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.

KEYWORDS: microspheres, matrix devices, naltrexone, poly(L-lactide), solvent evaporation

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. Naltrexone provides no euphoric effects, and there are no observable pharmacological consequences when a patient discontinues the drug. 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. Detoxified patients are advised to continue the naltrexone therapy for 4 to 8 months. 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. Many efforts have been made to develop novel systems to maximize patient compliance. 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. Martin et al used naltrexone-zinc tannate complex, a sparingly soluble form, to increase the duration of the antagonistic effect. Negishi et al 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 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. Some effort has also focused on the preparation of morphine-triggered naltrexone delivery systems. These studies have provided important data on the usefulness of implantation for naltrexone delivery. Bhargave et al 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. 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 (Tₙ) 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, Kelheim, 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 Tₙ 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