Effect of Drug Loading and Plasticizer on Drug Release from Polylactic Acid Film

Mohamed Mokhtar*[1] Abdurrahim A. Elouzi[2], Ebtisam Benomran[3] and Ebtesam Beshana[4]

[1]FDepartment of Pharmaceutics Faculty of Health Sciences, Sirte University, Sirte, Libya

[2]Department of Pharmaceutics Faculty of Pharmacy, Tripoli University

[3]Mergeb University School of Pharmacy, Elgomes-Libya

[4]Department of pharmaceutics, Faculty of Pharmacy, Zawia University, Zawia, Libya

* Corresponding author, email: mohamed.alhouni@su.edu.ly

00218910461127

Abstract

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 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. Differential Scanning Calorimetry was used to characterize and study thermal behavior of the film and the drug. Gel Permeation Chromatography GPC was used to characterize the molecular weight of the polylactic acid. Scanning Electron Microscopy was used to characterize the film surface at different drug loadings. X-ray powder diffraction was used to measure crystals peaks of the drug and the polylactic acid. 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.

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.[1-5]

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 105ºC to 106ºC 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.[9, 10]

Materials &Methods

Materials

Pentoxifylline (lot no: noj87), PLA high (lot no: 516988), Polysciences, Inc and Low molecular weight (lot no: R-020510) were obtained from Mc Mullen lab. All other materials and solvents were purchased from Laboratoire MAT (Montreal, Canada) and Sigma-Aldrich (St. Louis, MO) and used without further purification.

Methods

Characterization of PLA

Purification

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

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 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 calibration coefficient five mg of each standard was dissolved in 5 ml chloroform and 100 µl was injected. After the calibration coefficient was obtained then 50 mg of each sample was dissolved in 5 ml 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 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 0.6mm, Spraying system (spray gun, Badger250-4), and compressed air 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 other 20 minutes. Four dried and clean plates were arranged over a clean sheet for coating process. The polymeric solution which contains drug, the polymer and 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 weighted before and after the spraying process to calculate weight gain and drug content the film. Spraying the polymeric solution containing drug &DBS over the stainless plate and applying hot air to dry the film through numerous trial 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 absolutely anhydrous.

In vitro release study

Standard curve of the drug model with five different concentrations was prepared. Dilutions from 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 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 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 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 acids samples and films with different levels of plasticizer and drug loadings were determined. The sample weights ranged from 4mg to 22mg. Aluminum samples 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 a 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. 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 and discussion

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

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 weight has a melting point 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 which have been obtained from the DSC work.[11-15]

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

DSC results of different drug loadings with different levels of DBS of PLA film are shown in the 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 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 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 there is no Tg peak is detected. At 20 and 30 % DBS the Tg is not detected whatever the drug loading. The DSC shows that 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).

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

Scanning-electron microscopy

First, as is shown in scanning-electron microscopy for the films before dissolution that at low drug loadings level 10%, it appears that drug particles on the surface of the film explains 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 and 3 show that pore within the film increase 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

Figures 4 shows the results of X-rays 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) decreases as the drug loading level increases while the pentoxifylline peaks increases. The presence of diffraction peaks of 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 plasticizer on the basis of 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 it can be seen from the results 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 extent 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 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 it can been seen from the results of Figures 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 increase 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 mix 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 shows 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 have been dissolved.[25, 26]

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

As it is shown the drug release from films at 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]

For 10 and 20 % drug loading, as the plasticizer levels (DBS) increases 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 are 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 micro environment for diffusion extremely hydrophobic.[4, 27, 29, 32-34]

Conclusion

The aim of this study is to evaluate the release kinetics of the drug (pentoxifylline) from a polymeric matrix containing 50% low molecular weight PLA and 50 % of high molecular weight PLA. Other parameters such as drug loading levels and plasticizer levels are also evaluated. Adding plasticizer to the film formulation improves the physical properties of the film and increases the release rate. Drug release rate for 10% and 20% drug loading from the polymeric matrix increases as plasticizer level increases due to the decrease in crystallinity of the polymer, as evidenced by the decreasing Tg, which 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 which make the drug particles and matrix more hydrophobic. The release rate of the drug from the film can be controlled by adjusting drug loading. Surface area of the film is another parameter can be used to control the release rate of the drug from polymeric film.

Differential Scanning Calorimeter (DSC) shows that high and low molecular weights PLA have different Tg values. Tg values for the mixture of high and low molecular weight of PLA decreases as plasticizer is added. Tg value can only be detected at 10 and 20 % drug loadings and 10 % plasticizer. Differential Scanning Calorimeter (DSC) scans of the film at 10 % drug loading show no detectable drug peak, while the result of DSC scan for the same amount of drug theoretically contained in the film at 10 % drug loading can be detected. This indicates that most of the drug is solubilized in the polymer/plasticizer matrix. Photomicrographs by scanning electronic microscopy (SEM) before the dissolution of the films with different drug loading levels show that the presence of drug particles at the surface even at the 10% loading which is confirmed by X-ray diffraction analysis. The presence of drug particles increases as the drug loading levels increases. Photos of scanning electronic microscope (SEM) of films with increasing drug loadings after the dissolution show 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 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 fixed drug loading level. Second, at 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 plasticizer level different drug release rates can be obtained by controlling these parameters.

Acknowledgments

Mohamed Mokhtar thanks the Ministry of Higher Education, Libya for granting him a scholarship during his Ph.D.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Reference:

1. Lee, V.H.L. and J.R. Robinson, *Controlled drug delivery : fundamentals and applications*. 2nd ed. Drugs and the pharmaceutical sciences. v. 29. 1987, New York: Dekker. xix, 716 p.

2. Aulton, M.E., *Aulton's pharmaceutics : the design and manufacture of medicines*. 3rd ed. 2007, Edinburgh ; New York: Churchill Livingstone. x, 717 p.

3. Bendix, D., *Chemical synthesis of polylactide and its copolymers for medical applications.* Polymer Degradation and Stability

Biodegradable Polymers and Macromolecules, 1998. **59**(1-3): p. 129-135.

4. Ranade, V.V., *Drug Delivery Systems: 3A. Role of Polymers in Drug Delivery.* The Journal of Clinical Pharmacology, 1990. **30**(1): p. 10-23.

5. Mitragotri, S., P.A. Burke, and R. Langer, *Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies.* Nature Reviews Drug Discovery, 2014. **13**(9): p. 655-672.

6. Frinking, P.J., et al., *Effect of ultrasound on the release of micro-encapsulated drugs.* Ultrasonics, 1998. **36**(1-5): p. 709-12.

7. Langer, R., *New methods of drug delivery.* Science, 1990. **249**(4976): p. 1527-1533.

8. Agnihotri, S.M. and P.R. Vavia, *Drug loaded poly[Lac(Glc-Leu)] microparticles: Formulation and release characteristics.* Colloids and Surfaces B: Biointerfaces, 2009. **74**(1): p. 336-339.

9. Brittain, H.G. and K. Florey, *Analytical profiles of drug substances and excipients*. Vol. 25. 1992, San Diego ; Toronto: Academic Press. v.

10. Reynolds, J.E.F., et al., *Martindale : the extra pharmacopoeia*. 29th ed. 1989, London: Pharmaceutical Press. xxx, 1896.

11. Targhi, M.S., *preparatiopn and evaluation of sustained release.* these of Ph.D, 1990.

12. R. K. KULKARNI, E.G.M., A. F. HEGYELI, and FRED and R.K.K.K.C.P.C.N.F. Leonard, *Biodegradable Poly(1actic acid) Polymers.* J. BTOMEI). MATER. RES., 1971. **5**(3): p. 169-181.

13. Yu, L., *Amorphous pharmaceutical solids: preparation, characterization and stabilization.* Advanced Drug Delivery Reviews Characterization of the Solid State, 2001. **48**(1): p. 27-42.

14. Cheng, W.-T., S.-Y. Lin, and S.-L. Wang, *Differential Scanning Calorimetry with Curve-Fitting Program Used to Quantitatively Analyze the Polymorphic Transformation of*

Famotidine in the Compressed Compact. Drug Development and Industrial Pharmacy, 2008. **34**(12): p. 1368-1375.

15. Johari, G.P., et al., *Characterizing amorphous and microcrystalline solids by calorimetry.* Journal of Non-Crystalline Solids, 1990. **116**(2-3): p. 282-285.

16. Omelczuk, M. and J. McGinity, *The Influence of Polymer Glass Transition Temperature and Molecular Weight on Drug Release from Tablets Containing Poly(DL-lactic Acid).* Pharmaceutical Research, 1992. **9**(1): p. 26-32.

17. Raghavan, D., et al., *Mapping Polymer Heterogeneity Using Atomic Force Microscopy Phase Imaging and Nanoscale Indentation.* Macromolecules, 2000. **33**(7): p. 2573-2583.

18. Magonov, S.N., V. Elings, and M.-H. Whangbo, *Phase imaging and stiffness in tapping-mode atomic force microscopy.* Surface Science, 1997. **375**(2-3): p. L385-L391.

19. Zelko, R., et al., *Effect of plasticizer on the dynamic surface tension and the free volume of Eudragit systems.* International Journal of Pharmaceutics, 2002. **244**(1-2): p. 81-86.

20. Saettone, M.F., et al., *Effect of different polymer-plasticizer combinations on 'in vitro' release of theophylline from coated pellets.* International Journal of Pharmaceutics, 1995. **126**(1-2): p. 83-88.

21. Choi, K.-m., et al., *Plasticization of poly(lactic acid) (PLA) through chemical grafting of poly(ethylene glycol) (PEG) via in situ reactive blending.* European Polymer Journal, 2013. **49**(8): p. 2356-2364.

22. Piorkowska, E., et al., *Plasticization of semicrystalline poly(l-lactide) with poly(propylene glycol).* Polymer, 2006. **47**(20): p. 7178-7188.

23. Von Recum, H., et al., *Degradation of polydispersed poly(L-lactic acid) to modulate lactic acid release.* Biomaterials, 1995. **16**(6): p. 441-447.

24. Milner, S.T., T.A. Witten, and M.E. Cates, *Effects of polydispersity in the end-grafted polymer brush.* Macromolecules, 1989. **22**(2): p. 853-861.

25. Tongwen, X. and H. Binglin, *Mechanism of sustained drug release in diffusion-controlled polymer matrix-application of percolation theory.* International Journal of Pharmaceutics, 1998. **170**(2): p. 139-149.

26. Miyajima, M., et al., *Effect of polymer/basic drug interactions on the two-stage diffusion-controlled release from a poly(-lactic acid) matrix.* Journal of Controlled Release, 1999. **61**(3): p. 295-304.

27. Chieng, B.W., et al., *Plasticized poly(lactic acid) with low molecular weight poly(ethylene glycol): Mechanical, thermal, and morphology properties.* Journal of Applied Polymer Science, 2013. **130**(6): p. 4576-4580.

28. Korner, A., et al., *Molecular Information on the Dissolution of Polydisperse Polymers: Mixtures of Long and Short Poly(ethylene oxide).* The Journal of Physical Chemistry B, 2005. **109**(23): p. 11530-11537.

29. Soares, J.o.S. and P. Zunino, *A mixture model for water uptake, degradation, erosion and drug release from polydisperse polymeric networks.* Biomaterials, 2010. **31**(11): p. 3032-3042.

30. Hassouna, F., et al., *New approach on the development of plasticized polylactide (PLA): Grafting of poly(ethylene glycol) (PEG) via reactive extrusion.* European Polymer Journal, 2011. **47**(11): p. 2134-2144.

31. von Burkersroda, F., R. Gref, and A. Gopferich, *Erosion of biodegradable block copolymers made of poly(d,l-lactic acid) and poly(ethylene glycol).* Biomaterials, 1997. **18**(24): p. 1599-1607.

32. Wu, C. and J.W. McGinity, *Non-traditional plasticization of polymeric films.* International Journal of Pharmaceutics, 1999. **177**(1): p. 15-27.

33. Ugur, S., A. Dinc, and Y. Kislak, *Effect of molecular weight on the dissolution properties of polystyrene latex films.* Journal of Polymer Research, 2012. **19**(9): p. 1-10.

34. Raghavan, S.L., et al., *Crystallization of hydrocortisone acetate: influence of polymers.* International Journal of Pharmaceutics, 2001. **212**(2): p. 213-221.

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

Table 1: Data of low and high molecular weight PLA Characterized by Gel Permeation Chromatography

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

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

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

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

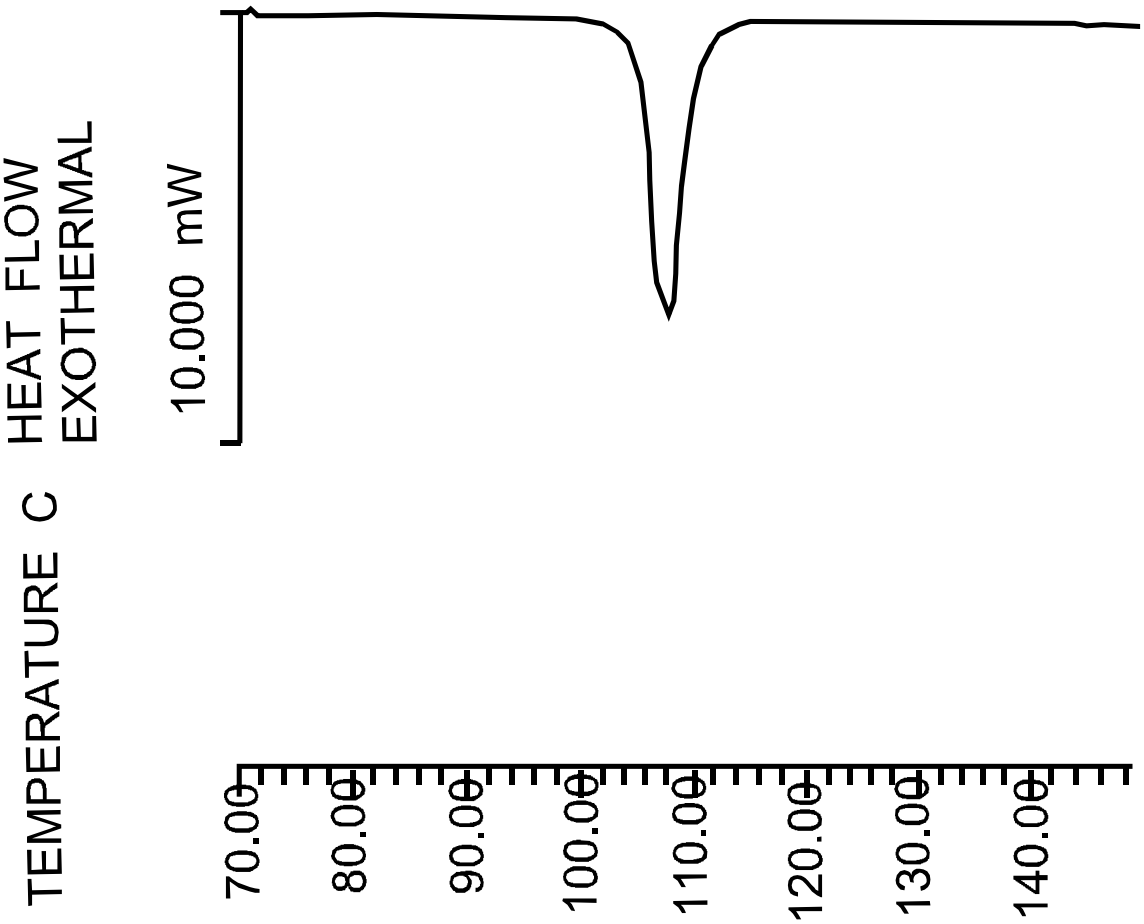

Figure 1: DSC scan of pure drug (pentoxifylline), at a theoretical 10% drug loading level.

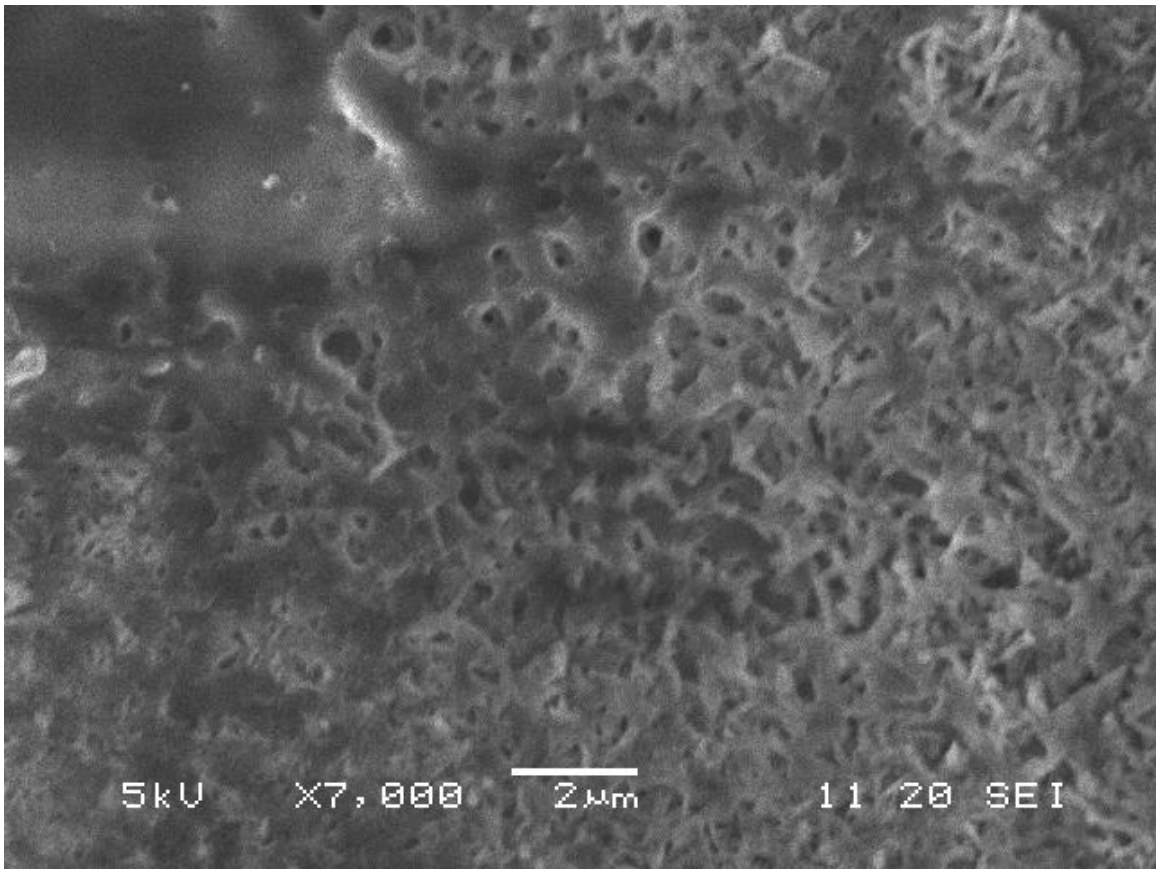

Figure 2: SEM photo of 20 % pentoxifylline film after dissolution showing pores after pentoxifylline particles were dissolved

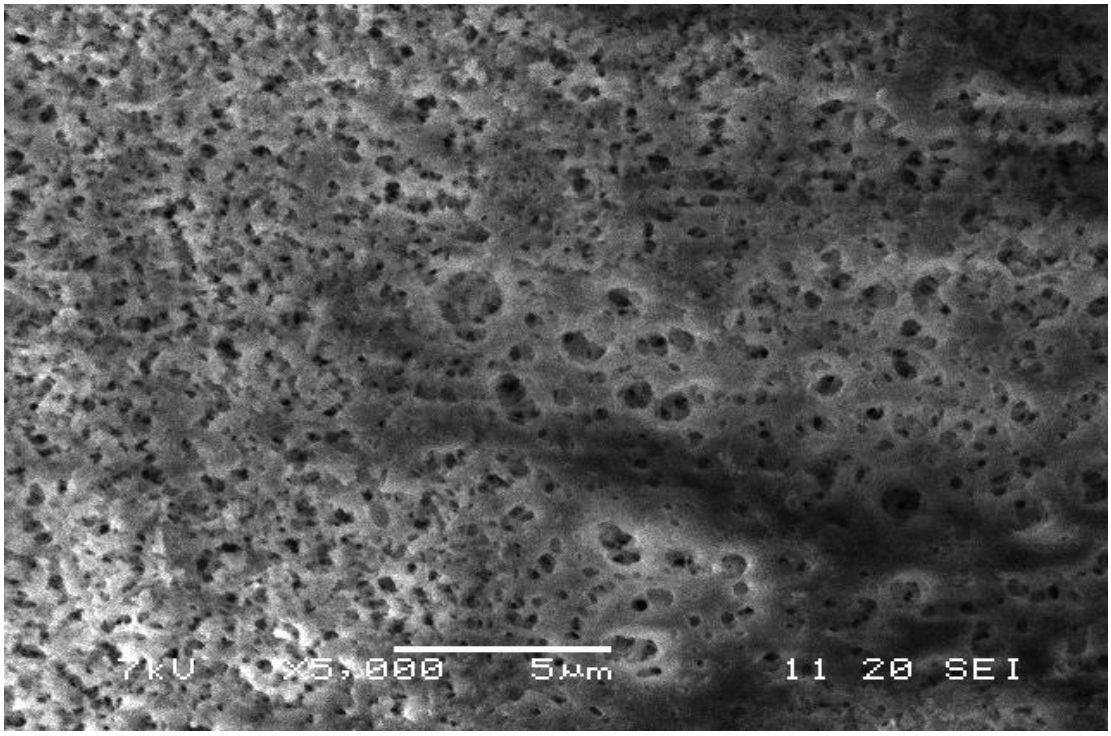

Figure 3: SEM photo of 60 % pentoxifylline film after dissolution showing the pores after pentoxifylline particles were dissolved

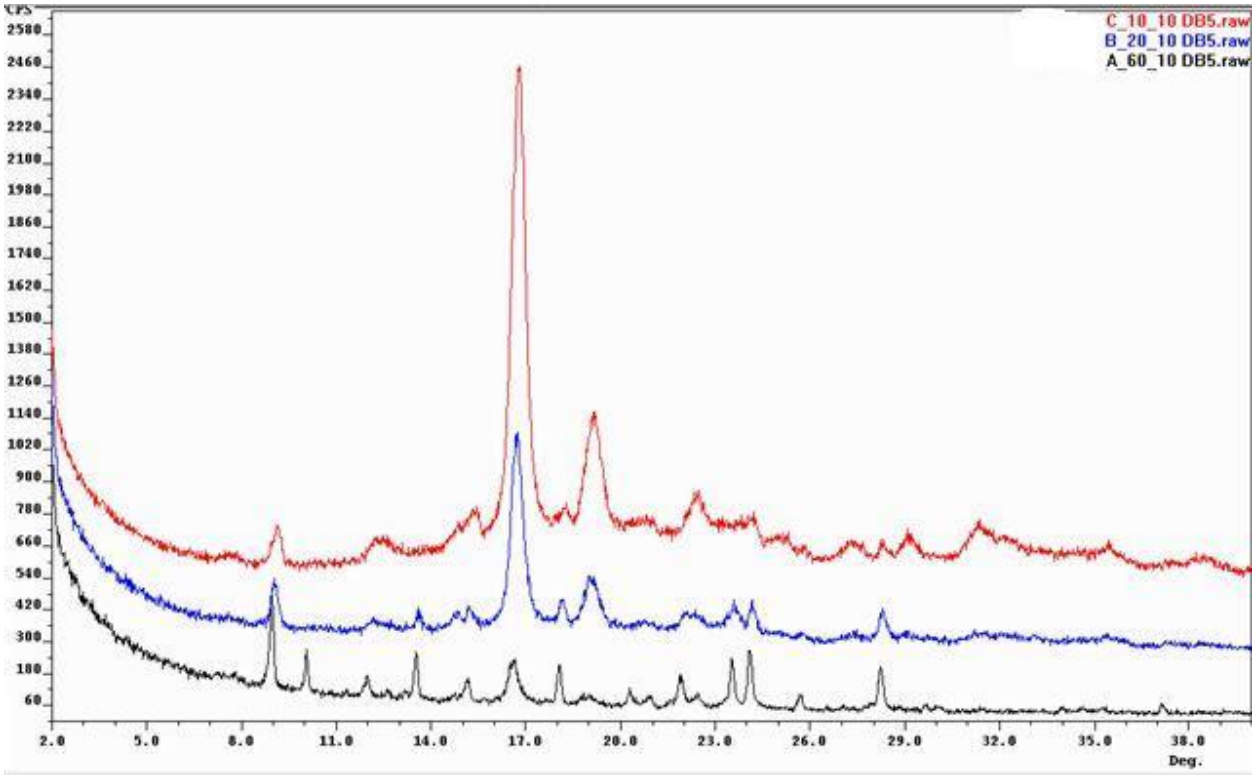

Figure 4: X-ray diffraction of samples of pentoxifylline (10%, 20% and 60%) film at a constant plasticizer level (DBS 10%) showing the drug peaks at 13.57, 15.13, 24.05 and 28.61.

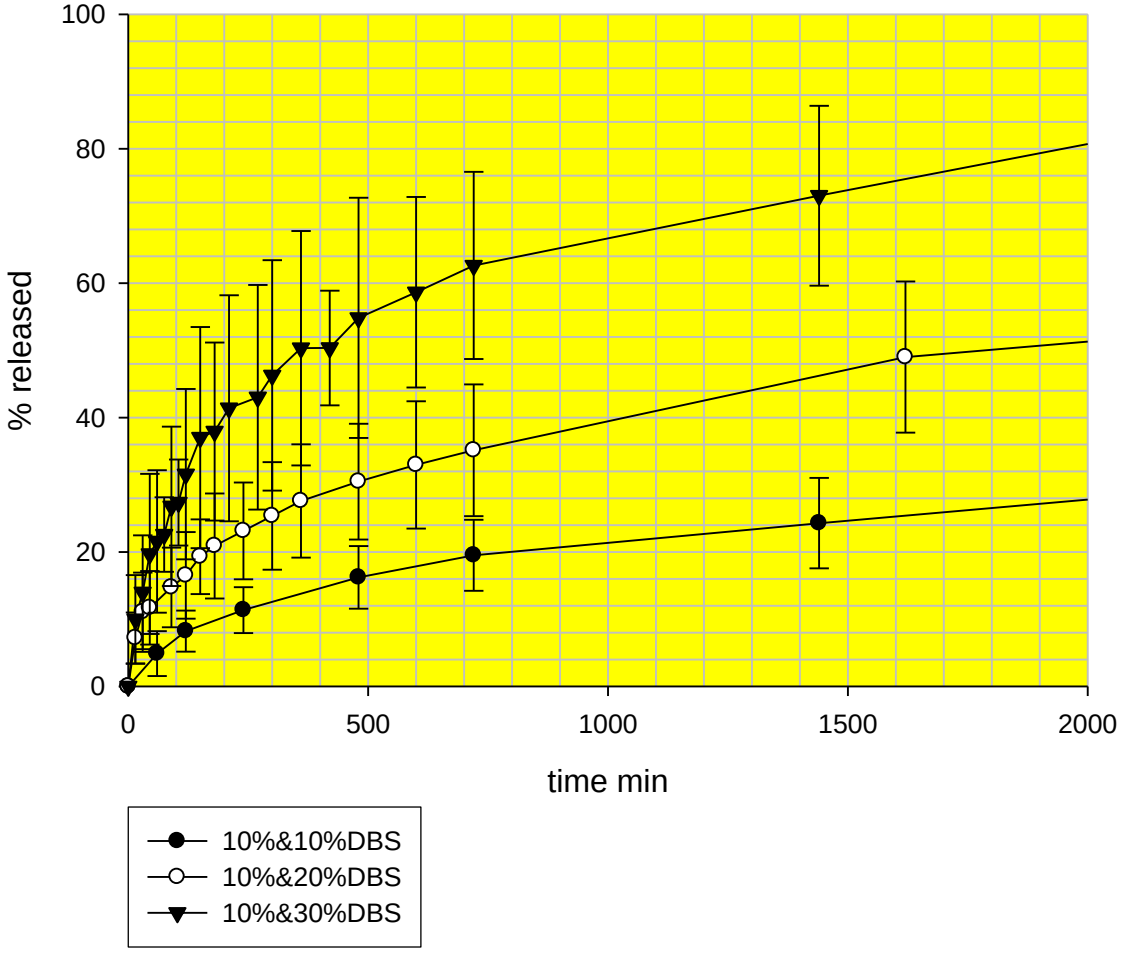

Figure 5: The effect of 10 % drug loading on the drug release of pentoxifylline at different plasticizer levels (10%, 20% and 30% DBS)

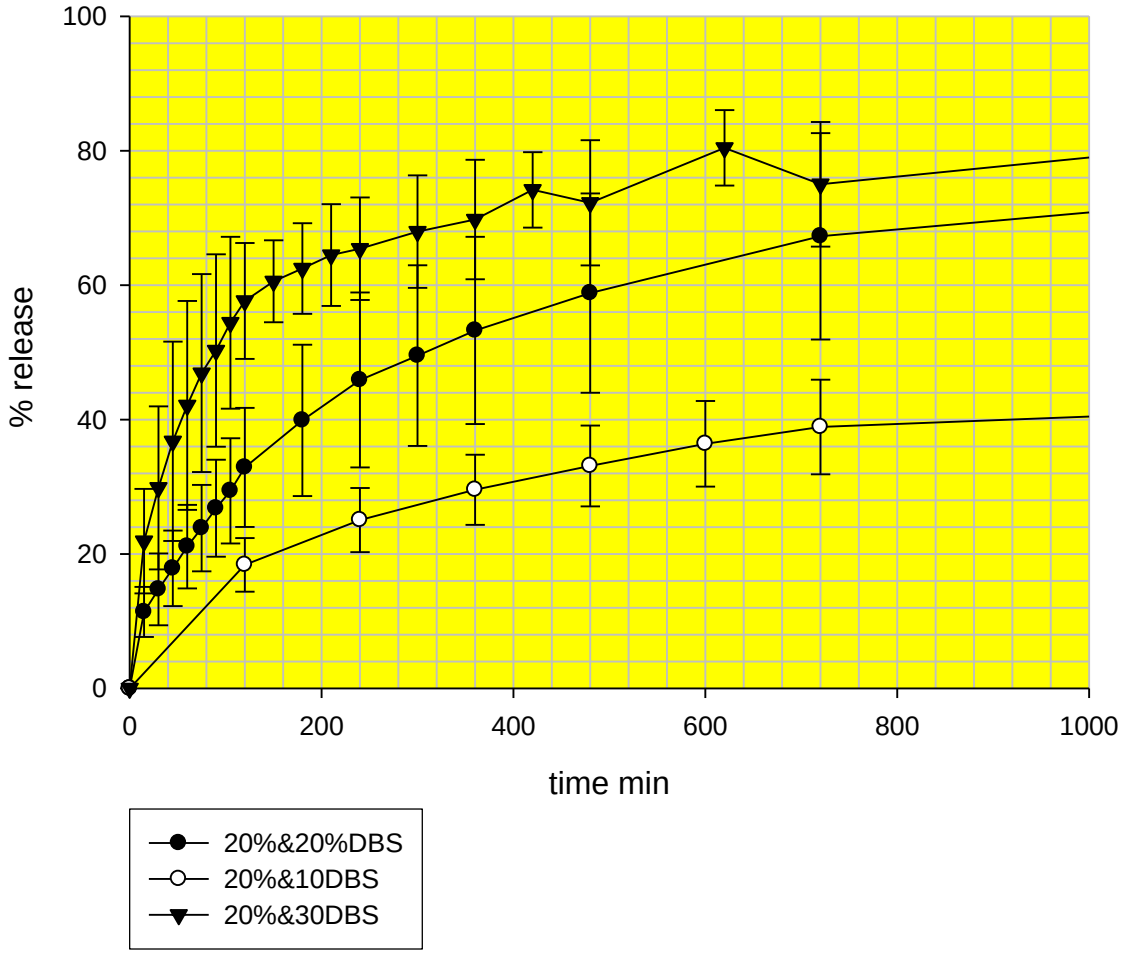

Figure 6: The effect of 20 % drug loading on the drug release of pentoxifylline at different plasticizer levels (10%, 20% and 30% DBS).

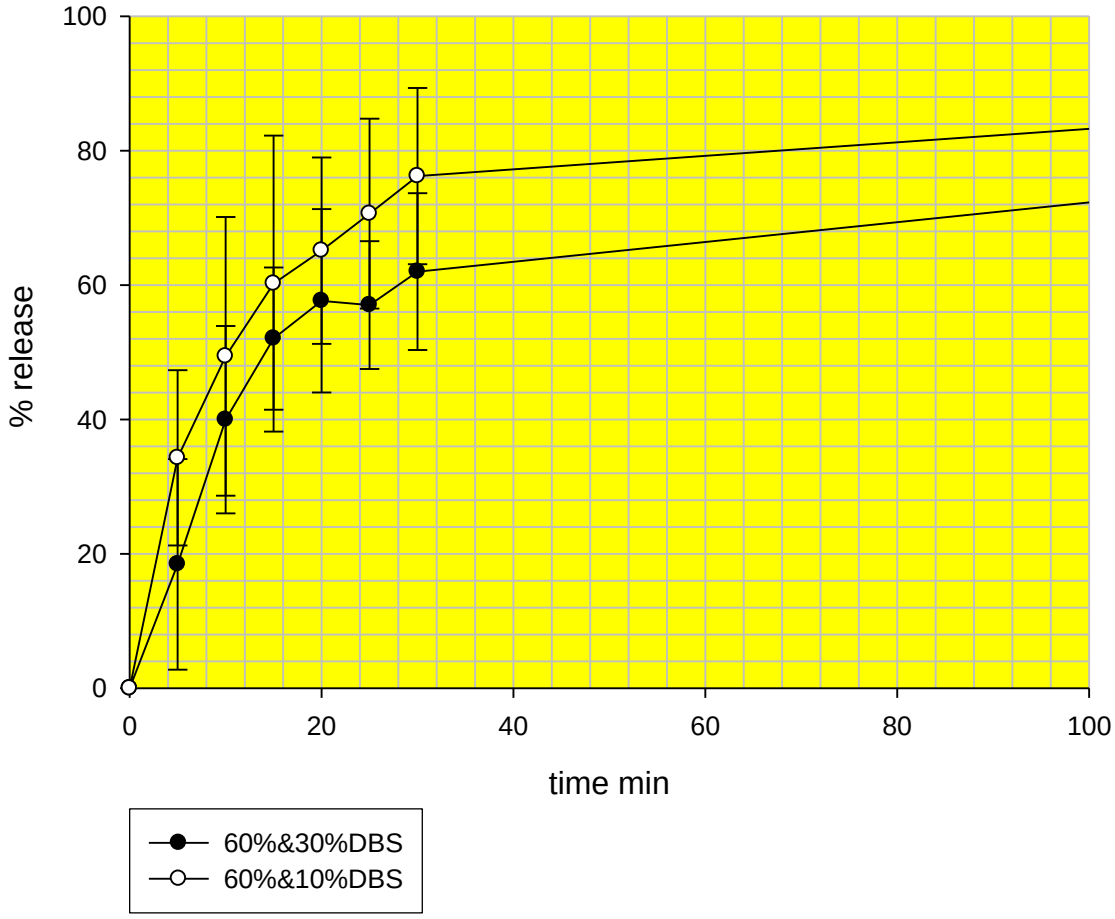

Figure 7: The effect of 60 % drug loading on the drug release of pentoxifylline at different plasticizer levels (10% and 30% DBS)