Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 329 (2007) 53–61
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Evaluation of ibuprofen-loaded microspheres prepared from novel copolyesters

C.J. Thompson [a], D. Hansford [a], S. Higgins [b], C. Rostron [b], G.A. Hutcheon [b], D.L. Munday [a,*]

[a] *School of Pharmacy, The Robert Gordon University, Aberdeen AB10 1FR, United Kingdom*
[b] *School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool L3 3AF, United Kingdom*

Received 15 June 2006; received in revised form 9 August 2006; accepted 15 August 2006
Available online 22 August 2006

Abstract

The utility of two novel linear random copolyesters to encapsulate and control the release of ibuprofen, via microspheres, was investigated. Various manufacturing parameters, including temperature, disperse phase volume and polymer:ibuprofen ratios were altered during the microsphere production. The effects of these changes on the morphological characteristics of the microspheres, yield, drug loading, encapsulation efficiency and drug release rates were examined. The diameter of the microspheres ranged from 36 to 89 μm and showed both smooth and ridged surfaces. Microsphere diameter was probably determined by the internal phase volume, while surface morphology was controlled by manufacturing temperature. Greater encapsulation efficiency was obtained by increasing the polymer:ibuprofen ratio and by reducing the internal phase volume. For all batches there was an initial burst drug release into phosphate buffer (pH 7.4) over the first 2–4 h, which was followed by a much slower release rate over the remaining time period. Drug release rates during both these phases were dependent upon the amount and nature of the polymer in the microspheres, noting that the more hydrophilic polymer provided faster release rates. Ibuprofen solubility appeared to play a dominant role in controlling release, although both encapsulation efficiency and microsphere morphology were also contributing factors.

Keywords: Polyesters; Microspheres; Emulsion solvent evaporation; Manufacturing parameters

1. Introduction

The process of microencapsulation has been used to produce microspheres containing both hydrophilic drugs, such as propranolol hydrochloride (Hombreiro-Pérez et al., 2003), 5-fluorouracil (Lin and Vasavada, 2000) and cephradin (Ustariz-Peyret et al., 2000) and hydrophobic drugs, such as nifedipine (Guyot and Fawaz, 1998; Hombreiro-Pérez et al., 2003), beclomethasone (El-Baseir and Kellaway, 1998) and ibuprofen (Bodmeier and Chen, 1989) entrapped within biodegradable polymers. The purpose of producing microspheres is to obtain controlled release of the drug and thus maintain therapeutic drug levels over a specified time period (Benoit and Puisieux, 1986; Prescott, 1989; Flandroy et al., 1993; Leroux et al., 1996; Mathiowitz et al., 1999). Short half-lives and poor bioavailability of certain drugs can be overcome by implanting the microspheres within the target tissue area thus minimising absorption into the systemic circulation (Benoit and Puisieux, 1986; Prescott, 1989; Flandroy et al., 1993; Leroux et al., 1996; Mathiowitz et al., 1999). Reduced drug plasma levels could minimise the incidence and severity of adverse side effects (Prescott, 1989; Mathiowitz et al., 1999).

Microspheres may be produced by several methods utilising emulsion systems (oil-in-water, oil-in-oil, water-in-oil-in-water), as well as by spray drying (Bakan, 1986; Watts et al., 1990; Giunchedi and Conte, 1995; Mathiowitz et al., 1999). The most common emulsion system used is oil-in-water (o/w), with the microspheres being produced by the emulsion solvent evaporation (ESE) method. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs (Conti et al., 1992; Flandroy et al., 1993; Whateley, 1993). The main disadvantage of this method is its limited ability to encapsulate hydrophilic drugs (Watts et al., 1990; Conti et al., 1992; Whateley, 1993; Mathiowitz et al., 1999; Jain, 2000) as partition-

* Corresponding author. Tel.: +44 1224 262511; fax: +44 1224 262555.
E-mail address: d.munday@rgu.ac.uk (D.L. Munday).

0378-5173/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2006.08.019

ing into the aqueous phase of the emulsion readily occurs. The effect is to reduce the drug loading compared with hydrophobic drugs (Watts et al., 1990; Conti et al., 1992; Whateley, 1993; Mathiowitz et al., 1999; Jain, 2000). A further effect of partitioning is the accumulation of drug crystals on the surface of microspheres which produces burst release of the drug on administration (Jain, 2000). The degree of burst release will generally depend upon the nature of the polymer, the polymer:drug ratio (Bodmeier and Chen, 1989; El-Baseir and Kellaway, 1998; Guyot and Fawaz, 1998; Hombreiro-Pérez et al., 2003; Karasulu et al., 2003) and the relatively affinities of the drug for the polymer and the aqueous phase (Tice and Cowsar, 1984).

The aliphatic semi-crystalline polyester, poly-ε-caprolactone (PCL), has been used in the field of controlled drug release. When used alone PCL produces controlled release over extended periods of up to 1 year (Sinha et al., 2004). However, due to its hydrophobic and semi-crystalline nature, the degradation of PCL is much slower than the established polymers based on poly(lactic acid) (PLA) derivatives. Both PCL and the PLA polymers tend to produce drug-loaded microspheres with an initial burst drug release. PLA derivatives also have the limitation that their properties cannot be varied beyond copolymer composition and molecular weight, and they have no chemical functionality which can be modified post-polymerisation, to enhance drug incorporation and release.

The two novel polyesters, used in this study, were enzymatically prepared from equimolar quantities of three monomers: ω-pentadecalactone, divinyl adipate and either propane-1,3-diol or glycerol (Namekawa et al., 2000). Due to the specificity of the chosen hydrolytic enzyme a linear random copolyester was prepared which has a chemical composition similar to PCL, but this time has a greater degree of disorder. The polyester prepared using glycerol, as one of its monomers, allows for a slight increase in the hydrophilicity of the polymer, as well as providing a functional group for possible covalent bonding or hydrogen bonding of the drug molecules (Thompson et al., 2006).

The objective of this work was to produce microspheres by the emulsion solvent evaporation (ESE) method using these novel polymers and incorporate ibuprofen, as a model hydrophobic drug. Ibuprofen was selected because of its capability to undergo conjugation to polymer SH-L510. The conjugated material will be the focus of future work and therefore allowing comparison of drug release between conjugated and non-conjugated batches. The morphological characteristics and the in vitro drug release rates from these microspheres were thus examined.

2. Materials and methods

2.1. Materials

The two polyesters were prepared in our laboratories (Liverpool John Moores University, UK), and their synthesis and analysis was detailed in our earlier work (Thompson et al., 2006). Specifically, the polymer prepared from: ω-pentadecalactone, divinyl adipate and propane-1,3-diol (code name SH-L509) had a $M_w = 15.7$ kDa, whereas the polymer prepared from: ω-pentadecalactone, divinyl adipate and glycerol (code name SH-L510) had a $M_w = 12.2$ kDa. These polymers were similar to those previously used to produce drug-free microspheres (Thompson et al., 2006). Ibuprofen, polyvinyl alcohol (PVA) (average molecular weight 30,000–70,000), sodium phosphate, sodium acid phosphate, sodium chloride and polysorbate 20 were purchased from Sigma–Aldrich Co. Ltd., UK. Dichloromethane (DCM) and chloroform (C), both of analytical grade, were obtained from Fisher Chemicals (Fisher Scientific UK Ltd., England).

Table 1
Manufacturing parameters used in production of microspheres

Batch	Temperature (°C)	DCM volume (mL)
1	24	2.5
2	24	1.5
3	37	2.5

2.2. Microsphere production

Ibuprofen-loaded microspheres were produced in triplicate at polymer:ibuprofen ratios of 4:1, 6:1 and 10:1 using both polymers. Briefly, the method involved co-dissolving 150 mg of polymer and selected weights of ibuprofen in DCM. The solution was dispersed in an aqueous phase consisting of 80 mL of a 0.2% (w/v) solution of PVA. The resulting emulsion was stirred for 30 min at 1000 ± 10 rpm on a magnetic stirrer at different temperatures. The manufacturing parameters used are shown in Table 1. Microspheres were then collected by filtration and dried at room temperature under vacuum until required for use.

2.3. Yield, drug loading and encapsulation efficiency

Dried microspheres were accurately weighed and the yield calculated as a percentage using Eq. (1):

$$\text{Yield} = \left(\frac{\text{weight of microspheres}}{\text{weight of polymer} + \text{weight of ibuprofen}}\right) \times 100 \quad (1)$$

A microsphere sample (10 mg) was dissolved in 10 mL of chloroform. The UV absorbance of the solution was measured using a Biomate 5 UV spectrophotometer (Thermo Spectronic, England) at 273 nm. Drug loading and encapsulation efficiency were determined in duplicate for all batches using Eqs. (2) and (3), respectively. Values were expressed as percentage:

$$\text{Drug loading} = \left(\frac{\text{weight of ibuprofen in microspheres}}{\text{microspheres sample weight}}\right) \times 100 \quad (2)$$

$$\text{Encapsulation efficiency} = \left(\frac{\text{actual weight of ibuprofen in sample}}{\text{theoretical weight of ibuprofen}}\right) \times 100 \quad (3)$$