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Evaluate Pentoxifylline Release from Polylactic Acid Film

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ABSTRACT

The objective of this study was to evaluate pentoxifylline release from polylactic acid (PLA) film. 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 Dibutyl sebacate (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. Gel Permeation Chromatography GPC was used to characterize the molecular weight of the polylactic acid. Differential Scanning Calorimetry was used to characterize and study the thermal behavior of the film and the drug. Scanning Electron Microscopy was used to characterize the film surface at different drug loadings. X-ray powder diffraction was used to measure the crystal peaks of the drug and the polylactic acid. Since the drug release rate is dependent on drug loading and plasticizer level, different drug release rates can be obtained by controlling these parameters. The effect of the plasticizer on the drug release rate has a different effect based on the drug loading levels. At low drug loading levels (10 and 20%), as the plasticizer level increases, the drug release rate increases, while at high drug loading (60%), the drug release rate decreases as the plasticizer level increases.

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INTRODUCTION

Several 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 [1-5].

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 [4, 6-8].

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 for at least 48 hours to treat a Founder's foot. 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 prolonging the useful life of the animal [9,10].

METHODS

Characterization of PLA

Gel Permeation Chromatography (GPC)

Molecular weight and polydispersity of polylactic acid samples were determined by Gel Permeation Chromatography (GPC) model ALC-202 liquid chromatography 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

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phenogel columns with nominal porosities ranging from 5u 10^3 to 5u 10^5 angstroms were used for all samples and the polystyrene standards. A standard curve from five different polystyrene molecular weights was created. In order to obtain a calibration coefficient, five mg of each standard was dissolved in 5 ml of chloroform, and 100 µl was injected. After the calibration coefficient was obtained then 50 mg of each sample was dissolved in 5 ml of chloroform, and 50 µl was injected to determine the molecular weight.

Preparation of polymeric solution and Plate coating process

Polymeric Solution Preparation

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

Plate coating process

Plate coating process was done by using stainless steel plates approximately 2cm x 2cm of known surface area thickness of 0.6mm, a Spraying system (spray gun, Badger250-4), and compressed air at 80 psi. Stainless steel plates were first placed in 1N HCL hydrochloric acid for 20 minutes, just once, and then the plates were put in the solvent DCM for another 20 minutes. Four dried and clean plates were arranged over a clean sheet for the coating process. The polymeric solution, which contains the drug, the polymer, and the plasticizer, was sprayed onto the first side of the plates. Model 202 Oster, as a source of hot air, was applied onto the plates after each spray to dry, to avoid condensation of the solvent on the plates and to produce a clear, homogenous film. The stainless-steel plates with known surface area are weighed before and after the spraying process to calculate weight gain and drug content in the film. Spraying the polymeric solution containing drug & DBS over the stainless plate and applying hot air to dry the film through numerous trials the experimental conditions such as spray time, distance of the spray, and drying time were optimized. The quality of the compressed air is critical and must be free of particulate matter, oil, and be anhydrous.

In vitro release study

A standard curve of the drug model with five different concentrations were prepared. Dilutions from the stock solution were used to prepare the standard curve. The plate that contained polylactic acid film was hanging down in the flask filled with phosphate buffer solution with a pH 7.4. The flask was put in a thermostated water bath shaker at 37Cº. Samples from the release solution were periodically removed using syringes from the flasks. The drug released into the medium buffer was assayed using a Hewlett Packard 8452A diode Array spectrophotometer and Ultrospec 2000 manufactured by Biocharm Ltd UV/Visible Spectrophotometers, Pharmacia Biotech at wavelength 274 nm. Percent drug release and amount of drug release are used to evaluate the kinetics of release from the different batches.

Polymeric film characterization

Differential Scanning Calorimeter (DSC)

Thermal characterization was carried out using a Mettler TC II TA processor differential scanning calorimeter. Two heating runs up to 200Cº and one cooling run at -40Cº at 10 K/min were done in duplicate. 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.

Scanning-electron microscopy (SEM) and Fracture technique

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

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 well as receiving slits of 0.5 and 0.2 mm. Scan range was set from 2 to 40 degrees 2theta using the step scan mode at a step size of 0.02 degrees 2theta and a count time of 2 seconds. Samples were placed on the low-background quartz disk. In order to obtain a good diffraction pattern, the films of different samples containing low molecular weight PLA, 10%, 20% and 60% drug and 10 % DBS are broken up slightly instead of grinding the samples. A high molecular weight PLA sample was used without grinding, and a standard holder was used. The instrument alignment is verified weekly using a corundum disk (NIST SRM 1976).

RESULTS

Characterization of PLA and the Film

Gel permeation chromatography (GPC)

As it is shown from the results of the GPC molecular weight determination of PLA for the low and high mol weight PLA used in this study, it can be seen

from (Table 1) that there is a significant difference in molecular weights between the two polylactic acids used in this study.

Table 1. Data of low and high molecular weight PLA characterized by Gel Permeation Chromatography

Sample	Mn	Mw	Mz	D
Low molecular weight	25375	64847	445045	2.6
High molecular weight	146038	252074	2225612	1.7

Differential Scanning Calorimeter

The effect of the solvent, dichloromethane (DCM), on the polymer after spraying and evaporation was evaluated by DSC. The results are shown in (Table 2) and demonstrate that at low molecular weights of PLA, DCM has no significant effect on the Tg and melting point of PLA. At high molecular weight of PLA, the Tg and melting point are significantly decreased. The mixture of high and low molecular weights has a melting point of around 165.4 and a Tg of 56.47. After adding DBS, the melting point and the Tg are decreased. Based on previous work and others, the PLA has Tg between 49 and 52 for PLA of molecular weight between 24.000 and 110.000 and a melting point of 172, which agrees with the results that have been obtained from the DSC work [11-15].

DSC results of different drug loadings with different levels of DBS of PLA film are shown in (Table 3). For pentoxifylline, at 10% loading, there is no pentoxifylline peak, which indicates the absence of crystalline drug and suggests that the drug is molecularly dispersed in PLA. As it is shown in

Table 2: The effect of residual solvent on m.p and Tg of PLA with and without plasticizer

Molecular Weight	Melting Point	Tg	Recrystallization Temperature
Low molecular weight 64847	137.7	47.95	
Low molecular weight/DCM	144.65	49.68	101
High molecular weight 252073	175.55	65.6	
High molecular Weight/DCM	170.6	60	102
Low & high molecular weight/DCM	165.4	56.47	
Low & high molecular weight /DCM/DBS	158	26.1	57.6

Figure 1, the DSC scan was carried out for the same amount of drug theoretically contained in the film at 10% drug loading, the drug peak can be easily seen. At 20 and 60 % loading, the intensity of pentoxifylline peaks is proportional to the quantity of drug in the film. At 10% DBS, there is no peak detected, while at 20and and 30% DBS, the peak is detected at different drug loading. The Tg is only detected at a level of 10% DBS for the 10 and 20 % drug loading, while at 60 % drug loading, no Tg peak is detected. 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 [16].

Table 3: DSC data of films with different drug loadings (pentoxifylline) and different plasticizer levels (DBS).

Drug loading %	Drug weight mg	DBS%	m.p	Tg	Pentoxifylline peak	DBS peak
10	0.8	10	159.4 154.3	50.17 25.93	–	–
20	1.3	10	1st153.3 2nd147.5	42.07 26.95	Small peak	–
60	8.2	10	141.2 135.6	-3.5	Peak	–
20	1.7	20	143.6	9.8	Small peak	Peak
10	0.9	30	146.9	–	–	Peak
20	1.5	30	145.3 141.5	–	Small	Peak
60	8.9	30	138.2 132.6	–	Peak	Peak

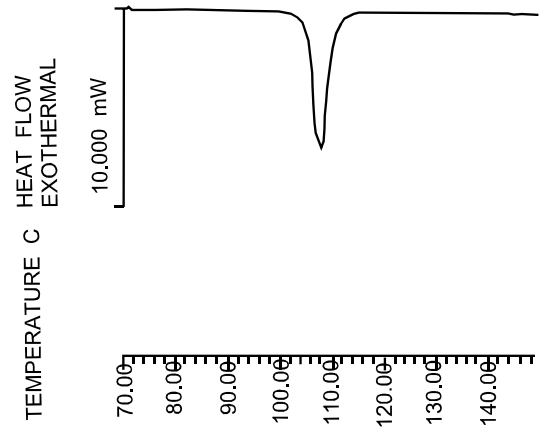

Figure 1: DSC scan of pure drug (pentoxifylline), at a theoretical 10% drug loading level.

Scanning-electron microscopy

First, as shown in scanning-electron microscopy for the films before dissolution that at a low drug loading level of 10%, it appears that drug particles on the surface of the film explain the initial burst that is observed in dissolution studies. 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. On the other hand, photos for films after dissolution (Figures 2 & 3) show that the pore within the film increases as drug loading levels increase [17,18].

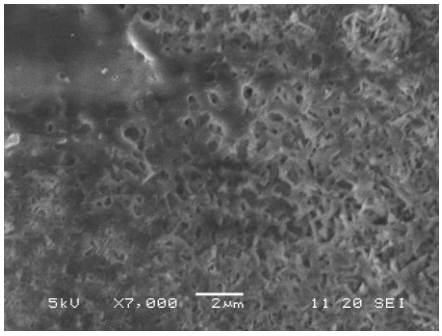

Figure 2: SEM photo of 20 % pentoxifylline film after dissolution, showing pores after pentoxifylline particles were dissolved

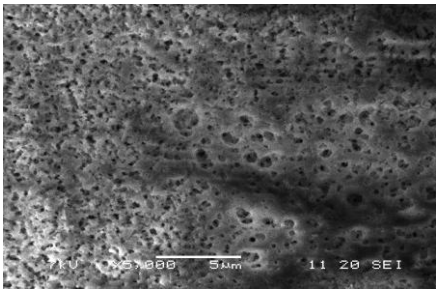

Figure 3: SEM photo of 60 % pentoxifylline film after dissolution, showing the pores after pentoxifylline particles were dissolved

Powder X-ray diffraction

(Figure 4) shows the results of X-ray diffraction at different drug loading levels (10%, 20% and 60%) and constant plasticizer level (DBS) (10%). (Figure 4) shows the major PLA peaks (16.5, 19) decrease as the drug loading level increases, while the pentoxifylline peaks increase. The presence of diffraction peaks of the drug (pentoxifylline) confirmed the presence of crystalline drug (pentoxifylline) dispersed in the matrix [9].

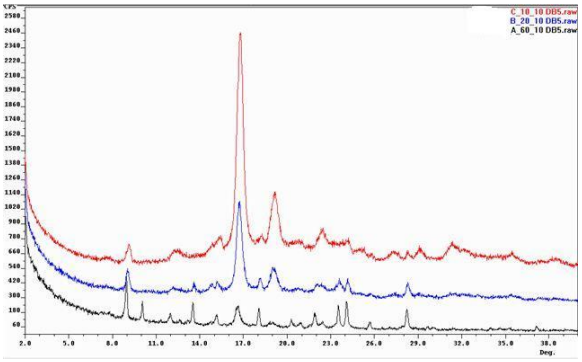

Figure 4: X-ray diffraction of samples of pentoxifylline (10%, 20% and 60%) film at a constant plasticizer level (DBS 10%) showing the drug peaks at 13.57, 15.13, 24.05, and 28.61.

Drug release studies

The drug release from different formulations of polylactic acid polymeric film was evaluated by using a USP dissolution system. The effect of drug loading with and without plasticizer on drug release was first evaluated. The plasticizer is used to modify the physical properties and release characteristics. Dibutyl Sebacate was selected as a plasticizer based on prior research [19-22].

Release from polymeric film (without a plasticizer)

Drug released from different formulations containing 50% low and 50 % high molecular weight of PLA with different drug loadings (20, 25, and 30%) was evaluated from spray-coated stainless-steel plates immersed in dissolution fluid. As can be seen from the results, with the 20% drug loading, there is 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 after the first hour of dissolution due to the film quality. 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. As a result of film cracking, an accurate evaluation cannot be achieved for the drug release from the film without a plasticizer [23,24].

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 %. At all levels of plasticizer, there were no signs of film cracking, as can be observed from the dissolution studies. As can be seen from the results of (Figure 5), at a 10% drug loading, as DBS level increases, the release rate increases due to a decrease in crystallinity of

the polymer, which results in higher diffusivity of the drug in the polymer [22,23,25-27].

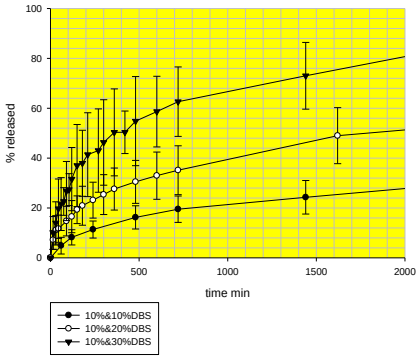

Figure 5: The effect of 10 % drug loading on the drug release of pentoxifylline at different plasticizer levels (10%, 20% and 30% DBS)

Figure 6 shows that for the 20% drug loading, increasing the level of plasticizer increases the release rate, and it is evident that the release rate is also much higher than at a 10% loading of drug. This is probably due to a mixed-mode release mechanism of diffusion through the polymer and porous diffusion from channels created as solid drug particles dissolve [28-30].

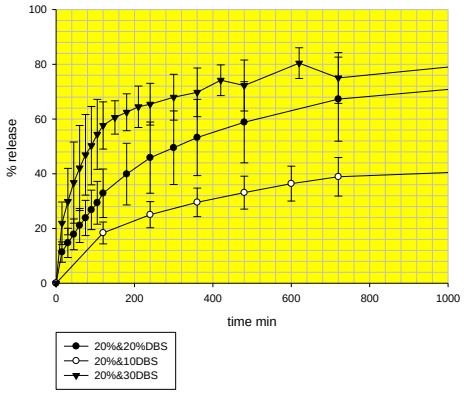

Figure 6: The effect of 20 % drug loading on the drug release of pentoxifylline at different plasticizer levels (10%, 20% and 30% DBS)

Figure 7, at 60% drug loading, there is no effect of the DBS on the drug release 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 are created as the drug particles are dissolved [25,26].

As it is shown, the drug release from films at a low level (10 %) of DBS plasticizer is highly dependent on drug loading (10, 20, and 60 %). As the drug loading level increases, there is a marked increase in the drug rate from the film, as indicated by the slope of the curves [31].

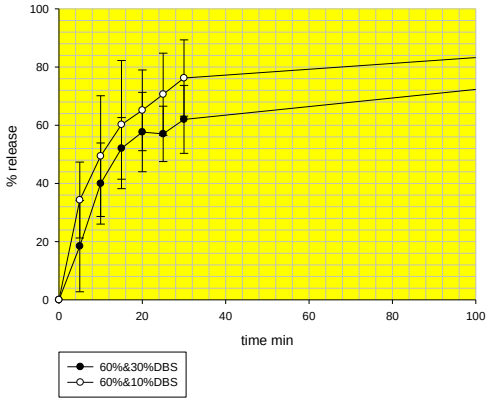

Figure 7: The effect of 60 % drug loading on the drug release of pentoxifylline at different plasticizer levels (10% and 30% DBS)

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 higher diffusivity of the drug in the polymer.

(Figure 7) shows that for the 60% drug loading, an inverse effect of the plasticizer (DBS) level on drug release kinetics is observed; the drug release rate decreases as the plasticizer level increases. This effect is due to the excess amount of plasticizer, which makes the drug particles and the microenvironment for diffusion extremely hydrophobic [4,27,29,32-34].

DISCUSSION

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, at low drug loading levels (10 and 20 %), increasing the plasticizer decreases the Tg of the polymeric film, resulting in increased drug release rate for a fixed drug loading level. Second, at high drug loading levels (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 plasticizer level, different drug release rates can be obtained by controlling these parameters.

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