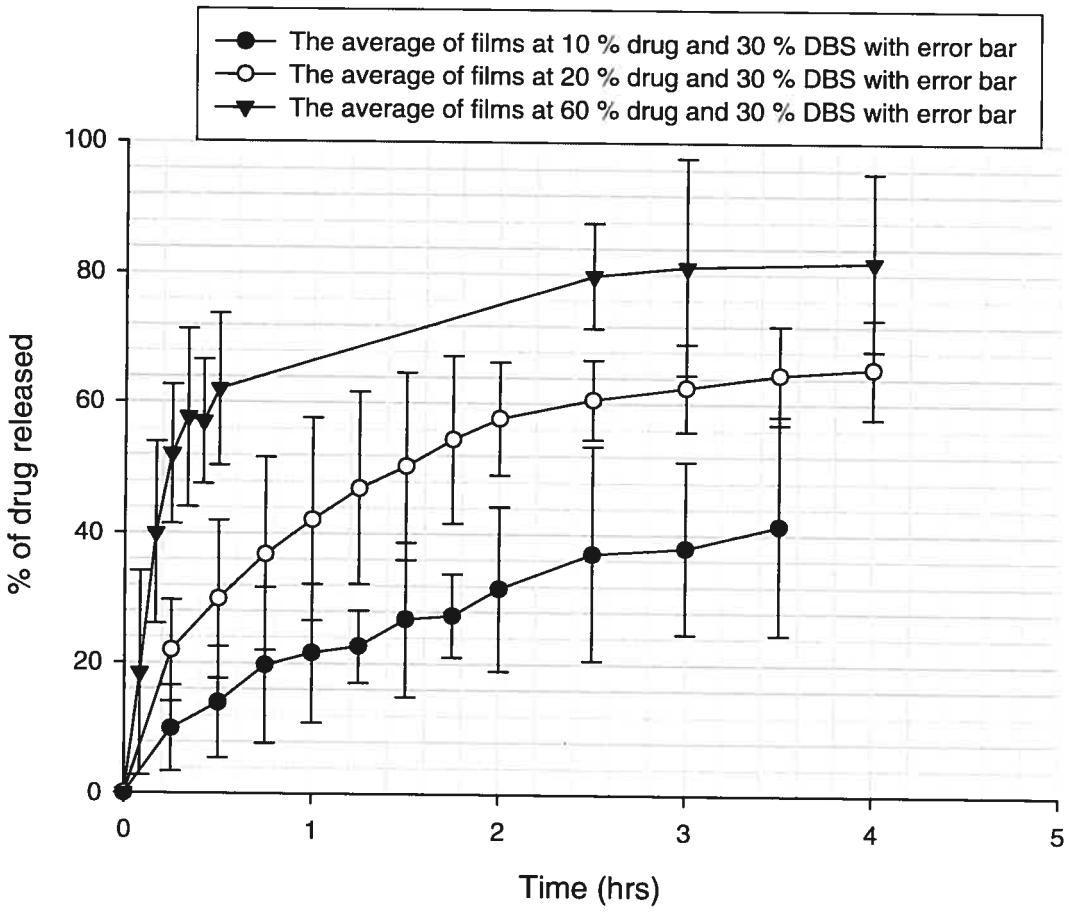


Figure 11: Percentage of drug released as function of time (hrs) for films containing 10 %, 20 %, and 60 % of pentoxifylline at a constant DBS level of 30 %(part-b)

Figures 9, 10 and 11 and Tables 6 and 7 show the effect of plasticizer levels on the release kinetic. For 10% and 20% drug loading, as the plasticizer levels (DBS) increase, the release rate increases. This is attributed to the decreasing crystallinity of the polymer, which results in a higher diffusivity of the drug in the polymer. For 60% drug loading, an inverse effect of the plasticizer (DBS) level on drug release kinetics is observed; due to the excess amount of plasticizer, which makes the drug particles and the

micro-environment for diffusion extremely hydrophobic, the drug release rate decreases as the plasticizer level increases. [45]

Drug loading (w/v)	Plasticizer level (v/v)	$T_{60\%}$
60%	10%	0.25 hour
20%	10%	45.00 hours
10%	10%	140.00 hours

Table 6: The effect of drug loading at constant plasticizer (10% DBS) on the release kinetics, $T60_{\%}$.

Drug loading (w/v)	Plasticizer level (v/v)	$T_{80\%}$
60%	30%	2.58 hours
20%	30%	17.66 hours
10%	30%	32.50 hours

Table 7: The effect of drug loading at constant plasticizer (30% DBS) on the kinetics release, $T_{80\%}$.

C. Characterization of the film

1. Differential scanning calorimetry

Molecular weight	Melting point °c	Tg °c	Recrystallization temperature °c
Low mol. Wt 64847	137.70	48.00	
Low mol.wt/DCM	144.65	50.00	101
High mol.wt 252073	175.55	66.00	
High mol. Wt/DCM	170.60	60.00	102
Low & high mol.wt/DCM	165.40	56.00	
Low & high mol.wt /DCM/DBS	158.00	26.00	58

Table 8: The effect of residual solvent on m.p. and Tg of PLA with and without plasticizer.

DSC was used to evaluate the effect of the solvent, dichloromethane (DCM), on the polymer after spraying and evaporation. The results, shown in Table 8, demonstrate that DCM has no significant effect on the Tg and melting point of PLA at low molecular weights of PLA. At a high molecular weight of PLA, the Tg and melting point are significantly decreased. The mixture of high and low molecular weight has a melting point around 165.40 C° and a Tg of 54.00 C° to 56.00 C°. After adding DBS, the melting point and the Tg are decreased. Based on previous work, the PLA has a Tg between 49.00 C° and 52.00 C° for a PLA with a molecular weight between 24.000 and 110.000 and a melting point of 172.00 C°, which agrees with the results that have been obtained from the DSC work.[30, 59]

The DSC scans of Figure 13 and 14 show the decrease in Tg and the melting point of the mixture of low molecular weight and high molecular weight of PLA after adding DBS.

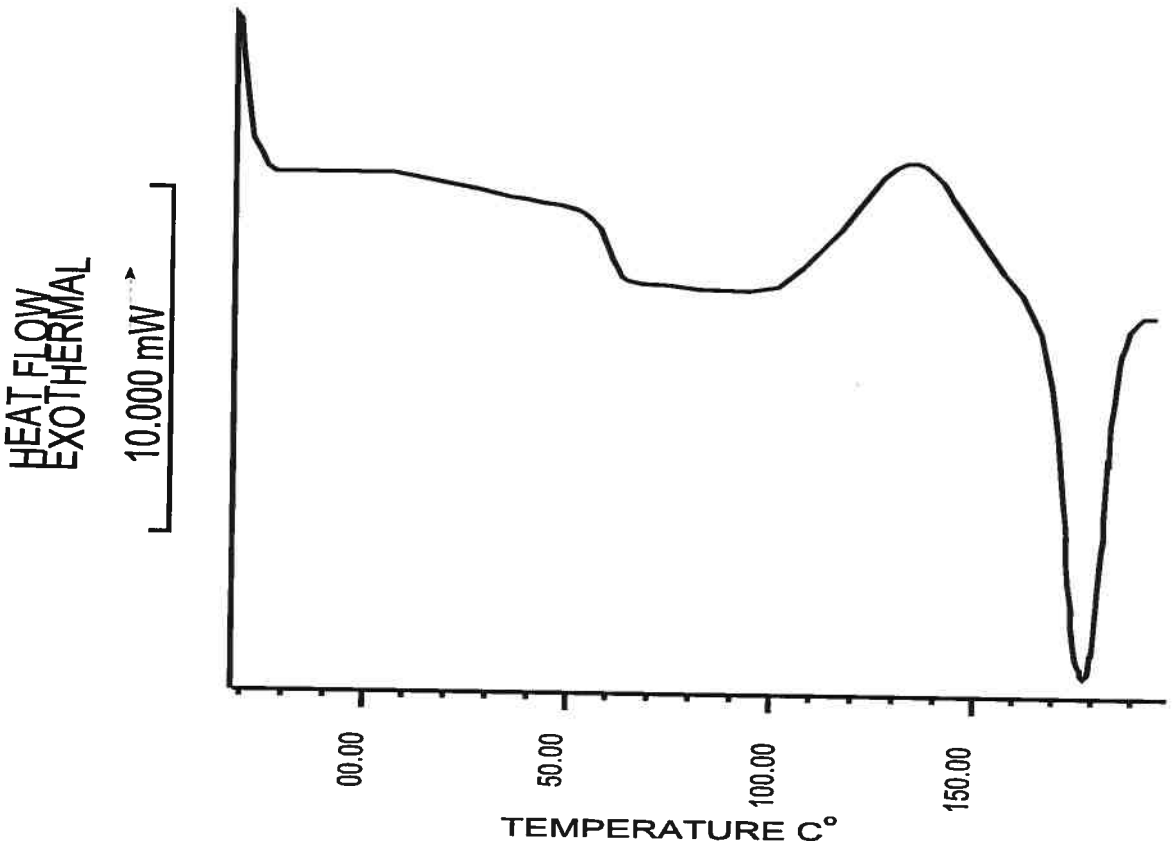


Figure 12: DSC scan of a mixture of low- and high-molecular-weight PLA dissolved in the solvent dichloromethane (DCM) without DBS after a second run showing the Tg

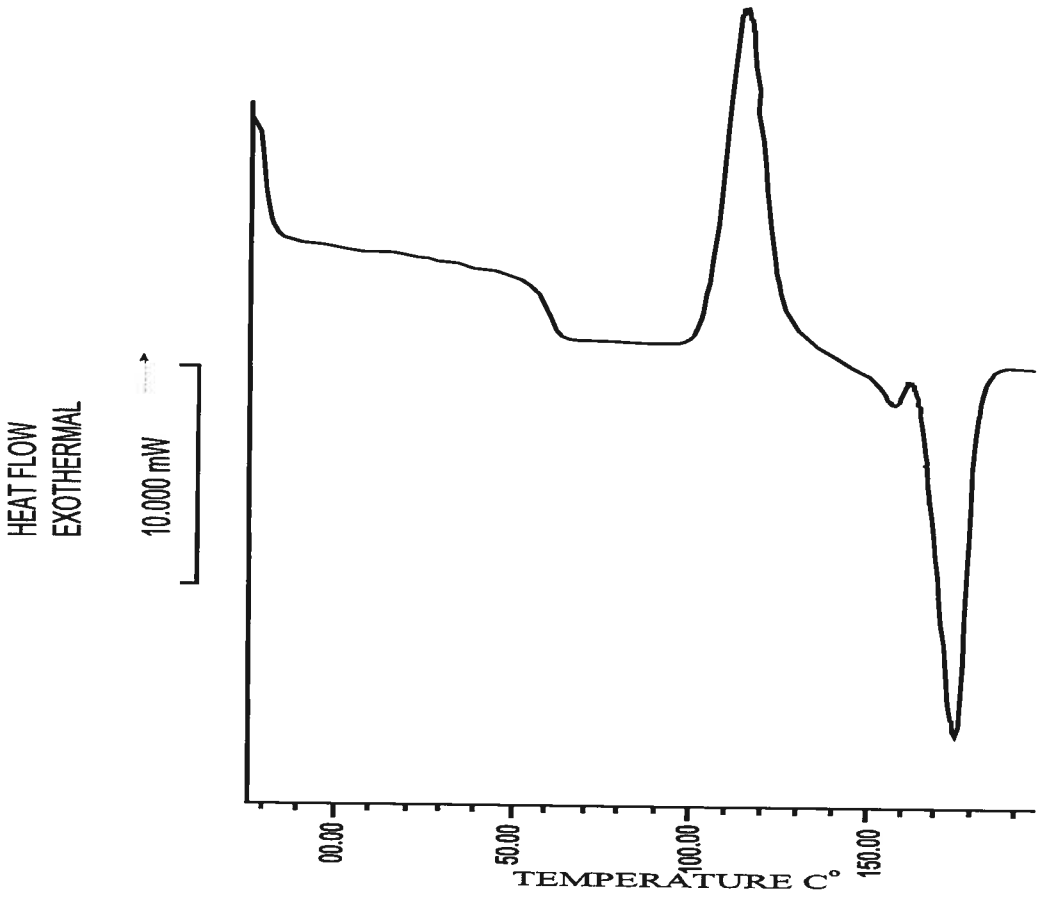


Figure 13: Second run of a mixture of low- and high-molecular-weight with plasticizer DBS dissolved in the solvent dichloromethane (DCM).

Table 9 and Figures 15 to 18 show the DSC results of different drug loadings with different levels of DBS of PLA film. There is no peak for pentoxifylline at 10% loading, which indicates the absence of crystalline drug and suggests that the drug is molecularly dispersed in PLA. As Figure 13 shows, when the DSC scan was carried out for the same amount of drug theoretically contained in the film at 10% drug loading, the drug peak could easily be seen.

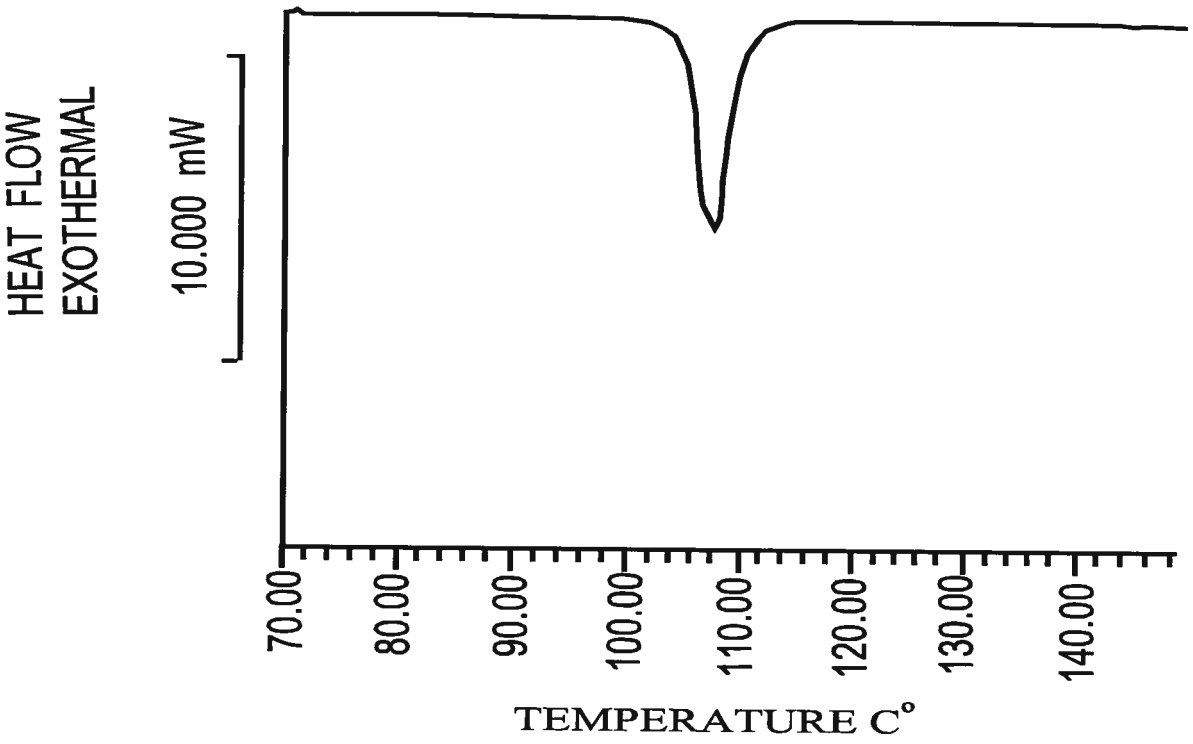


Figure 14: DSC scan of pure drug (pentoxifylline) at a theoretical 10% drug loading level

Drug loading %	Drug weight mg	DBS%	m.p. °c	Tg °c	Pentoxifylline peak	DBS peak
10	0.8	10	159.40 154.30	50.00 26.00	–	–
20	1.3	10	1st 153.30 2nd 147.50	42.00 27.00	Small peak	–
60	8.2	10	141.20 135.60	-3.50	Peak	–
20	1.7	20	143.60	10.00	Small peak	Peak
10	0.9	30	146.90	–	–	Peak
20	1.5	30	145.30 141.50	–	Small	Peak
60	8.9	30	138.20 132.60	–	Peak	peak

Table 9: DSC data of films with different pentoxifylline loadings and different DBS levels

At 20% and 60% loading, Figures 16 and 17 show that the intensity of the pentoxifylline peaks is proportional to the quantity of drug in the film. The Tg 26.00 C° is only detected at a level of 10% DBS for the 10% and 20% drug loading, while no Tg peak is detected at 60% drug loading. At 20% and 30% DBS, the Tg is not detected, whatever the drug loading. The DSC shows that the melting point decreases as drug loading and DBS levels increase.

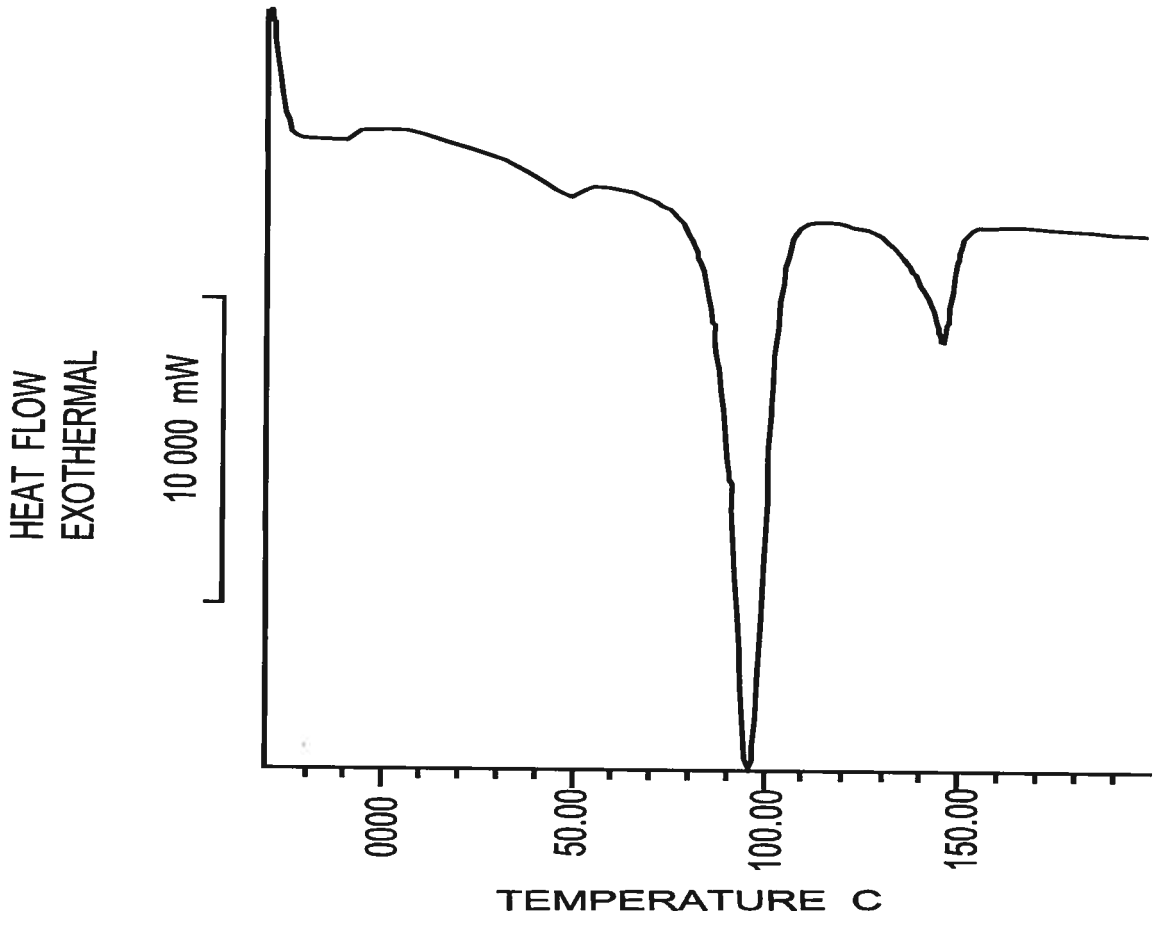


Figure 15: DSC scans of 60% pentoxifylline and 30% DBS after the first run showing pentoxifylline peak.

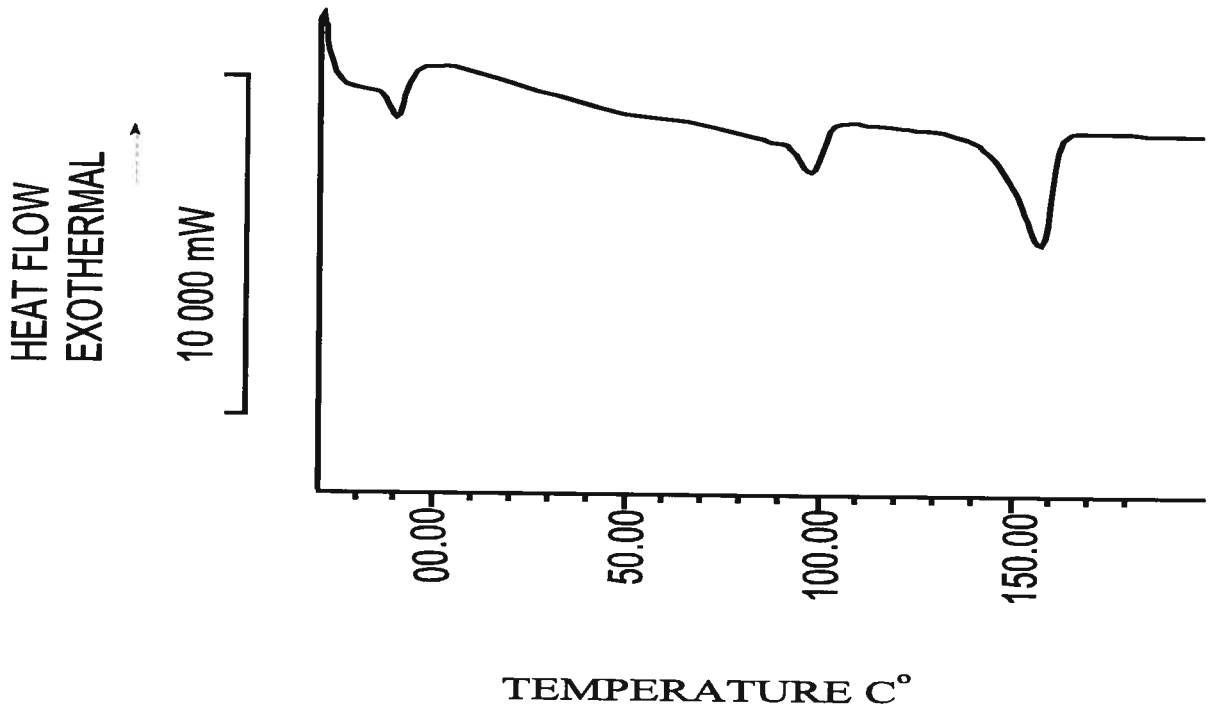


Figure 16: DSC scan of 20% pentoxifylline and 30% DBS after the first run showing a pentoxifylline peak.

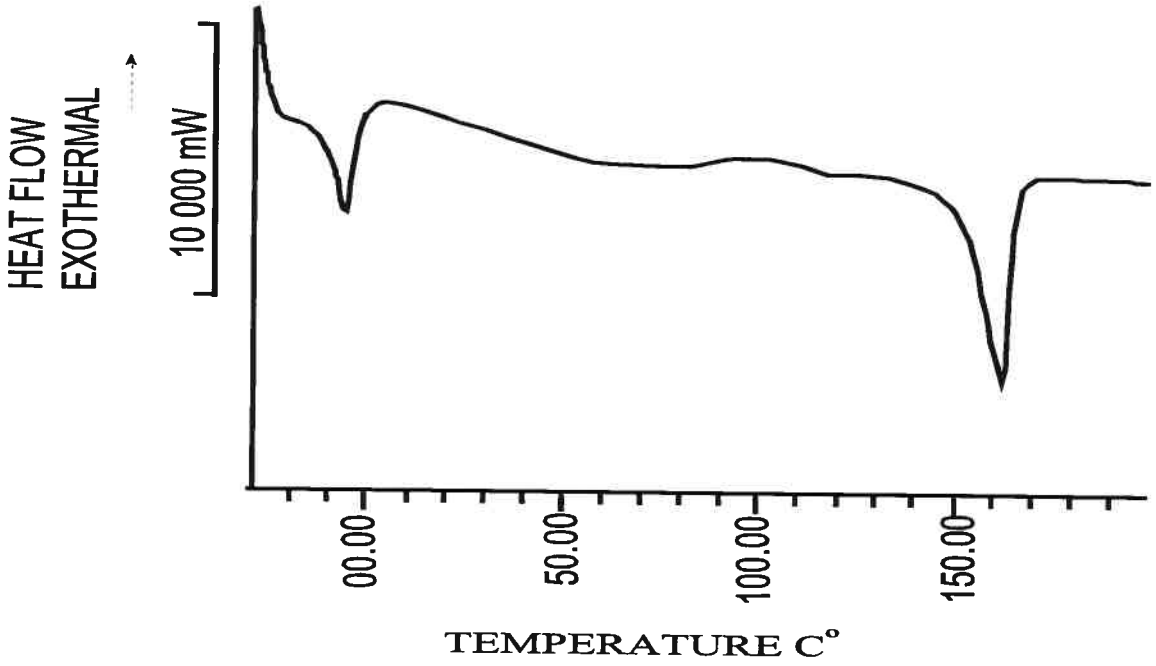


Figure 17: DSC scans of 10% Pentoxifylline and 30% DBS after the first run showing a plasticizer peak and the absent of the drug (pentoxifylline) peak.

2. Scanning-electron microscopy

As is shown in Figures 19, 20, and 21, in scanning-electron microscopy for the films before dissolution at low drug loading level 10%, it appears that drug particles on the surface of the film explain the initial burst that is observed in dissolution studies.

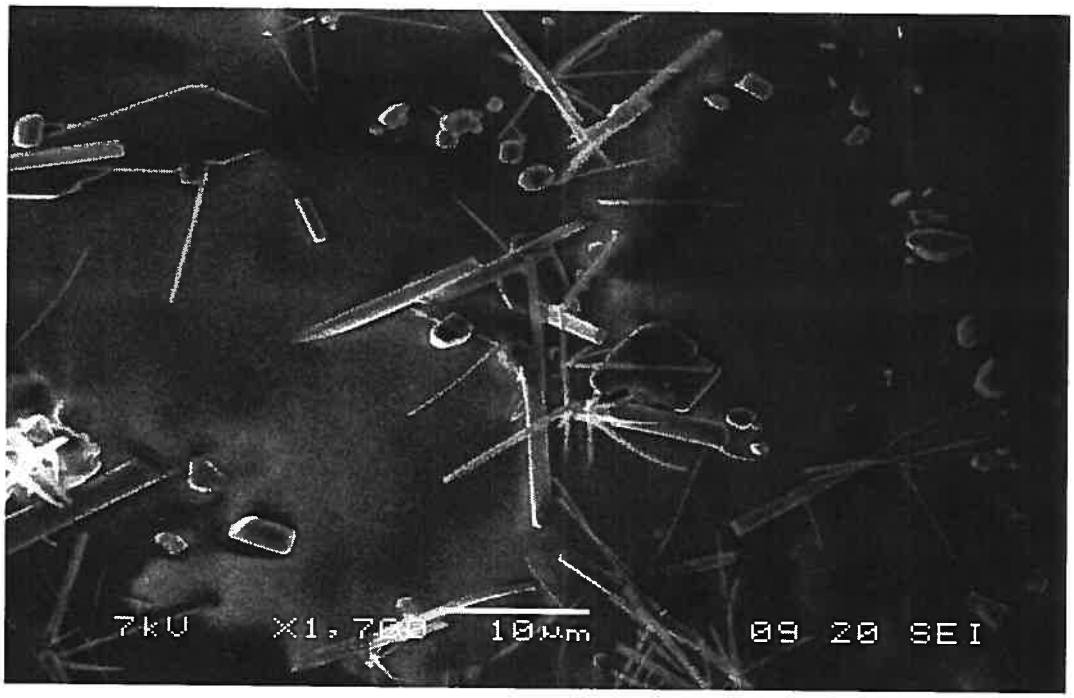


Figure 18: SEM photo of 10% pentoxifylline and 10% DBS film before dissolution showing drug crystals on the film surface.

At 20% drug loadings, a greater amount of drug particles on the surface can be seen. At higher drug loading levels, 60%, the drug particles seem to cover the surface of the film, which explains the very high release rate.

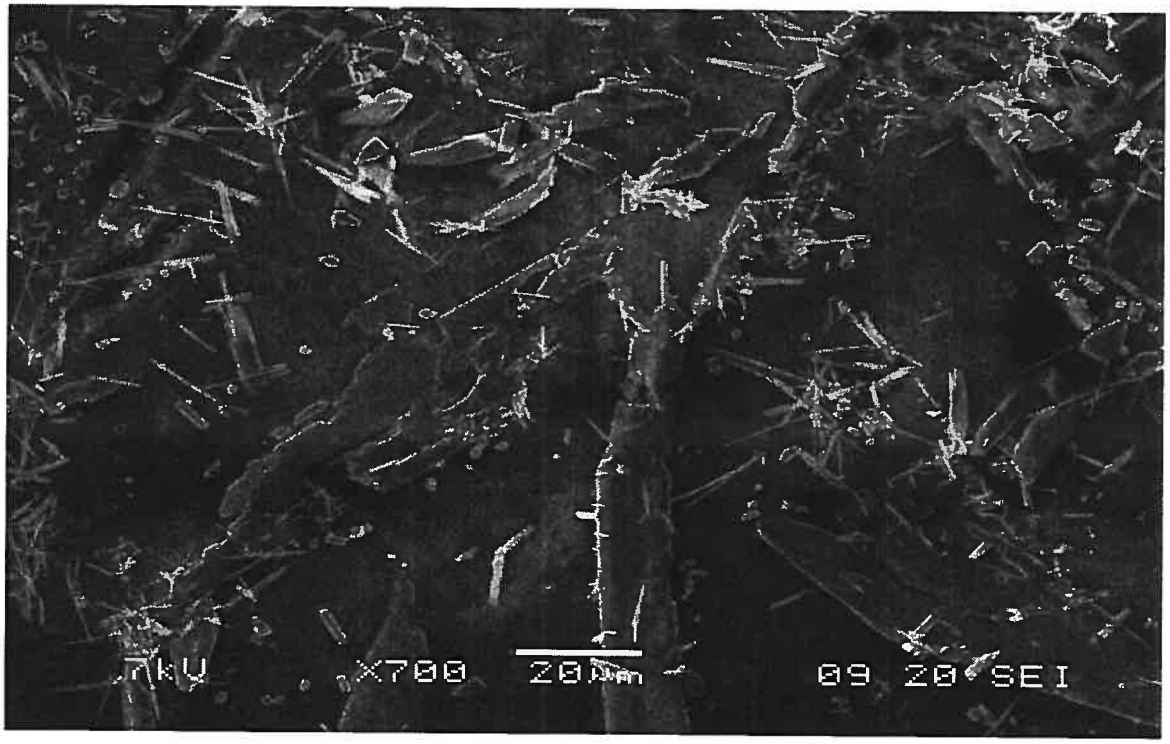


Figure 19: SEM photo of 20% pentoxifylline and 10% DBS film before dissolution showing more drug crystals on the film surface.

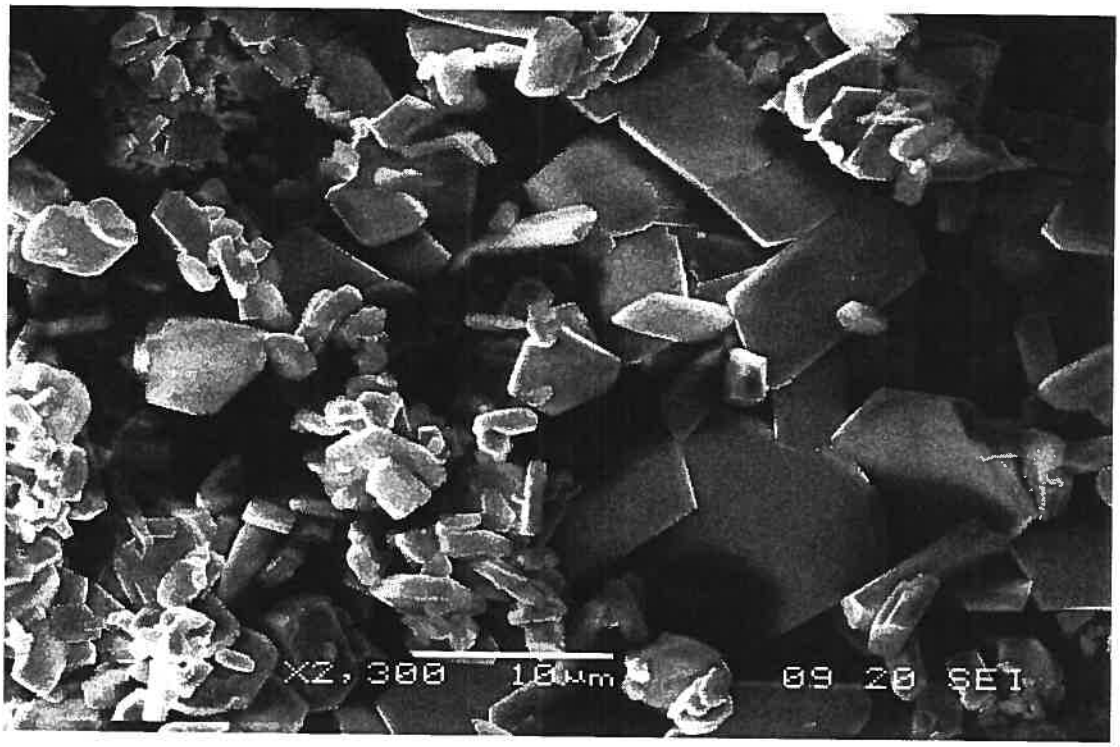


Figure 20: SEM photo of 60% pentoxifylline film before dissolution, showing drug crystals covering the film surface

On the other hand, Figures 22 and 23, photos for films after dissolution, show surface pores within the film increase as drug loading levels increase. Figure 21 at 60% loading demonstrates a greater pore density and more homogeneous distribution of pores across the surface, where Figure 20 at 20% loading shows areas where there seems to be no pores. Close evaluation of the pore structure in Figure 21 shows that there are pores within the major pores.

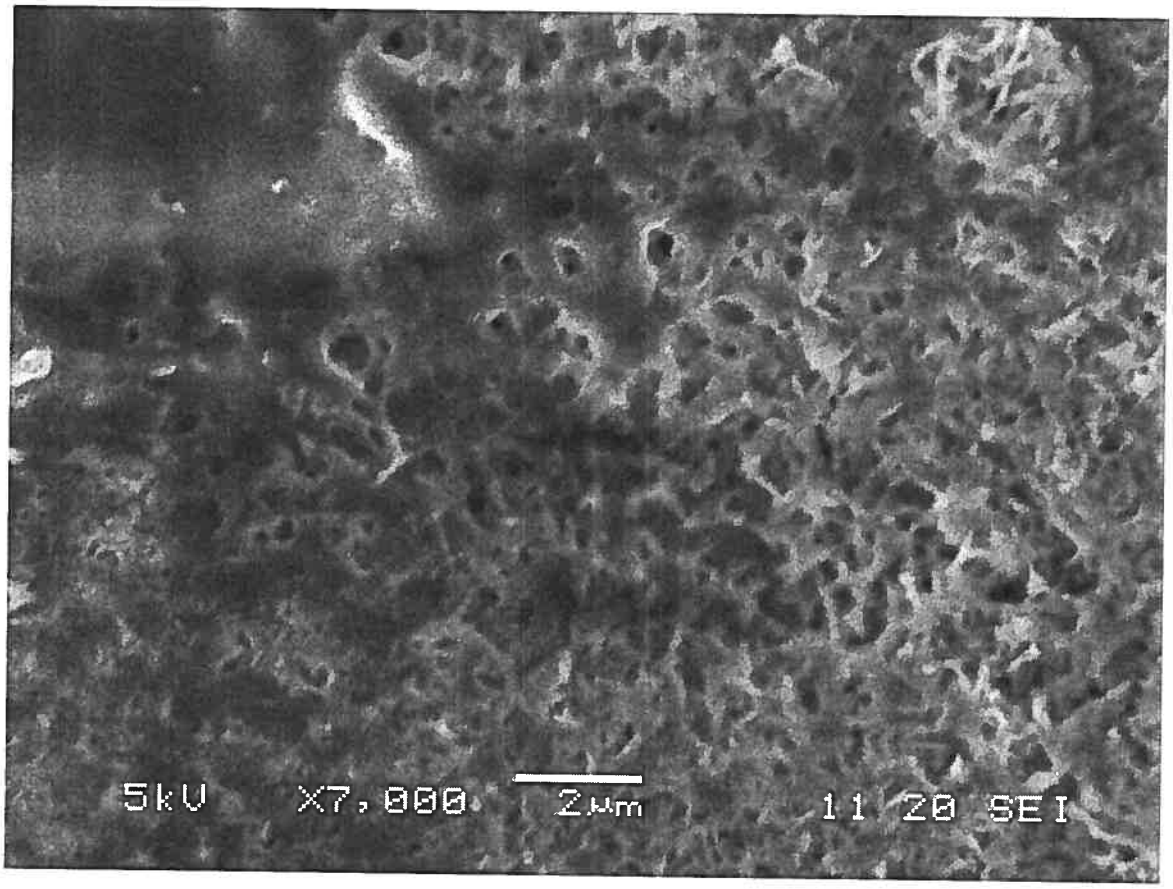


Figure 21: SEM photo of 20% pentoxifylline and 10% DBS film after 48 hours dissolution, showing pores after pentoxifylline particles were dissolved

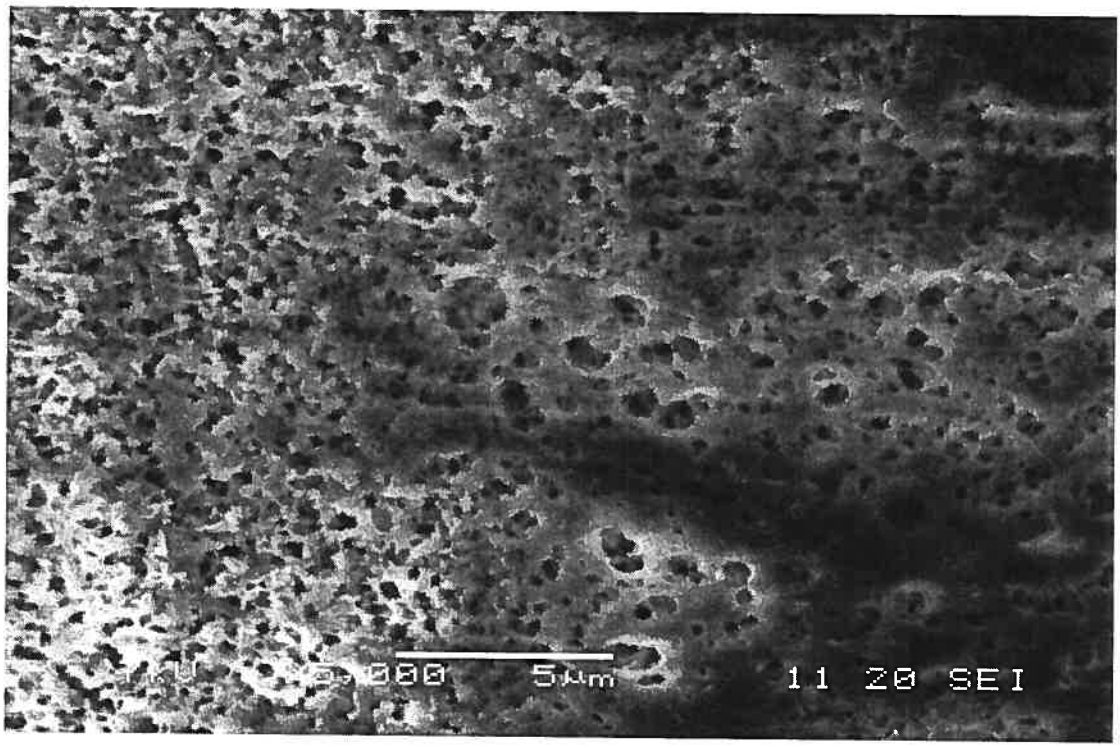


Figure 22: SEM photo of 60% pentoxifylline film after 3 hours dissolution, showing the pores after the dissolution of the pentoxifylline particles.

Figure 24 shows a photomicrograph of a cross section of a film with a 60 % drug loadings after 3 hours dissolution, which demonstrates a very extensive porous network extending from the surface. This suggests a significant internal pore structure that would explain the much higher release rate of the 60% loading.

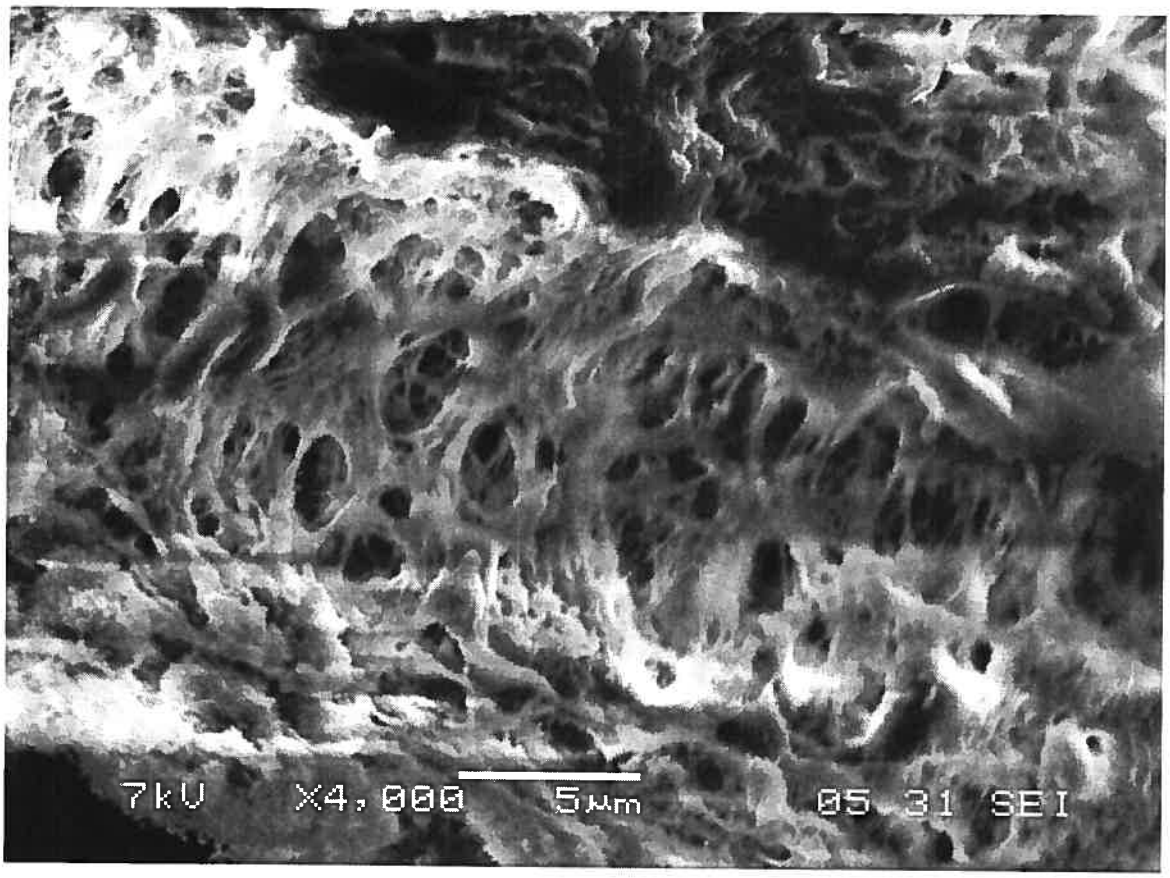


Figure 23 : SEM photo of freeze fracture of 60% pentoxifylline film after 3 hours dissolution, showing the pores after the dissolution of the pentoxifylline particles.

IV. Conclusion

This study aimed to evaluate the release kinetics of the drug model (pentoxifylline) from a polymeric matrix containing 50% low molecular weight PLA and 50% high molecular weight PLA. Other parameters, such as drug loading levels and plasticizer levels, were also evaluated. Adding plasticizer to the film formulation improves the physical properties of the film and increases the release rate. The drug release rate for 10% and 20% drug loading from the polymeric matrix increases as the plasticizer level increases, due to the decrease in the crystallinity of the polymer, as evidenced by the decreasing Tg. This results in higher diffusivity of the drug in the polymer. At low drug loading (10% and 20%), the release rate can be controlled by adjusting the plasticizer level. At 60% drug loading, the release rate decreases as the plasticizer level increases, due to the excess amount of plasticizer that makes the drug particles and matrix more hydrophobic and more slowly soluble. The release rate of the drug from the film increases as drug loading increases. Although not studied here, increasing the surface area of the film is another parameter that can be used to control the release rate of the drug from the polymeric film.

The Differential Scanning Calorimeter (DSC) shows that high and low molecular weight PLAs have different Tg values. Tg values for the mixture of high and low molecular weights of PLA decreases as plasticizer is added. The Tg value can only be detected at 10% and 20% drug loadings and 10 % plasticizer, which indicates significant residual crystallinity. Differential

Scanning Calorimeter (DSC) scans of the film at 10% drug loading show no detectable drug peak, while a DSC scan of the film at 10% drug loading can detect the same amount of drug, thus indicating that most of the drug is solubilized in the polymer/plasticizer matrix at this loading level.

Scanning electronic microscopy (SEM) photomicrographs before the dissolution of the films with different drug loading levels shows the presence of drug particles at the surface, even at the 10% loading. This is confirmed by X-ray diffraction analysis. The presence of drug particles increases as the drug loading levels increase. Scanning electronic microscope (SEM) micrographs of films with increasing drug loadings after dissolution shows an increasing porosity, which explains the increasing release rates with increasing loading.

This work has demonstrated that plasticizer and drug loading levels can be used to control drug release rate. The plasticizer has an unexpected effect on the drug release rate. First, as expected, increasing the plasticizer at low drug loading levels (10% and 20%) decreases the Tg of the polymeric film, which results in an increased drug release rate for a fixed drug loading level. Second, at a high drug loading level (60%), the plasticizer has an inverse effect on the drug release rate, whereby the release rate decreases as the plasticizer level increases. Since the drug release rate is dependent on drug loading and the plasticizer level, different drug release rates can be obtained by controlling these parameters.

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