JOURNAL OF MATERIALS PROCESSING TECHNOLOGY 209 (2009) 348–354

journal homepage: www.elsevier.com/locate/jmatprotec

Drug distribution within poly(ε-caprolactone) microspheres and in vitro release

Xudong Wang, Yingjun Wang, Kun Wei, Naru Zhao, Shuhua Zhang, Jingdi Chen*

Biomaterials Research Department of Materials Science and Engineering, South China University of Technology, The Key Laboratory of Specially Function Materials and Advanced Manufacturing Technology, Ministry of Education, Guangzhou 510640, China

ARTICLE INFO

Article history:
Received 11 December 2006
Received in revised form
18 January 2008
Accepted 2 February 2008

Keywords:
Microspheres
Drug distribution
Poly(ε-caprolactone)
In vitro release
Model drug

ABSTRACT

Poly(ε-caprolactone) (PCL) microspheres loaded two model compounds (*p*-nitroaniline and rhodamine B) with different water solubilities were prepared by an s/o/w single emulsion solvent evaporation method. The microspheres morphology was investigated by scanning electron microscopy, drug loading and encapsulation efficiency were calculated. Drug distribution within microsphere matrix was studied by confocal laser scanning microscopy. *p*-Nitroaniline, as a more hydrophobic compound, distributed more evenly in the matrix, while the more hydrophilic compound rhodamine distributed close to the surfaces of microspheres. The in vitro release profiles therefore were different. This study helps to further understand the drug release mechanism from microsphere matrix, and design effective long-term drug delivery system.

1. Introduction

Biodegradable polymer microspheres are widely studied because of their nontoxic property and biodegradability. Among these polymers, poly(lactic acid), poly(glycolic acid), especially their copolymer—poly(lactic-co-glycolic acid) (PLGA) have been investigated extensively as drug delivery system (Chandy et al., 2002; Shi et al., 2003; Fu et al., 2005), But their acidic degradation products and possibility of initiating inflammatory limit their developments.

Poly(ε-caprolactone) (PCL), as one of the most popular synthetic polymers, has been researched as biodegradable carrier for controlled drug release (Dhanaraju et al., 2006; Lim et al., 1998; Barbato et al., 2001). PCL is suitable for controlled drug release because of its high permeability to many drugs and biocompatibility in physiological environments (Murthy, 1997). Preparation methods of microspheres were primarily determined by the solubility of the drug and the polymer in various solvent systems, such as: single emulsion solvent evaporation (Perez et al., 2000), double emulsion solvent evaporation (Dhanaraju et al., 2006; Cleek et al., 1997) or spray drying technique (Chu et al., 2006) and so on. Among these techniques, s/o/w emulsion solvent evaporation method is a convenient and effective technique to incorporate water-soluble or water-insoluble drugs into polymer microspheres (Shi et al., 2003; Xue and Shi, 2004).

Degradation of PCL is very slow comparing many other polymers (Pitt, 1990). Mechanism of drug release from PCL microspheres is often dominated by drug diffusion from microsphere matrix, which makes PCL microspheres suitable for long-term drug release system (Sinha et al., 2004). Drug distribution within polymer microspheres has very important influence on drug diffusion rate from polymer matrix. Drug molecules close to the surface of microspheres are prone to

* *Corresponding author*. Tel.: +86 20 87114645; fax: +86 20 85261559.
E-mail address: adongwx@163.com (X. Wang).
0924-0136/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jmatprotec.2008.02.004

diffuse from matrix faster. Drug distribution depends on the "compatibility" between drugs and polymers (Shi et al., 2003; Berkland et al., 2004; Pack and Pollauf, 2006). In this paper, we choose two model compounds, *p*-nitroaniline and rhodamine B, with varying water solubility to investigate the influences of drug contribution on drug release mechanism. These studies provide references to design long-term and sustained release drug delivery system.

2. Materials and methods

2.1. Materials

PCL (MW 10,000) was purchased from Sigma–Aldrich. *p*-Nitroaniline and rhodamine B was purchase from Sigma. All other chemicals used were of analytical grade.

2.2. Preparation of microspheres

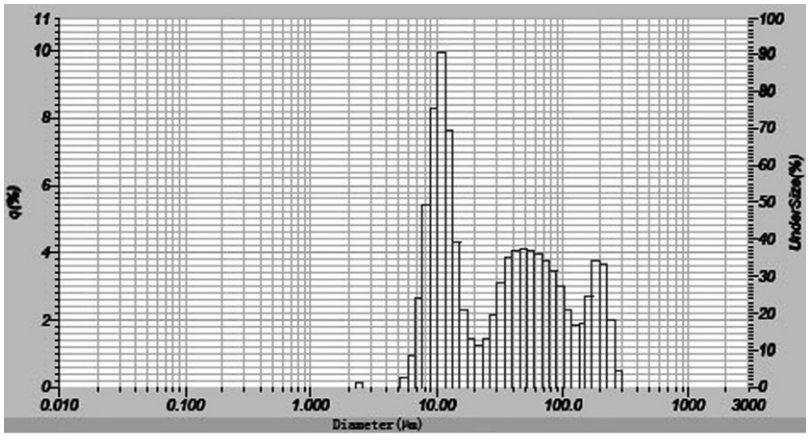
PCL microspheres were fabricated using a modified s/o/w single emulsion solvent evaporation method (Xue and Shi, 2004). Briefly, 10 ml of solutions of 20% w/v PCL in DCM containing various amounts of *p*-nitroaniline or rhodamine B were mixed with the aid of ball-milling. The mixtures were then pour into 300 ml of 0.2% w/v methylcellulose and stirred vigorously. After completion of solvent evaporation, the microspheres were hardened, filtered, washed and lyophilized for a minimum of 24 h. The products were kept at 4 °C before further analysis.

2.3. Microspheres size and surface morphology

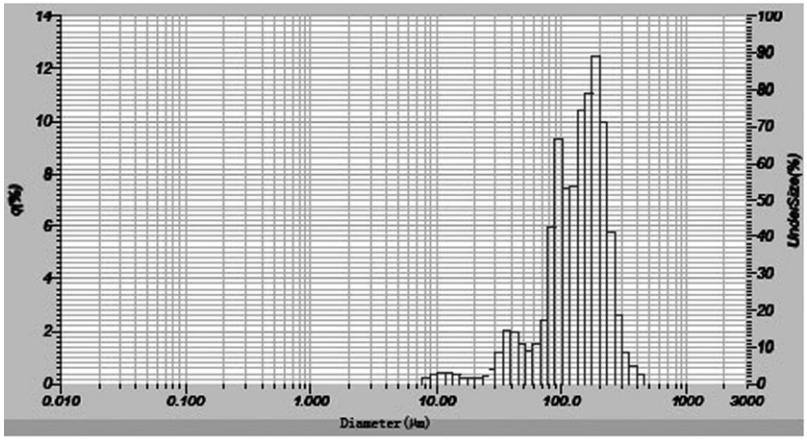
The average size and size distribution data were determined by laser scattering particle size distribution analyzer (LA-950, Hortiba). Microsphere surface morphology was observed by scanning electron microscopy. Several drug microspheres were sprinkled onto one side of the double-side adhesive stub. The stub was then sputter coated with conductive gold prior to imaging.

2.4. Drug content of microspheres

Drug content and encapsulation efficiency of microspheres were determined using a UV-visible spectrophotometer (UV755B, Cany). To this, 5 mg of microsphere samples were dissolved in 1 ml of methylene chloride, and then *p*-nitroaniline or rhodamine B content was determined using a UV-spectroscopy method at the wavelength of 358 nm or 550 nm, respectively. The drug encapsulation efficiency was



P-nitroaniline-loaded microspheres(8.20%)



P-nitroaniline-loaded microspheres(8.20%)

Fig. 1 – Size distribution of *p*-nitroaniline-loaded and rhodamine-loaded microspheres.