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Synthesis of lidocaine-loaded PLGA microparticles by flow focusing Effects on drug loading and release properties

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ABSTRACT

In the present work, two methods for the preparation of lidocaine-loaded PLGA microparticles are compared. The differences between the polymeric particles obtained by solvent evaporation (SEVM) or flow focusing (FF) were studied by means of scanning electron microscopy and surface thermodynamics determinations. A detailed investigation of the capabilities of the polymer particles to load this drug is described. The physical state of the drug in the polymeric particles and the existence of interactions between both entities were studied by differential scanning calorimetry. The main factors determining the lidocaine incorporation and the release kinetics were the synthesis procedure followed, the amount of drug dissolved in the organic phase during the synthesis routine, the type of polymer (molecular weight and end chemical groups) and the size and the hydrophobic/hydrophilic properties of the particles. The FF technology allowed higher drug incorporations and slower release kinetics. The release studies showed a biphasic profile probably due to diffusion-cum-degradation mediated processes.

1. Introduction

Local anaesthetics are widely used in the treatment of both acute and chronic pain, but their usefulness is limited by the short duration of the local anaesthetic effect that generally lasts for only few hours (Nurkeeva et al., 2002). Lidocaine is a local anaesthetic type amide, that can be considered as a model molecule for hydrophobic drug encapsulation because of its small molecular weight and low water solubility (Görner et al., 1999). Lidocaine has a faster onset of action and a higher length of action than amino ester anaesthetics. However, its therapeutic potential is restricted by its short plasma half-life (1.5–2 h). In order to increase the therapeutic index of this molecule in the treatment of pain, with respect to its effectiveness and safety, biodegradable microspheres have been used as drug delivery systems to achieve a localized and sustained drug release. This will reduce the dose needed to obtain a pharmacological effect and, therefore, the incidence of systemic effects (Chen et al., 2004). Moreover, a long-term drug delivery system will be an ideal candidate to improve drug adherence and to ensure continued optimum drug dosage levels that maximize the benefits of therapy.

Microencapsulation is a very common method for elaborating delivery systems for drugs and vaccines (Freitas et al., 2005). Microspheres can be prepared using different strategies, although most of them are modifications of three basic techniques: solvent extraction/evaporation, phase separation (coacervation) and spray-drying (Aftabrouchad and Doelker, 1992). However, traditional drug microencapsulation methods do not provide particles with the desired drug loading, and, moreover, a complementary treatment (filtration or sieve systems) is also needed to obtain particles with a monodisperse size distribution. Therefore, an easy methodology is needed for the preparation of particles with a suitable drug loading, a homogeneous shape and a narrow size distribution in the nanometer or micrometer range (Martín-Banderas et al., 2005).

Poly(lactic-co-glycolic) acid block copolymers (PLGA) are polyesters commonly used for the microencapsulation of therapeutics and antigens. Their use as drug delivery systems is due to their excellent biocompatibility and biodegradability properties. Moreover, PLGA-based microparticles offers many advantages in comparison to other materials used as drug carriers (Kumar et al., 2001). Several methods can be followed in the preparation of PLGA microparticles; however, the success of the technique is determined by many factors related to the drug (solubility, partition

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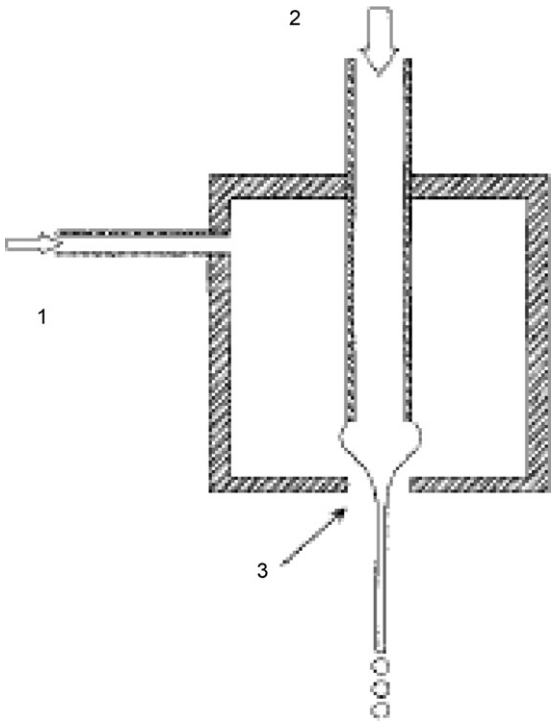

Fig. 1. Flow focusing atomizer: focusing fluid (1), focused fluid (2), and meniscus (3).

coefficient, etc.) and the polymer (composition, molecular weight, end chemical groups, etc.) (Fu et al., 2005).

The flow focusing (FF) technique (Gañán-Calvo, 1998) can efficiently control the production of monodisperse simple or encapsulated particles, in the micron or sub-micron range, in just one step and without additional purification procedures. The FF technology is based on a useful microfluidic concept resulting from the combination of hydrodynamic forces with a specific geometry. Briefly, a FF device (Fig. 1) consists of a pressurized chamber with a continuous focusing fluid (gas or liquid) provision. Inside, a hydrodynamic "funnel shaped lens" is created when the flowing focusing fluid undergoes a pressure drop across an orifice. By feeding an immiscible liquid flow into this hydrodynamic funnel made by the focusing fluid, a steady thin jet of immiscible liquid is created in the core of the co-flowing focusing stream, giving rise to a micro- or nanojet that leaves the chamber through the orifice together with the focusing fluid. The jet diameter is much smaller than the diameter of the exit orifice, thus precluding any contact. Capillary instability breaks up the stationary jet into droplets of homogeneous size.

This versatile technique allows the control of the size, the surface characteristics and the internal structure of the elaborated systems (Martín-Banderas et al., 2005), and presents several advantages in comparison to other traditional encapsulation technologies: (i) compatibility with different fluid mixtures (liquid–liquid, liquid–gas) using simple liquids, polymeric solutions, emulsions, suspensions or melted solids. (ii) Production, without external excitation sources and additional purification steps, of smaller particles with narrow size distribution, in just one step. (iii) Suitability for the encapsulation of labile compounds (proteins, cells, etc.), as because of the special flow geometry, the particle generating fluid is subjected to low stresses, this making the FF technique most adequate for the encapsulation of labile compounds (proteins, cells, and similar entities). (iv) Control of the particle design, involving freely chosen morphology, surface treatment, and composition (e.g., homogeneous particles, two-phase capsules, or hollow capsules). (v) High performance and applicability to industry large-scale production (Martín-Banderas et al., 2005).

In this work we describe the preparation of lidocaine-loaded PLGA microparticles with long-lasting effects, using two techniques, the FF technology and a traditional method based on solvent evaporation (SEVM). A comparative study is carried out to check the influence of both techniques on the: (i) size and morphology, and surface thermodynamics of the polymers; (ii) physical state of the drug in the PLGA particles; and (iii) drug loading and release kinetics of the particles. The release studies are performed with the aim of evaluating the dissolution behavior of these systems in the administration site. In the present paper, a parenteral route is intended for the local administration of these systems, and hence a physiological pH condition has been reproduced.

2. Materials and methods

2.1. Materials

Lidocaine, a model drug for hydrophobic encapsulation, was purchased from Sigma–Aldrich (Germany). Poly(lactic-co-glycolic) acid block copolymers (PLGA 50:50) Resomer® RG 502 (Mw: 12,000; inherent viscosity: 0.24 dl/g), Resomer® RG 502H (Mw: 12,000; inherent viscosity: 0.19 dl/g), Resomer® RG 504 (Mw: 48,000; inherent viscosity: 0.5 dl/g) and Resomer® RG 504H (Mw: 48,000; inherent viscosity: 0.53 dl/g) were obtained from Boehringer Ingelheim (Germany). All other chemicals used were of analytical quality from Panreac (Spain), except from formamide (Aldrich, USA) and polyvinyl alcohol [PVA, Mw: 16,000; Fluka (Germany)]. Water used in the experiments was deionized and filtered (Milli-Q Academic, Millipore, France).

2.2. Methods

2.2.1. Preparation of the lidocaine-loaded PLGA microparticles

The preparation of the microparticles by means of the solvent evaporation method involves the following procedure: 250 mg of PLGA was dissolved at room temperature in 10 ml of ethyl acetate. In the resulting solution, different amounts of lidocaine (6.25–50 mg) were dissolved. This organic phase was added to a 0.3% (w/v) PVA solution and homogenized at 8000 rpm during 8 min (Heidolph DIAX 900, Germany). The obtained emulsion was stirred at 300 rpm for at least 12 h with a magnetic stirrer hotplate SM6 (Jepson Bolton, UK), under room conditions, in order to evaporate the organic solvent. The obtained PLGA particles were collected by centrifugation at 3000 rpm during 25 min (Orto Alresa, mod. Digicen, Spain) and washed twice with 5 ml of water in order to remove the weakly adsorbed (or simply mechanically adhered) lidocaine. Finally, microparticles were frozen in liquid nitrogen and lyophilized (Telstar Cryodos, Spain).

The synthesis of the PLGA particles by means of the flow focusing technology involves the dissolution of lidocaine (6.25–50 mg) in a solution containing 250 mg of PLGA in 10 ml of ethyl acetate. The resulting solution was sprayed, using a standard FF nozzle fixed at 5 ml/h and 100 mbar, inside a chamber with an inlet temperature of $60 \pm 10\,^{\circ}C$. The formed particles were collected at the bottom of the chamber as a dry powder on a plate, freeze–dried and stored at $4\,^{\circ}C$.

The formulations used in the synthesis of the PLGA particles by both methods are collected in Table 1. Lidocaine-loaded PLGA copolymers (Resomer® RG 504 and Resomer® RG 504H) obtained by the FF method were discarded because of their high viscosity, useless for our drug delivery purposes. All the formulations were prepared in triplicate.