AAPS PharmSciTech (© 2012)
DOI: 10.1208/s12249-012-9781-8

Research Article

Preparation and Investigation of Sustained Drug Delivery Systems Using an Injectable, Thermosensitive, *In Situ* Forming Hydrogel Composed of PLGA–PEG–PLGA

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Received 8 November 2011; accepted 28 March 2012

Abstract. *In situ* gelling systems are very attractive for pharmaceutical applications due to their biodegradability and simple manufacturing processes. The synthesis and characterization of thermosensitive poly(D,L-lactic-co-glycolic acid) (PLGA)–polyethylene glycol (PEG)–PLGA triblock copolymers as *in situ* gelling matrices were investigated in this study as a drug delivery system. Ring-opening polymerization using microwave irradiation was utilized as a novel technique, and the results were compared with those using a conventional method of polymerization. The phase transition temperature and the critical micelle concentration (CMC) of the copolymer solutions were determined by differential scanning calorimetry and spectrophotometry, respectively. The size of the micelles was determined with a light scattering method. *In vitro* drug release studies were carried out using naltrexone hydrochloride and vitamin B12 as model drugs. The rate and yield of the copolymerization process *via* microwave irradiation were higher than those of the conventional method. The copolymer structure and concentration played critical roles in controlling the sol–gel transition temperature, the CMC, and the size of the nanomicelles in the copolymer solutions. The rate of drug release could be modulated by the molecular weight of the drugs, the concentration of the copolymers, and their structures in the formulations. The amount of release *versus* time followed zero-order release kinetics for vitamin B12 over 25 days, in contrast to the Higuchi modeling for naltrexone hydrochloride over a period of 17 days. In conclusion, PLGA–PEG1500–PLGA with a lactide-to-glycolide ratio of 5:1 is an ideal system for the long-acting, controlled release of naltrexone hydrochloride and vitamin B12.

KEY WORDS: hydrogel; naltrexone; PLGA–PEG–PLGA; thermosensitive; triblock copolymer; vitamin B12.

INTRODUCTION

Naltrexone hydrochloride is a specific opioid antagonist that is used to maintain abstinence after withdrawal in detoxified opioid-dependent patients (1–3). Naltrexone was the first drug to receive FDA approval to treat alcohol dependence (4–7). Because of the extensive first-pass metabolism in the liver, only 5–20 % of the oral dosage of this drug reaches the systemic circulation unchanged (4,8). In addition, there are certain side effects associated with its oral administration, such as abdominal pain, nausea, and vomiting (9). The major problem with naltrexone usage is the motivation and poor compliance of addicted patients (10–12). Therefore, developing a controlled-release parenteral formulation of which a single injection may release the drug over a week, month, or even longer is especially desirable. Early trials have suggested that the sustained release of naltrexone may be appropriate for the management of either alcohol or opioid dependence (5,13,14). There are several systems for the subcutaneous implantation of naltrexone hydrochloride (9,15–17), but this route of administration requires intricate technology, and it is too expensive (8).

In the past few years, a number of smart hydrogels have been reported for various biomedical applications, including drug delivery (18–21), gene delivery (22–24), cell encapsulation (25,26), and tissue engineering (27). Injectable *in situ* forming gels are one type of stimuli-sensitive polymers. These gels are fluid at room temperature, but in the body, they quickly convert to a very high viscous gel (28). Injectable gel-forming matrices have several advantages over other implantable systems that convert into the final form before

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Published online: 18 April 2012