Preparation of a polymeric reservoir naltrexone delivery device: effect of PEG content of the PLA membrane on drug release

Rassoul Dinarvand†, Shadi H Moghadam, Pantea Sayar, Mahsa Alaee & Fatemeh Atyabi

†Author for correspondence
Tehran University of Medical Sciences, Department of Pharmaceutics, Faculty of Pharmacy, Tehran
PO Box 14155–6451, Iran
Tel.: +98 216 912 686
Fax: +98 216 959 055
dinarvand@tums.ac.ir

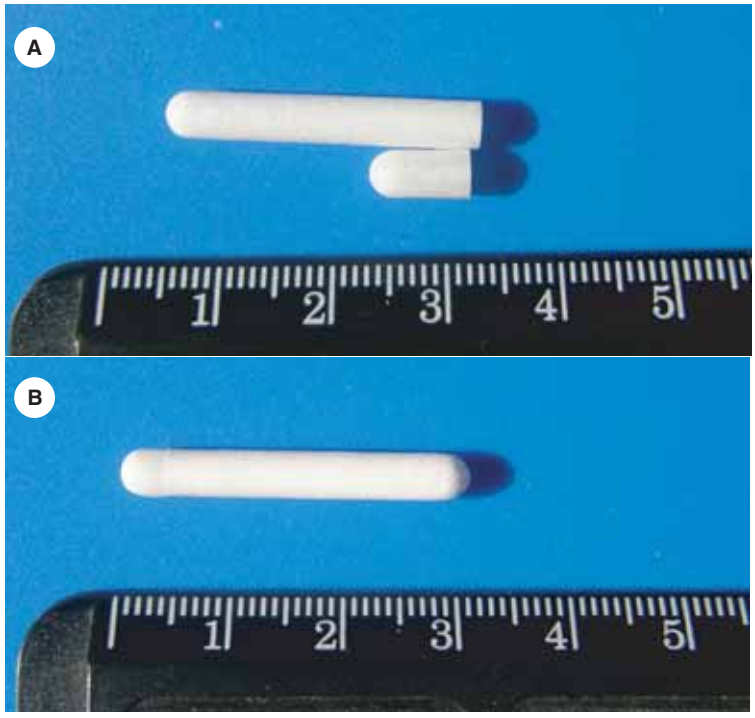
Background: Naltrexone is an orally active opioid agonist that has the potential for use as a treatment option for opiate addiction. However, in order for the drug to be effective, sufficient blood levels must be maintained for 4 to 8 months, which typically requires self-administration by the patient, resulting in complications. **Aim:** The aim of this study was to develop a polymeric reservoir device containing naltrexone. **Materials & methods:** The reservoir device was prepared using high-molecular-weight poly-L-lactide and the cylindrical device by dipping a stainless-steel rod in a methylene chloride solution of polylactic acid (PLA). High-molecular-weight PLA was used to take advantage of the low biodegradation rate of the polymer, in order to obtain constant drug release from the device based on the diffusion mechanism rather than biodegradation of the polymer. The impact of the polymeric device weight and polyethyleneglycol content of the polymeric membrane of the device on the release of naltrexone from the device was studied. **Results:** Rate of drug release from the reservoir device was shown to be successfully regulated by controlling the device weight as well as the amount of hydrophilic additive in the polymeric membrane of the device. The higher the amount of the hydrophilic content of the polymeric membrane, the faster the rate of drug release from the device. **Conclusion:** Prepared reservoir devices released their drug content through the use of a high-molecular-weight PLA. The presence of NaCl as an osmotic agent did not affect the release profile of naltrexone – an indicator that diffusion is the mechanism of release of naltrexone from the PLA reservoir system.

Keywords: cylindrical implant, naltrexone, opioid antagonist, PEG, polylactide, polymeric drug delivery, reservoir device

Drug dependence is a chronic disease with a high rate of relapse. According to the World Drug Report 2004, heroin is one of the most serious illicit drugs abused and is the leading cause of illicit substance-abuse-related mortality and emergency room visits [1]. Hence, in order to help opiate addicts permanently quit using the drug, it is very important to prevent relapse after successful detoxification. A pharmacologic treatment that can be useful for this purpose is the opioid antagonist naltrexone [2]. Naltrexone is currently given orally as tablets or capsules daily. Naltrexone is orally active with a relatively short half-life and subject to extensive hepatic first-pass metabolism [3,4]. This opioid antagonist provides no euphoric effects and there are no observable pharmacologic consequences when a patient discontinues the drug [5]. For naltrexone treatment to be effective, sufficient blood levels must be maintained for at least 4 to 8 months [4]. This typically requires the patient to self-administer dosages of the drug several times a week. The main drawback of the naltrexone treatment protocol is patient compliance. A possible means of improving patient compliance and concomitant rehabilitation is by the use of controlled drug-delivery systems of opioid antagonists [6,7].

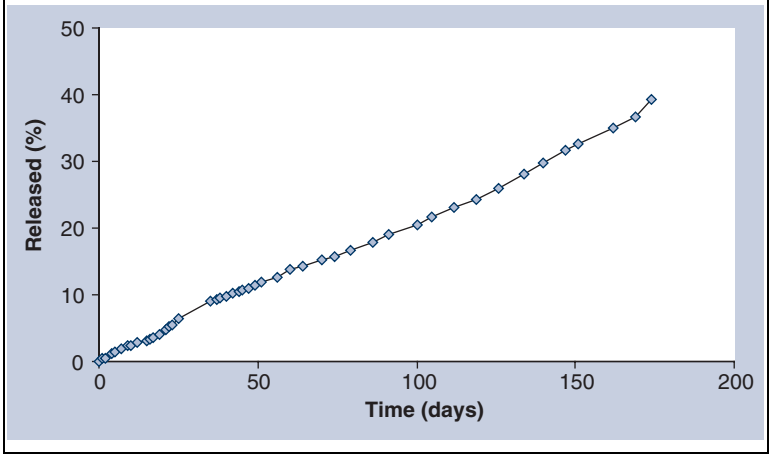
Many efforts have been made to develop novel systems to maximize patient compliance [8–12]. There have been different studies using biodegradable beads containing naltrexone as an opiate antagonist in animals [13–15]. Negishi and colleagues obtained 28 days of *in vitro* release of the antagonist by covalently coupling naltrexone to a biodegradable poly-(α-amino acid) backbone [16]. However, attention has been focused on the preparation of polymeric injectable microparticles or implants of naltrexone. Sharon and Wise prepared 1.5-mm diameter beads composed of naltrexone and polylactide-co-glycolide [17]. Microcapsules prepared from glutamic acid/ethyl glutamate copolymer-released naltrexone at a rate of 20 to 25 µm/h for 30 days [18]. Some effort has also focused on the preparation of morphine-triggered naltrexone delivery systems [8,19,20]. These studies have provided important data on the usefulness of implantation for naltrexone delivery.

Figure 1. The body and cap of L-polylactic acid device (A) before and (B) after being joined together.



Bhargave and colleagues studied the effects of naltrexone pellet implantation on narcotic tolerance and physical dependence in the rat [21]. However, studies on the application of naltrexone implantation for human use are not so convincing [22]. This is mainly due to the fact that, as mentioned before, for naltrexone treatment to be effective, sufficient blood levels must be maintained for at least 4 months. Therefore, a delivery device that is able to deliver the daily required dose of naltrexone for at least 4 months is needed. As the delivery devices proposed thus far have been designed to deliver naltrexone for only 30 days or less, more studies are needed to prepare a suitable naltrexone delivery system.

Figure 2. Naltrexone release of L-polylactic acid device with 15 mg device weight during a 180-day period.



Polyesters of lactic and glycolic acid are the most commonly used synthetic biodegradable materials for use as implantable or injectable biodegradable carriers for the controlled release of drugs. Their long clinical usage in surgical sutures underlines their biocompatibility in physiologic environments where they are hydrolyzed into metabolic products that are eliminated from the body [23,24]. Since biodegradable polymers are chemically unstable, in spite of their undeniable benefits, they are not generally used to prepare reservoir-type delivery systems [25]. In general, reservoirs have some advantages over the matrix type, including eliminating the burst release of drug molecules and providing a constant rate of release over a substantial portion of their lifetime. The possibility of higher loading levels of the active ingredient is another advantage of reservoir devices over matrix devices. This, in turn, yields an economy of materials, minimizing costs, and making the preparation of controlled-release systems of less potent substances feasible. This also provides for higher rates of release and therefore, a higher compound-loading level for a given device lifetime. In addition, filling a preformed reservoir with drug eliminates the exposure of drug molecules to heat organic solvents and shear stresses that cause inactivation of unstable molecules in matrix systems. Of these, the main advantage is the ability to release drug content at a constant rate. In such systems, where the polymer membrane serves as the barrier, drug release is controlled by Fickian diffusion of the drug through the membrane. As long as the drug concentration in the reservoir remains well above saturation and the membrane thickness is small relative to the other dimensions of the device, this relationship proposes that the drug release rate should be constant over time (zero order) as long as release is diffusion controlled.

In this study, high-molecular-weight poly-L-lactide was selected owing to its proven safety and lack of toxicity, its flexibility to be processed into a variety of physical dosage forms and its slow degradation rate (~24 months).

Reservoir-type cylindrical devices were prepared using a simple dip-casting technique and filled with naltrexone. Effect of the properties of device body, addition of hydrophilic polymer to the body and osmotic agent to the core on naltrexone release rate were also studied.

Figure 3. Polylactic acid device after 1 year incubation in dissolution medium.

Materials & methods

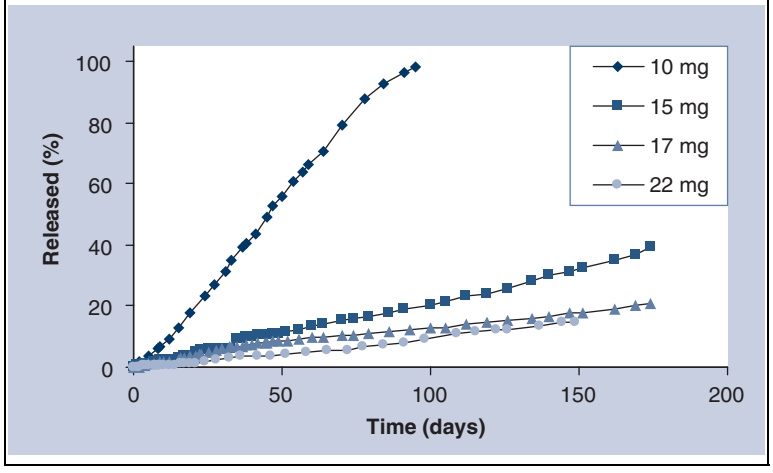
Materials

Poly-L-lactide Resomer L210 was purchased from Boehringer Ingelheim (Germany). Naltrexone was kindly donated by Francopia (France). PEG400, 1000 and 4000, NaCl, and methylene chloride were obtained from Merck (Germany). All other chemicals were of analytical grade and used as received.

Preparation of the cylindrical device

A dip-casting method was used for the preparation of cylindrical polymeric devices. A stainless steel rod (4 mm in diameter) was dipped into a solution of PLA in dichloromethane (DCM) for 2 sec. The rod was then air dried for 10 sec. The dipping and drying procedure was repeated several times to obtain the desired device weight. In order to find the optimum casting solution, different concentrations (1.5, 2 and 2.5% w/v) of PLA in DCM were examined. In some formulations, different amounts of PEG 400, 1000 or 4000 as hydrophilic agents were added to the polymeric solution. The device was then stored at room temperature for 24 h to dry.

Figure 4. Effect of device weight on naltrexone release from L-polylactic acid devices.



The reservoir devices were filled with 150 mg naltrexone or a mixture of naltrexone:NaCl (1:1 weight ratio). The cylinders were sealed with a cap, made by the same procedure used to make the body. Body and cap were joined together with small amounts of DCM.

In vitro *release studies*

The sealed cylinder was placed in a vial containing 25 ml of ethanol:phosphate buffer (10% v/v) medium. The vials were kept in a water bath shaker system at 37 ± 0.5°C. At various time intervals, 5 ml of the medium was removed for drug release measurement and 5 ml of fresh medium was added to the vials. To maintain the system at sink condition, the devices were transferred into fresh release medium once weekly. The amount of naltrexone released was determined spectrophotometrically at 28 nm.

Scanning electron microscopy

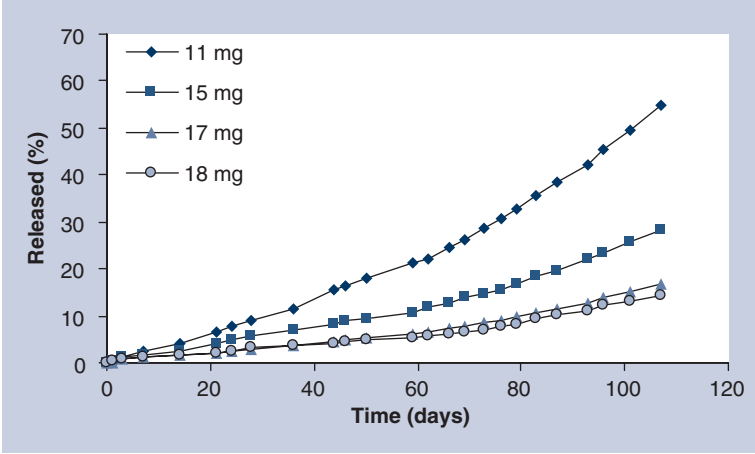
The membranes were mounted on metal stubs with double-sided adhesive tape, coated with gold for 4 mins and examined under a scanning electron microscope (SEM) (DSM 960A).

Results & discussion

Using the 2% w/v solution of poly-L-lactide in DCM provided a suitable concentration for the preparation of cylindrical devices. The polymeric membrane prepared using lower or higher concentrations of PLA in DCM, was either heterogeneous with high porosity or noneven surface. The length of the body of the polymeric devices prepared in this study was 27 mm. Their inner diameter was 4 mm. The length of the cap was 7 mm (Figure 1).

As the devices all had the same size (length and diameter), the net weight of the device was considered as representative of the membrane thickness. The membrane thickness of a polymeric device with the weight of 15 mg was 0.16 mm. Figure 2 shows the drug release from a polymeric device with weight of 15 mg. As can be seen, this device released its content during 150 days according to the zero order kinetics ($r^2 = 0.996$). The device completely kept its integrity even after 1 year incubation in dissolution medium (Figure 3). The high molecular weight of the PLA used in this study (680,000 Da) allowed the drug content of the reservoir to be released before biodegradation of the polymeric device was completed. The slow PLA degradation may be due to its low water permeability and its low density of end groups, which catalyze backbone degradation [26]. This result demonstrated the

Figure 5. Effect of device weight on naltrexone release from PLA:PEG4000 (10:1) devices.



suitability of this kind of PLA for preparation of slow release, implantable reservoir systems with a constant release rate for several months.

As all devices were of the same length, the empty polymeric device weight was considered representative of the membrane thickness. The effect of the device weight on the rate of naltrexone release from PLA devices is shown in Figure 4. As can be seen, the device with a weight of 2 mg had a very slow release rate and only about 10% of its drug content was released within 3 months. Release rate from devices weighing 17 mg was the same as those that weighed 22 mg. By decreasing the weight of the devices to 15 mg, the naltrexone release rate increased to 20% in the same duration of time. By decreasing the device weight to 10 mg, a remarkable increase in naltrexone release rate was observed. The same pattern was also observed for the devices made of PLA:PEG4000 (10:1) (Figure 5). This effect was to be expected since the thickness of reservoir interferes with the diffusion of naltrexone through the membrane due to increases in the diffusion path length and decreases in the porosity of the membrane [26,27].

The release rate of naltrexone from devices made only of PLA was very slow. The reduction of reservoir weight improved the release rate but there was a limitation on membrane thickness reduction. The mechanical strength of the devices

Figure 6. Effect of addition of different amounts of PEG4000 to the devices body on naltrexone release rate.

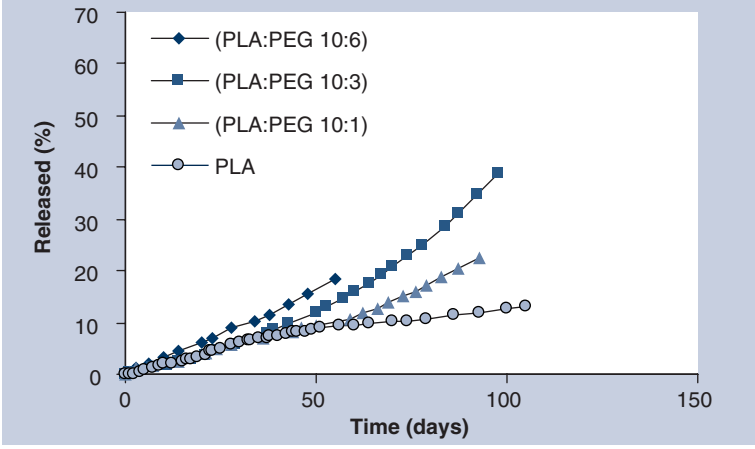
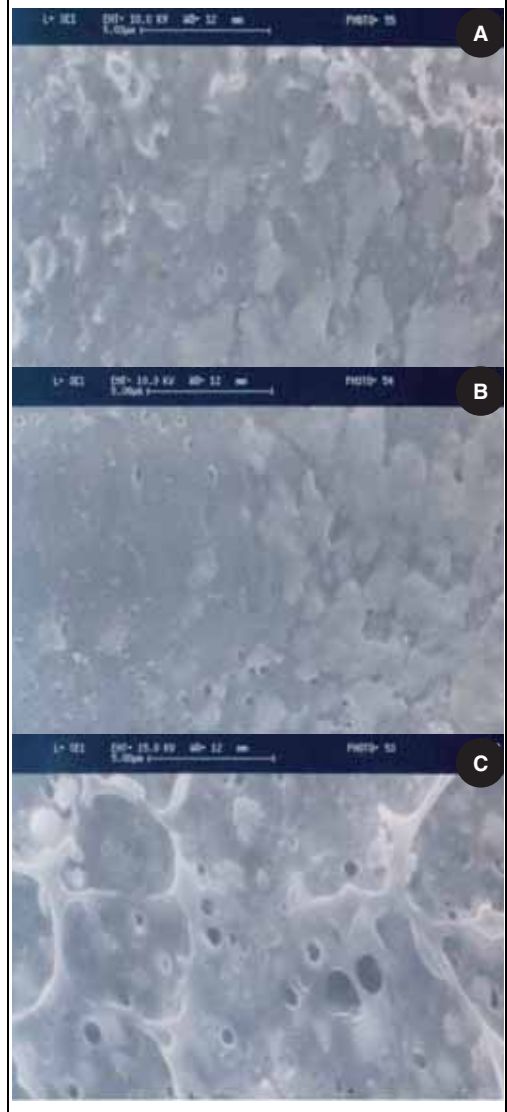
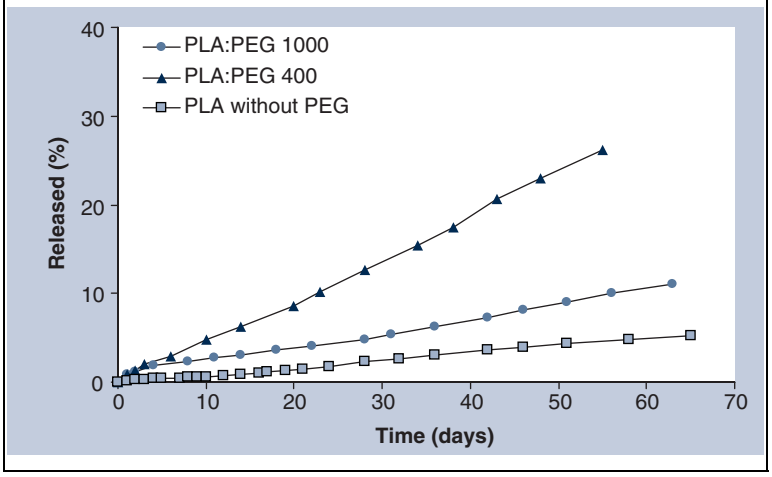


Figure 7. Scanning electron micrograph of PLA devices with different amounts of PEG4000 after 120 days dissolution.



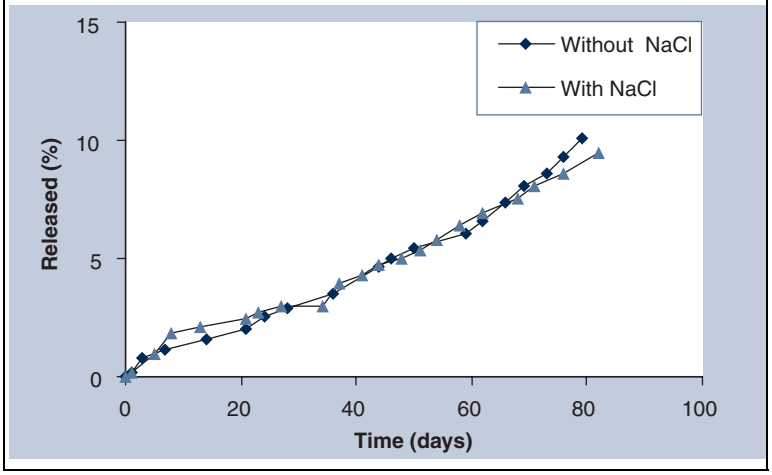
A: PLA; **B:** PLA:PEG (10:1) and **C:** PLA:PEG (10:5).

Figure 8. Effect of PEG molecular weight on naltrexone release rate from PLA:PEG (10:5) devices.



with a device weight less than 15 mg was too low. Therefore, attempts were made to increase the release rate by adding a hydrophilic polymer to the device structure instead of decreasing the device weight. PEG was selected as the hydrophilic polymer due to its safety and solubility in different solvents [28]. The rate of drug release from devices with 10 to 25% w/w PEG4000 was not increased during the first 30 days of the drug-release experiment (Figure 6). However, a faster rate of drug release from these devices was seen from day 30 of drug release. The release rate was proportional to the content of PEG in the polymeric device. Raising the PEG ratio up to 40% w/w accelerated the rate of drug release from the devices. This increase in the rate drug release from devices containing PEG4000 could be attributed to an increase in the hydrophilicity of the reservoir membrane and thus enhancement of water penetration and formation of aqueous channels within the membrane which lead to the faster diffusion of drug molecules [29].

Figure 9. Effect of addition of NaCl as an osmotic agent inside the reservoir on naltrexone release profile from PLA devices.



SEM pictures of devices composed of different ratios of PLA:PEG after 120 days soaking in dissolution medium (Figure 7). These images show that after dissolution, more pores and cavities were created by PEG solubilization in the devices made of PLA:PEG (10:5) compared with PLA alone or PLA:PEG (10:1). Also, mixing of PEG with PLA decreases the T_g of PLA, which is proportional with PEG content [30]. The effect of PEG molecular weight on naltrexone release rate forms devices with 15 mg device weight and PLA:PEG ratio of 10:5 (Figure 8). Over a period of 45 days, devices made of PLA:PEG4000 released 4% of their naltrexone content. This amount was 8 and 20% for the same ratio of PLA:PEG1000 and PLA:PEG400 devices, respectively. This increase with lower molecular weight PEG could be attributed to an easier leaching out of low-molecular weight PEG from device structure and thus, creation of more pores and channels within the membrane which in turn increases the drug release rate.

The effect of addition of NaCl as an osmotic agent inside the devices on release profile is shown in Figure 9. It was observed that the presence of NaCl did not affect the release rate of naltrexone. This result could be attributed to the high molecular weight of PLA which makes it more resistant to osmotic pressure [26].

Expert opinion

A simple dip-casting technique was used for the preparation of implantable reservoir-type drug-delivery systems containing naltrexone. By using a high-molecular weight PLA, the prepared reservoir devices released their drug content, primarily through a diffusion mechanism. The devices released their drug content in a 6-month period according to zero-order kinetics. Addition of PEG as a hydrophilic polymer increased the rate of naltrexone release from the devices. By choosing the appropriate amount of PEG of different molecular weights, the rate of drug delivery required to have a therapeutic effect can be determined.

Acknowledgements

This study was supported by National Research Council of Islamic Republic of Iran, Grant No. NRCI-5982. We are grateful to Francopia, France and Kich SA, Iran for the donation of naltrexone.

Highlights

- Naltrexone, currently administered orally, is one of the opioid antagonists used for the treatment of drug addicts.
- For naltrexone treatment to be effective, sufficient blood levels must be maintained for at least 4–8 months, which is the main drawback of an oral drug delivery system.
- In recent years, attention has been focused on the preparation of polymeric injectable microparticles or implants of naltrexone.
- In this study poly-(L-lactide) was used for the preparation of a reservoir-type cylindrical device using a simple dip-casting technique and filled with naltrexone.
- Effect of the properties of device body, addition of hydrophilic agents to the body and osmotic agents to the core on naltrexone release rate were studied.
- By using a high-molecular weight poly-L-lactic acid, the prepared reservoir devices released their drug content mainly through the mechanism of diffusion at a constant rate (zero order release kinetics) for at least 6 months.
- Addition of polyethylene glycol (PEG) as a hydrophilic polymer increased the rate of naltrexone release from the devices.
- By choosing the appropriate amount of PEG of different molecular weight, it was possible to determine the rate of drug delivery required to have a therapeutic effect.

Bibliography

1. No authors listed. *World drug report.* 1, United Nations publication, Austria (2004).
2. Kirchmayer U, Davoli M, Verster AD, Amato L, Ferri A, Perucci CA. A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence. *Addiction* 97(10), 1241–1249 (2002).
3. Bullingham RE, McQuay HJ, Moore RA. Clinical pharmacokinetics of narcotic agonist-antagonist drugs. *Clin. Pharmacokin.* 8, 332–343 (1983).
4. No authors listed. *PDR, Physicians' Desk Reference, 53rd Edn.* Medical Economics Company Inc., NJ, USA, 936–938 (1999).
5. Way WL, Fields HL, Way EL. Opioid analgesics and antagonists. In: *Basic and clinical pharmacology, 7th Edn.* Katzung BG (Ed.), Appleton and Lange, CT, USA 512–513 (1998).
6. Oslen JL, Kncl FA. A review of parentral sustained release naltrexone systems, In: *NIDA research monograph No. 28.* Willet RE, Barnett G. (Eds), DHHS publication, DC, USA 187–193 (1981).
7. Sharon AC, Wise DL. Development of drug delivery systems for use in treatment of narcotic addiction. In: *NIDA research monograph No. 28.* Willet RE, Barnett G (Eds), DHHS publication, DC, USA 194–213 (1981).
8. Roskos KV, Tefft JA, Fritzinger BK, Heller H. Development of a morphine-triggered naltrexone delivery system. *J. Control. Rel.* 19, 145–160 (1992).
9. Bodmier R, McGinity JW. The preparation and evaluation of drug-containing poly(DL-lactide) microspheres formed by the solvent evaporation method. *Pharm. Res.* 4, 465–471 (1987).
10. Maa YF, Heller J. Controlled release of naltrexone pamoate from linear poly(ortho esters). *J. Control. Rel.* 14, 21–28 (1990).
11. Misra AL, Pontani RB. An improved long-acting delivery system for narcotic antagonists. *J. Pharm. Pharmacol.* 30, 325–326 (1978).
12. Nitsch MJ, Banakar UV. Implantable drug delivery. *J. Biomat. App.* 8, 247–265 (1994).
13. Pechnick RN, Terman GW. The role of opiate receptors in the potentiation of pentobarbital sleeping time by the acute and chronic administration of opiates. *Neuropharmacology* 26, 1589–1593 (1987).
14. Bardo MT, Neisewander JL. Chronic naltrexone supersensitizes the reinforcing and locomotor-activating effects of morphine. *Pharmacol. Biochem. Behav.* 28, 267–273 (1987).
15. Yamaguchi K, Anderson JM. Biocompatibility studies of naltrexone sustained release formulations. *J. Control. Rel.* 19, 299–314 (1992).
16. Negishi N, Bennet DB, Cho C *et al*. Coupling of naltrexone to biodegradable poly-(α-amino acids). *Pharm. Res.* 4, 305–310 (1987).
17. Sharon AC, Wise DL. Development of drug delivery systems for use in treatment of narcotic addiction, In: *NIDA research monograph No. 28.* Willet RE, Barnett G (Eds), DHHS publication, DC, USA 194–213 (1981).
18. Sidman KR, Schwope AD, Steber WD, Rudolph SE. Use of synthetic polypeptides in the preparation of biodegradable delivery systems for narcotic antagonists. In: *NIDA Research Monograph No. 28.* Willet RE, Barnett G. (Eds), DHHS publication, DC, USA 214–231 (1981).
19. Tefft JA, Roskos KV, Heller J. The effect of lipase on the release of naltrexone from triglyceride-coated cellulose acetate phthalate microspheres. *J. Biomed. Mat. Res.* 26, 713–724 (1992).
20. Nakayama GR, Roskos KV, Fritzinger BK, Heller J. A study of reversibly inactivated lipases for use in a morphine-triggered naltrexone delivery system. *J. Biomed. Mat. Res.* 29, 1389–1396 (1995).
21. Bhargave HN, Matwyshyn GA, Gerk PM *et al*. Effects of naltrexone pellet implantation on morphine tolerance and physical dependence in rat. *Gen. Pharm.* 25, 149–155 (1994).
22. Chiang CN, Hollister LE, Gillespie HK, Foltz RL. Clinical evaluation of a naltrexone sustained release preparation. *Drug Alcohol Depend.* 16, 1–8 (1985).
23. Rothen-Weinhold A, Besseghir K, Gurny, R. Analysis of the influence of polymer characteristics and core loading on the in vivo release of a somatostatin analogue. *Eur. J. Pharm. Sci.* 5, 303–313 (1997).
24. Mehta RC, Jeyanthi R, Calls S, Thanoo BC, Burton KW, DeLuca PP. Biodegradable microspheres as depot system for patenteral delivery of peptide drugs. *J. Control. Rel.* 29, 375–384 (1994).
25. Markland P, Yang VC. Biodegradable polymers as drug carriers. In: *Encyclopedia of Pharmaceutical Technology*. Swarbrick J, Boylan JC (Eds), Vol. 2, Marcel Dekker Inc., NY, USA, 141–142 (2002).
26. Lemmouchi Y, Schacht E, Lootens C. *In vitro* release of trypanocidal drugs from biodegradable implants based on poly(ε-caprolactone) and poly(D,L-lactide). *J. Control. Rel.* 55(1), 79–85 (1998).

27. Marcotte N, Polk A, Goosen MF. Kinetics of protein diffusion from a poly(D,L-lactide) reservoir system. *J. Pharm. Sci*. 79(5), 407–410 (1990).
28. Jiang W, Schwendeman SP. Stabilization and controlled Release of Bovine Serum Albumin Encapsulated in Poly(D,L-lactide) and Poly(ethylene glycol) microsphere blends. *Pharm. Res.* 18(6), 878–885 (2001).
29. Kang F, Singh J. Effect of Additives on the Release of a Model Protein From PLGA Microspheres. *AAPS PharmSciTech.* 2(4), 30 (2001).
30. Martin O, Averous L. Poly(lactic acid): plasticization and properties of biodegradable multiphase systems. *Polymer* 42, 6209–6219 (2001).

Affiliations

Rassoul Dinarvand
Tehran University of Medical Sciences, Department of Pharmaceutics, Faculty of Pharmacy, Tehran PO Box 14155–6451, Iran
Tel.: + 98 216 912 686
Fax: +98 216 959 055
dinarvand@tums.ac.ir

Shadi H Moghadam
Tehran University of Medical Sciences, Department of Pharmaceutics, Faculty of Pharmacy, Tehran PO Box 14155–6451, Iran

Pantea Sayar
Tehran University of Medical Sciences, Department of Pharmaceutics, Faculty of Pharmacy, Tehran PO Box 14155–6451, Iran

Mahsa Alaee
Tehran University of Medical Sciences, Department of Pharmaceutics, Faculty of Pharmacy, Tehran PO Box 14155–6451, Iran

Fatemeh Atyabi
Tehran University of Medical Sciences, Department of Pharmaceutics, Faculty of Pharmacy, Tehran PO Box 14155–6451, Iran