Preparation of Biodegradable Microspheres and Matrix Devices Containing Naltrexone

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ABSTRACT

In this study, the use of biodegradable polymers for microencapsulation of naltrexone using solvent evaporation technique is investigated. The use of naltrexone microspheres for the preparation of matrix devices is also studied. For this purpose, poly(L-lactide) (PLA) microspheres containing naltrexone prepared by solvent evaporation technique were compressed at temperatures above the Tg of the polymer. The effect of different process parameters, such as drug/polymer ratio and stirring rate during preparation of microspheres, on the morphology, size distribution, and in vitro drug release of microspheres was studied. As expected, stirring rate influenced particle size distribution of microspheres and hence drug release profiles. By increasing the stirring speed from 400 to 1200 rpm, the mean diameter of microspheres decreased from 251 μm to 104 μm. The drug release rate from smaller microspheres was faster than from larger microspheres. However, drug release from microspheres with low drug content (20% wt/wt) was not affected by the particle size of microspheres. Increasing the drug content of microspheres from 20% to 50% wt/wt led to significantly faster drug release from microspheres. It was also shown that drug release from matrix devices prepared by compression of naltrexone microspheres is much slower than that of microspheres. No burst release was observed with matrix devices. Applying higher compression force, when compressing microspheres to produce tablets, resulted in lower drug release from matrix devices. The results suggest that by regulating different variables, desired release profiles of naltrexone can be achieved using a PLA microparticulate system or matrix devices.

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INTRODUCTION

Naltrexone is an opiate antagonist used mainly as an adjunct to prevent relapse in detoxified opioid-dependent patients. It is currently given orally as tablets or capsules in a daily dose of 50 mg. Naltrexone is orally active with a relatively short half-life and subject to extensive hepatic first-pass metabolism.[1] Naltrexone provides no euphoric effects, and there are no observable pharmacological consequences when a patient discontinues the drug.[2] For naltrexone treatment to be effective, a sufficient level of the drug concentration must be maintained. The minimum effective concentration of naltrexone for the treatment of opiate addiction is estimated to be in the range of 0.5 to 1.0 ng/mL.[3,4] Detoxified patients are advised to continue the naltrexone therapy for 4 to 8 months.[5] This treatment typically requires the patient to self-administer dosages of the drug several times a week. The main drawback in naltrexone treatment protocol is patient compliance. A possible means of improving patient compliance and concomitant rehabilitation is the use of controlled drug delivery systems of opioid antagonists.[6,7] Many efforts have been made to develop novel systems to maximize patient compliance.[8-12] There have been different studies using biodegradable beads prepared by the National Institute on Drug Abuse on the use of naltrexone as an opiate antagonist in animals.[13-16] Martin et al[17] used naltrexone-zinc tannate complex, a sparingly soluble form, to increase the duration of the antagonistic effect. Negishi et al[18] obtained 28 days of in vitro release of the antagonist by covalently coupling naltrexone to a biodegradable poly(α-amino acid) backbone. However, most attention has been focused on the preparation of polymeric injectable microparticles or implants of naltrexone. Sharon and Wise[7] prepared 1.5-mm diameter beads composed of naltrexone and poly(lactide-co-glycolide). Microcapsules prepared from glutamic

acid/ethyl glutamate copolymer released naltrexone at a rate of 20 to 25 µg/h for 30 days.[19] Some effort has also focused on the preparation of morphine-triggered naltrexone delivery systems.[8,20,21] These studies have provided important data on the usefulness of implantation for naltrexone delivery. Bhargave et al[22] studied the effects of naltrexone pellet implantation on narcotic tolerance and physical dependence in rats. However, studies on the application of naltrexone implants for human use have not been as convincing.[23] More studies are needed to prepare a suitable naltrexone delivery system. The main objective of the present study was to prepare naltrexone microspheres and matrix devices using poly(L-lactide) (PLA), a biodegradable polymer approved by the Food and Drug Administration for human use.

Naltrexone microspheres were prepared using a solvent evaporation method. The effect of different formulation parameters on drug release from microspheres was studied. Naltrexone matrix devices were prepared by compression of naltrexone microspheres at temperatures above the glass rubber transition temperature (T_g) of the polymers.

MATERIALS AND METHODS

Materials

Naltrexone was donated by Francopia (Paris, France). PLA, with an inherent viscosity of 3.6 dL/g (determined in chloroform 0.1% at 25°C) and molecular weight of 285 000 g/mol was supplied by Boehringer Ingelheim (Ingelheim am Rhein, Germany). Polyvinyl alcohol (PVA) 87% to 89% hydrolyzed with molecular weight 72 000 g/mol and monobasic potassium phosphate, sodium bicarbonate, and toluene (all of analytical grade) were supplied by Merck (Darmstadt, Germany). Dichloromethane (DCM) was purchased from Kiankaveh Pharmaceuticals and Chemical Complex Inc (Saveh, Iran). Ethanol 97% vol/vol was supplied by Estalak Co (Tehran, Iran). Other materials were of analytical grade and were used as received.

Microsphere Preparation

Emulsification/solvent-evaporation method was used for preparation of naltrexone microspheres. Appropriate amounts of PLA were added to 10 mL methylene chloride to provide concentrations of 2.5%, 3%, 3.5%, and 4% wt/vol; then different amounts of naltrexone were dissolved in the polymer solution to give 1% to 2.5% wt/vol drug solutions to yield theoretical drug loading of 20%, 30%, 40%, or 50% wt/wt, respectively. The solution was then added drop-wise to a 200-mL aqueous phase solution containing 0.5% wt/vol poly(vinyl alcohol) (PVA), while the mixture was stirred by an overhead stirrer (Heidolf RZR2100, Kelhein, Germany) to form a stable oil/water emulsion system at room temperature (25 ± 2°C). Stirring was continued for up to 5 hours to allow the evaporation of methylene chloride and the formation of solid microspheres. Microspheres were filtered, washed with distilled water, and dried overnight until no weight loss was observed.

Microsphere Characterization

Morphology of microspheres was studied using scanning electron microscopy (Stereoscan 360 microscope, Leica Cambridge, Cambridge, UK). Particle size of microspheres was determined using standard sieves with mesh size of 90, 150, and 300 µm and laser scattering (Mastersizer, Malvern Instruments, Worcestershire, UK). Total drug content of microspheres was determined by dissolving the microspheres in methylene chloride followed by using UV spectrophotometry (Cecil 9000, Cecil Instruments Ltd, Cambridge, UK) at 281 nm, and drug loading efficiency was calculated as the actual drug content divided by theoretical drug content multiplied by 100.

Matrix Device Preparation

Matrix devices were prepared by compression molding of biodegradable microspheres containing naltrexone. Known amounts of microspheres were transferred to a die with a diameter of 12 mm and a depth of 50 mm and kept in an oven (Gallenkamp hot box oven, Loughborough, UK) for 120 minutes at 120°C (above the T_g of polymer) and then compressed by a punch at 550 to 750 KN force. Naltrexone is stable at this temperature.

Drug Release

Microsphere drug release experiments were carried out in 0.2 M phosphate buffer (pH 7.4) containing 20% vol/vol ethanol to maintain sink conditions. Twenty-five milligrams of naltrexone microspheres were put in a small vial containing 25 mL of phosphate buffer, the release medium. The vial was rotated at 60 rpm and, was maintained at 37 ± 0.2°C in a thermostat water bath. The phosphate buffer was replaced with fresh solution daily. The drug content of the release medium
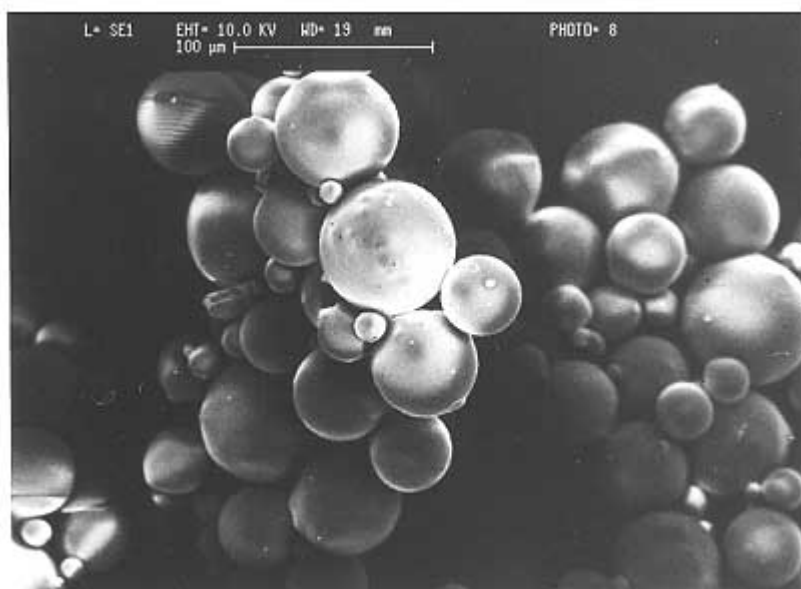
Figure 1. SEM photograph of PLA microspheres containing 30% naltrexone prepared at 400 rpm.

was determined using UV spectrophotometry at 281 nm.

Drug release studies from matrix devices were carried out using a USP24-NF19 paddle type dissolution apparatus (Kavosh, Tehran, Iran). Devices were accurately weighed to 50 mg and placed in a phosphate buffer solution containing 20% vol/vol ethanol in $37 \pm 0.2°C$ and then rotated at 60 rpm. Samples were withdrawn and assayed spectrophotometrically at 281 nm at different time intervals.

RESULTS AND DISCUSSION

Morphology and Size Distribution

It was shown that microspheres prepared in this study at stirring rates of 400 and 800 rpm were spherical with smooth surfaces (**Figure 1**). However, increasing the stirring rate to 1200 rpm caused microspheres to become slightly irregular.

The effect of stirring rate on the particle size of microspheres is shown in **Figure 2**. It can be seen that by increasing the rate of stirring from 400 to 1200 rpm, the mean size of microspheres decreased from 251 to 104 μm. This was expected because high stirring rates provide the sheering force needed to separate the oil phase into smaller droplets.[24]

By increasing the concentration of PLA, the mean particle size of microspheres increased (**Figure 3**). This

observation may be attributed to an increase in the viscosity of the dispersed phase, making the coalescence of emulsified dispersed droplets easier.[25]

Formulations prepared with drug loading of up to 40% produced spherical particles with smooth surfaces (**Figure 1**). However, high drug-loaded microspheres (50%) were not as smooth as low drug-loaded microspheres, and their surfaces were covered with drug crystals or broken particles (**Figure 4**).

Drug Loading Efficiency

Drug loading efficiency of PLA microspheres prepared in this study was shown to be approximately 70% (**Table 1**).

Drug Release

The effect of particle size on drug release from microspheres is shown in **Figures 5** and **6**. **Figure 5** shows the drug release from microspheres with 20% drug loading but different particle sizes. It can be seen that particle size does not affect the rate of drug release from microspheres with low drug loading (20%). This may be because of the high efficiency of drug encapsulation by PLA. Lower drug contents create fewer pores within the polymeric network; hence lower rate of drug diffusion is observed.
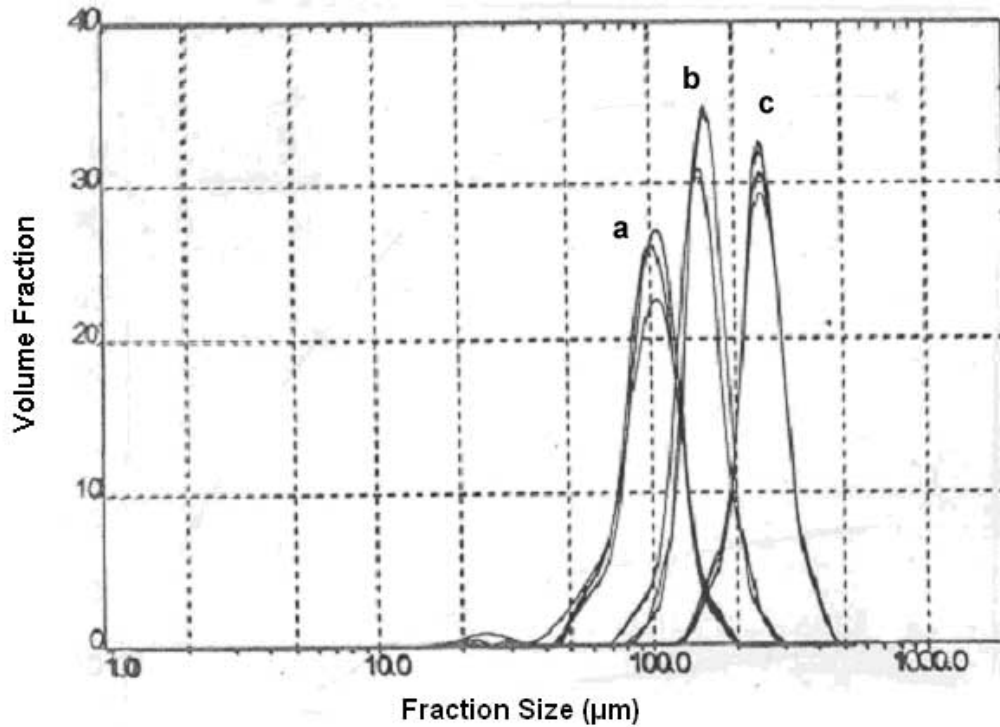
Figure 2. Effect of stirring rate on particle size of PLA microspheres containing 40% naltrexone: (a) 1200, (b) 800, and (c) 400 rpm.
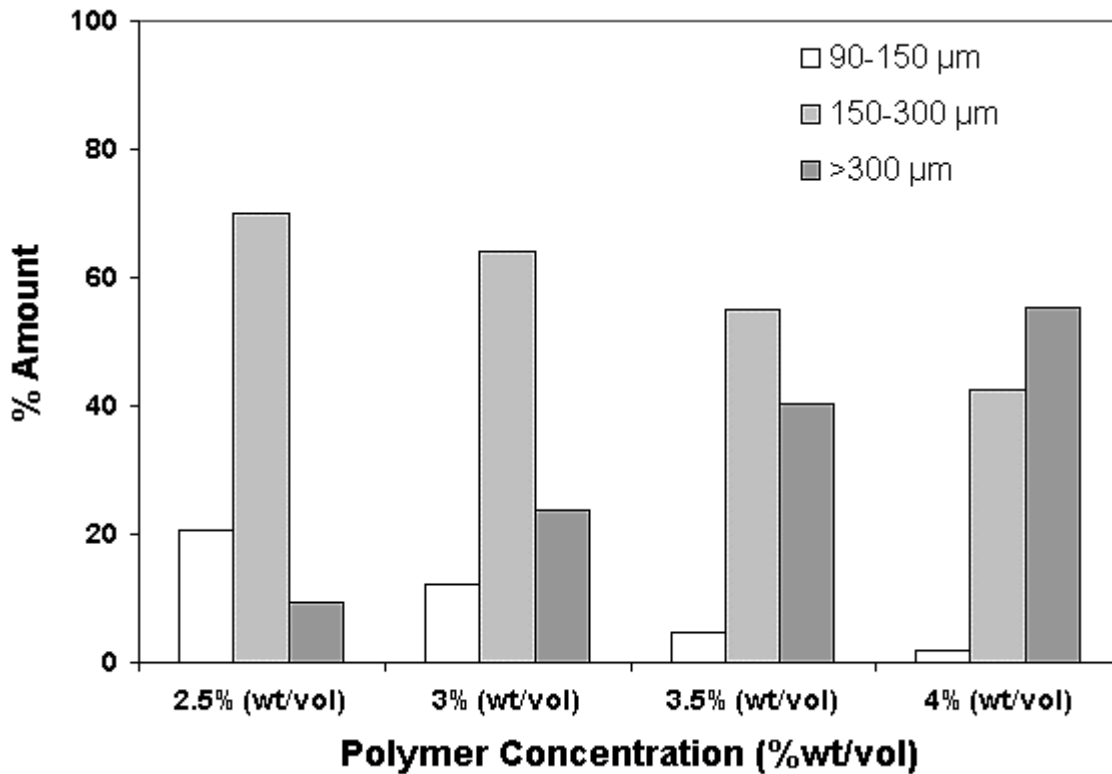

Figure 3. Effect of PLA concentration on particle size of microspheres: (a) 2.5% (wt/wt), (b) 3% (wt/wt), (c) 3.5% (wt/wt), and (d) 4% (wt/wt).
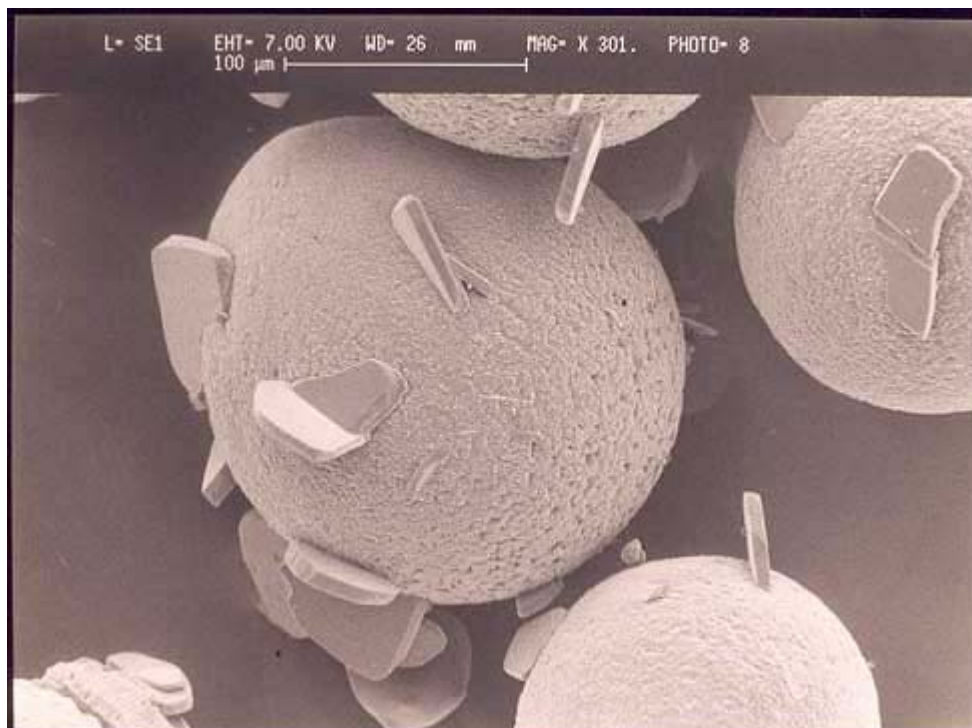
Figure 4. SEM photograph of PLA microspheres containing 50% naltrexone.

Table 1. Targeted and Actual Drug Loading of PLA Microspheres Containing Naltrexone*

Sample	Stirring Rate (rpm)	Targeted Drug Loading (%)	Actual Drug Loading (%)	Drug Loading Efficiency (%)
Mic-2-4	400	20	12.4	62
Mic-3-4	400	30	23.1	77
Mic-4-4	400	40	27.5	69
Mic-5-4	400	50	46.8	93
Mic-2-8	800	20	14.3	71
Mic-3-8	800	30	21.5	72
Mic-4-8	800	40	29.6	74
Mic-5-8	800	50	38.1	76
Mic-2-12	1200	20	15-1	76
Mic-3-12	1200	30	22.1	74
Mic-4-12	1200	40	54.1	110
Mic-5-12	1200	50	32.5	65

Figure 6 shows drug release from microspheres of different particle sizes with drug loading of 40%. It is shown that drug release is affected by particle size when drug loading is high (40%). In the case of smaller microspheres, greater surface area produces a higher number of drug molecules at the surface of microspheres ready for faster release.[26]

The effect of drug loading of microspheres on naltrexone release from microspheres is shown in **Figure 7**. It can be seen that by increasing the amount of drug loading from 20% to 50%, the rate of drug release from the microspheres increases dramatically. With higher drug loading, more drug molecules are available at the surface of microspheres, leading to higher initial release.[27]
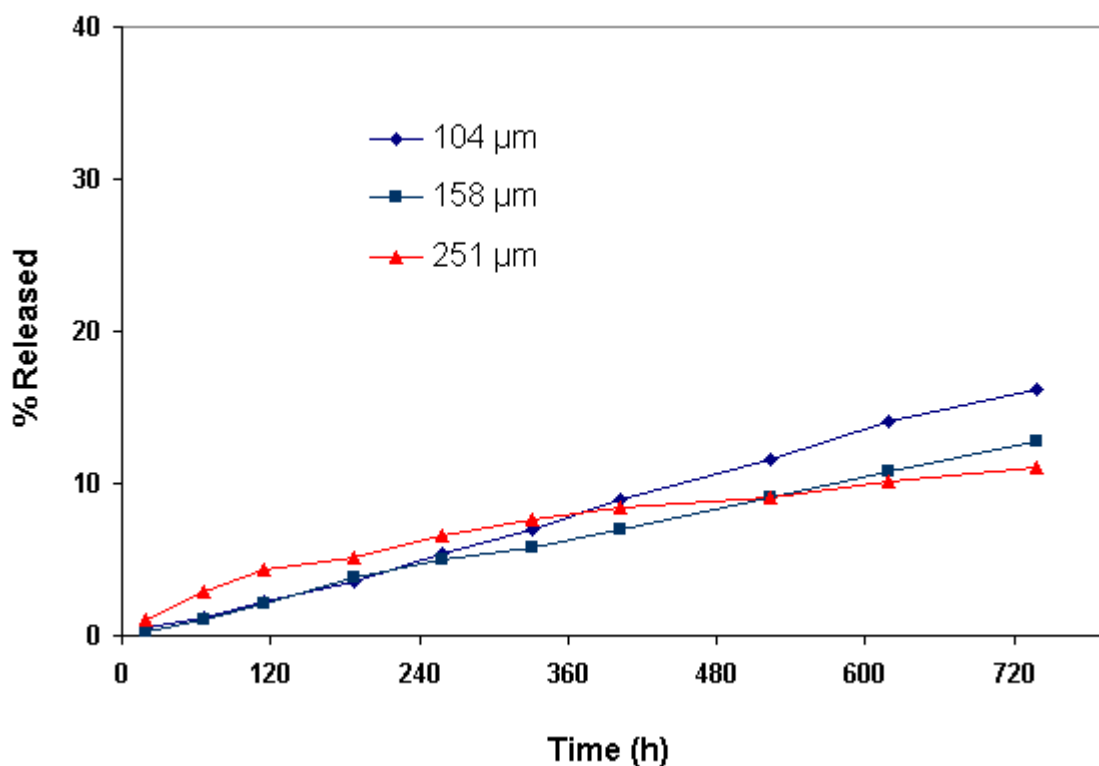
Figure 5. Effect of particle size on drug release from microspheres with 20% drug loading.
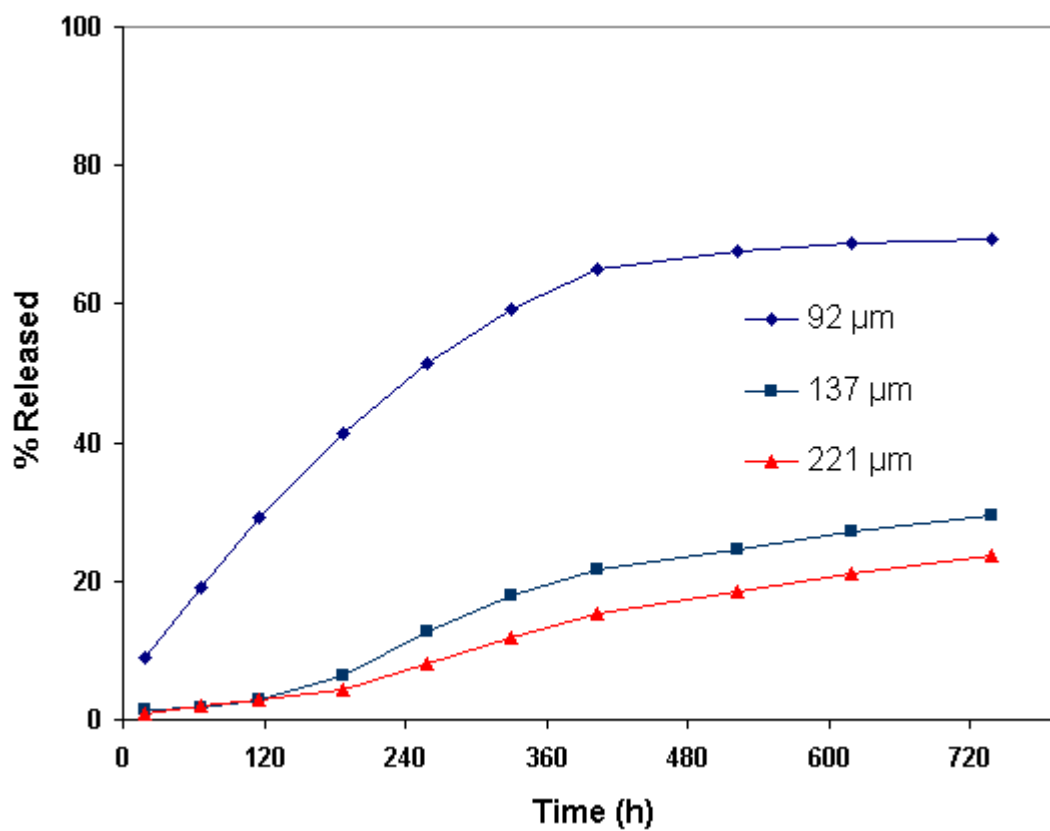

Figure 6. Effect of particle size on drug release from microspheres with 40% drug loading.
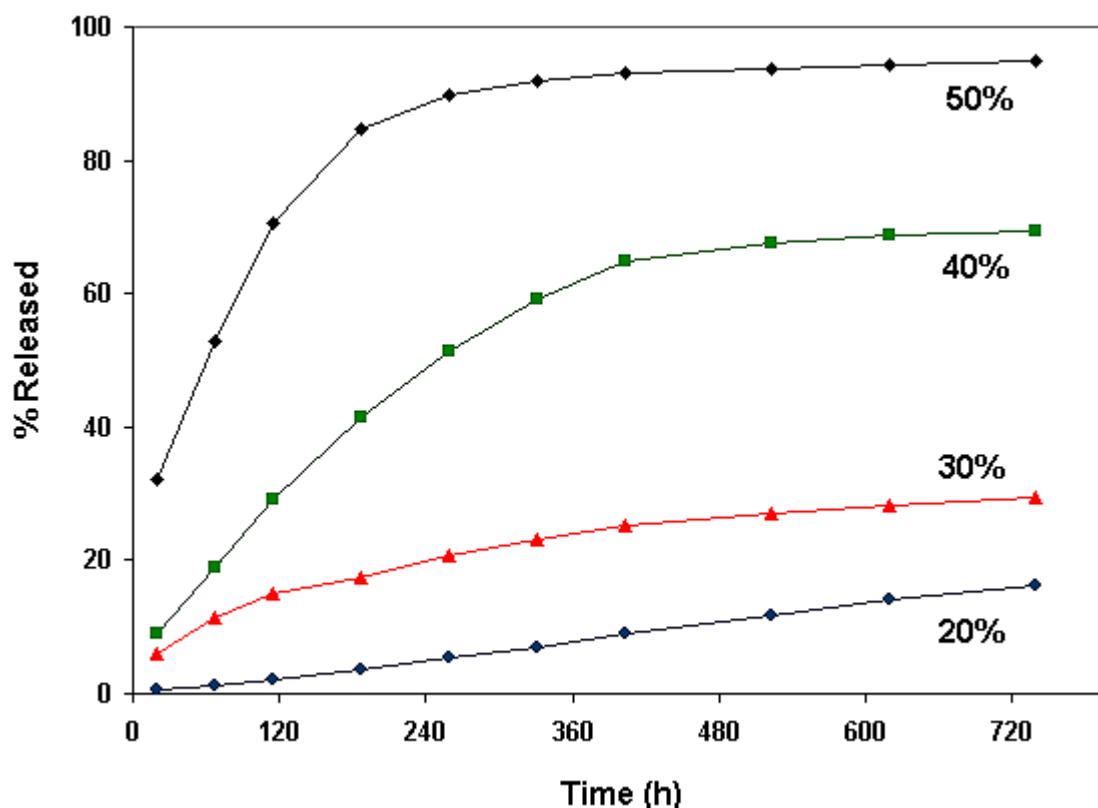
Figure 7. Effect of drug loading on drug release from microspheres with the same size range.

Also, by increasing the amount of drug loading, a point will be reached when the solid drug particles will begin to form continuous pores or channels within the matrix. Under these circumstances, the path of least resistance for drug molecules will be diffusion within the channels formed from areas where drug has previously leached out from the matrix.[28,29] Therefore, as the amount of drug content is increased and drug leaches out from the polymer, the matrix becomes more porous and a faster drug release rate occurs.

The profile of drug release from microspheres with theoretical drug loading of 20% and 30% seems to be different from that of microspheres with drug loading of 40% and 50%. These results show that the mechanism of drug release from high drug-loaded microspheres may be different from that of low drug-loaded microspheres. Although the kinetics of drug release from both groups of microspheres are nearly the same, drug release from high drug-loaded microspheres is closer to the first order model of kinetics. (**Table 2**).

Tabletting or compression molding of PLA microspheres containing naltrexone may be regarded as a method of prolonging drug release while maintaining a sufficient rate of drug release without the initial burst

effect associated with high drug-loaded microspheres.[30] As a semicrystalline polymer, PLA is not compressible at low temperatures. Therefore, all matrix devices were prepared by compression molding of PLA microspheres at temperatures of up to 120°C, well above the T_g of the polymer used in this study (65.9°C).

Table 2. Correlation Coefficient (r^2) for Drug Release from Microspheres, Curve Fitted According to Zero Order and First Order Kinetics

Drug Loading	Correlation Coefficient (r^2)	
	Zero Order	First Order
20%	0.998	0.997
30%	0.886	0.909
40%	0.828	0.898
50%	0.603	0.810

Figure 8 shows the effect of compression force on drug release from matrix devices prepared using naltrexone microspheres with drug loading of 30%. **Figure 9** shows the effect of drug loading of micro-
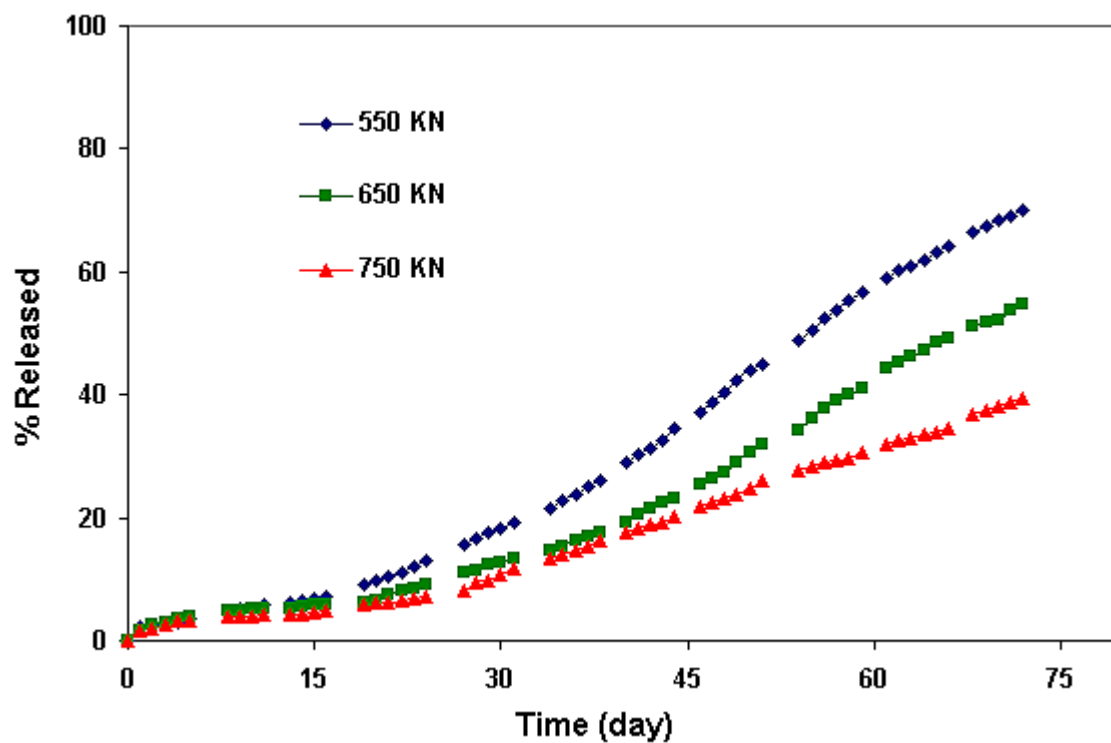
Figure 8. Effect of compression force on drug release from PLA matrix devices containing 30% naltrexone.
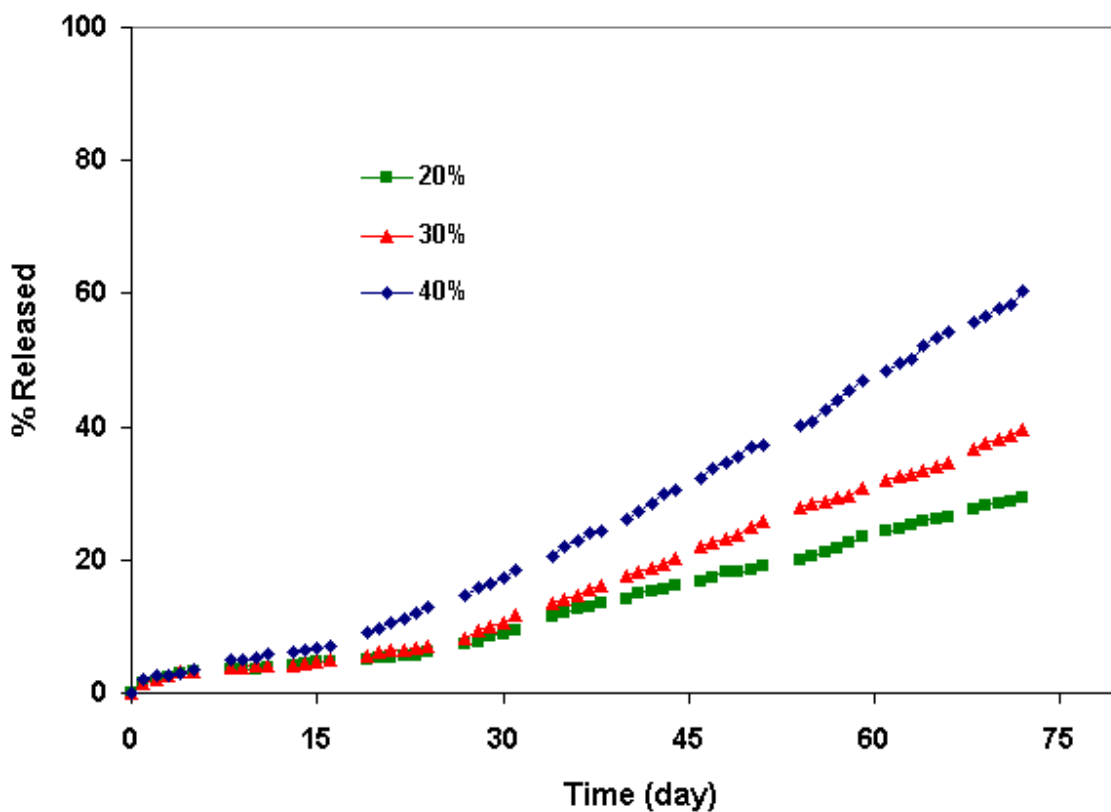

Figure 9. Effect of drug loading on drug release from PLA matrix devices prepared using 750KN force.

spheres used on drug release from matrix devices prepared at 750 KN.

It can be seen that the rate of drug release from devices compressed at lower force (550 KN) is higher than those compressed at higher force (750 KN). As expected, drug release from devices with higher drug loading is greater than those with lower drug content. The cumulative amount of release per unit area depends directly on the amount of drug initially loaded and the matrix porosity. Matrix porosity is decreased when the compression force is increased. Drug release kinetics of the biodegradable matrix devices is considered to be Fickian.[31] However, the release profile of matrix devices reported here did not follow the Fickian model of kinetics. This deviation may be due to the limited release time of the experiments in this study. Another reason for this drug release profile may be the effect of both drug diffusion and bulk erosion of the matrix device on drug release pattern.[32] As expected, matrix devices prepared in this study showed poor mechanical properties.[33] This behavior may be attributed to the high crystallinity of PLA.[34] High crystallinity of a polymer can induce more brittle and less ductile behavior into a polymer matrix.[35,36] Therefore, the use of biodegradable polymers with lower T_g such as poly(lactide-co-glycolide) may show better mechanical properties.

CONCLUSSION

Poly(L-lactide) microspheres containing naltrexone could be prepared with various particle sizes and in-vitro patterns of drug release. Their characteristics could be controlled by applying different parameters such as stirring rate and drug content. The size of microspheres and their drug content determine the rate and pattern of drug release. Smaller and high drug-loaded microspheres show faster drug release. A more controlled and sustained drug-release profile could be achieved by compression molding of microspheres. Desired drug release rate could be obtained by varying the compression force and the amount of drug loading.

ACKNOWLEDGEMENTS

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