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Preparation of microspheres containing low solubility drug compound by electrohydrodynamic spraying

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ABSTRACT

Micro- and nanoparticle formulations are widely used to improve the bioavailability of low solubility drugs. In this study, electrospraying is introduced as a method for producing drug-loaded microspheres at ambient conditions. PLGA microspheres containing celecoxib, a low solubility drug, were prepared with the objective of producing near-monodisperse microspheres with the drug in a stable amorphous form. We found that it is possible to produce near-monodisperse celecoxib-loaded PLGA microspheres at different polymer:drug ratios. The microspheres produced were in the size range 1–5 μm depending on the polymer:drug ratio and had smooth surfaces. Thermal analysis further indicates that celecoxib is present in an amorphous form inside the microspheres. Drug dissolution studies showed an initial burst release followed by a period of sustained release with the dissolution curve depending on the polymer:drug ratio. Electrospraying is thus a promising method for producing amorphous microspheres of low solubility drugs such as celecoxib. The microsphere properties may be further optimized to achieve an appropriate dissolution profile with the aim of increasing oral bioavailability of low solubility drugs.
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1. Introduction

Low solubility drugs account for an estimated 40% of all new drugs developed and present a universal challenge for the drug development industry (Lipinski, 2002). A general problem with low solubility drugs is their insufficient bioavailability, which often results in unsatisfactory consequences for patients. It is known from the Noyes–Whitney equation that a reduction in the drug particle size scale increases its dissolution rate and thereby enhances the bioavailability of the drug (Hörter and Dressman, 2001; Noyes and Whitney, 1897). Numerous methods exist for producing such small particles and many of these are used in drug formulation, with the most commonly used methods being solvent evaporation from emulsions, wet/dry milling, precipitation, and spray drying (Billon et al., 2000; Horn and Rieger, 2001; Kesisoglou et al., 2007; Nornoo et al., 2009; Rabinow, 2004). Although these particle generating techniques are successfully used, each of them has their disadvantages and may not be suitable for certain compounds or applications (Kesisoglou et al., 2007; Zgoulli et al., 1999). Another route to increasing the drug dissolution rate is by preparing the drug in an amorphous form. Drugs in the amorphous form have higher Gibbs free energy than stable crystal forms and thereby also have higher drug dissolution rates than the corresponding crystalline drugs. However, amorphous drugs are generally also less stable than crystalline drugs and can be difficult to keep amorphous even under appropriate storing conditions (Yu, 2001).

Electrospraying is an attractive technique for preparing particles in nano- to meso-scale and is suitable for use in drug delivery systems as well as many other applications (Pareta and Edirisinghe, 2006; Reyderman and Stavchansky, 1995; Xie et al., 2006; Xu and Hanna, 2006). Electrospraying makes use of a strong electric field to break up a liquid containing the material of interest into a continuous stream of finely dispersed particles in a one step process. Enayati et al. (2011), Hayati et al. (1986) and Jaworek (2007) provide details on the background of the electrospraying process for producing particles. The size and surface morphology of particles produced by electrospraying can be controlled to some extent, by adjusting the operation and formulation parameters. There are generally notable advantages in using electrospraying in comparison with conventional preparation methods. Firstly, it is a one-step process that does not make use of any template or surfactants and is performed at ambient temperature and pressure. Moreover, near-monodisperse particles can be produced under controlled conditions (Edirisinghe and Jayasinghe, 2004).

Poly-lactic-co-glycolic acid (PLGA) is widely used as a carrier material in drug delivery systems due to its biocompatibility and its degradation into glycolic acid and lactic acid within the body (Klose et al., 2008). PLGA has previously been used together with electrospraying for drug delivery purposes with successful production

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of particles (Enayati et al., 2010). In this article electrospraying is presented as a method for preparing PLGA micro-particles containing the drug celecoxib (CEL), an alternative approach to increase the dissolution rate of low solubility drugs. CEL was used as a model drug in the present work due to its very low aqueous solubility (5 μg/mL) and because it is well described in literature and safe to work with (Chawla et al., 2003). CEL is a non-steroidal, anti-inflammatory drug or, more specifically, a selective cyclooxygenase-2 (COX-II) inhibitor, which is widely used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain (Thakkar et al., 2004). It is weakly acidic with a pKa of 11 and typically comes as a crystalline powder. There are more than 4 types of CEL crystalline polymorphs of which type III with characteristic needle-shaped crystals is the most stable. CEL is associated with undesirable properties such as cohesiveness, low compressibility and bulk density and it is found that increasing the dissolution rate of CEL improves its oral bioavailability (Chawla et al., 2003; Dolenc et al., 2009; Paulson et al., 2001). The purpose of with mixing PLGA and CEL is to try preventing a possible agglomeration and crystal growth of CEL in the produced particles.

There have been many studies in which CEL micro-/nano- particles have been produced using various techniques such as emulsion or milling. However, to our best knowledge CEL particles have never been prepared using electrospraying. Although electrospraying has been used to prepare many types of drugs ranging from peptides to small molecule drugs it is not known whether CEL can be sprayed and stay in amorphous form or if it will precipitate into crystalline structures. Furthermore, it is not known how the CEL will interact with PLGA and how they will be distributed within the prospective particles prepared using electrospraying. The overall objective of this study was to examine whether electrospraying is a suitable technique for preparing near-monodisperse polymer micro-spheres containing a low solubility drug.

2. Materials and methods

2.1. Materials

Celecoxib crystalline powder was acquired from Dr. Reddy, Hyderabad, India (Mw = 381.38 g/mol). Poly(D,L-lactide-co-glycolide) (PLGA; 50:50 Resomer RG503H, Mw = 33 000 kDa) was purchased from Boehringer Ingelheim (Ingelheim, Germany). Acetone (99.9% HPLC grade) and acetonitrile (99.9% HPLC grade) were purchased from Sigma–Aldrich (Poole, UK).

2.2. Preparation and characterization of solutions

Spraying solutions with PLGA and CEL were prepared by adding PLGA and/or CEL to acetone and stirring using a magnetic stirrer until a clear solution was formed. Five spraying solutions (S1–S5) with different ratios of PLGA and CEL were prepared, all with a total solute content of 5% (w/v). The spraying solutions were characterized to measure liquid properties such as surface tension, viscosity and density, all at ambient temperature (20–25 °C). Viscosity was measured using a U-tube viscometer (75 mL Cannon-Fenske Routine Viscometer, Cannon Instruments, USA), Surface tension was determined using a Kruss tensiometer (Model-K9, Kruss GmbH, Germany) and densities were calculated from the literature (Smallwood, 1996; Arnold et al., 2007; Chawla et al., 2003). Both the viscometer and tensiometer were calibrated before measurement using either ethanol or distilled water where values are known.

2.3. Particles preparation

Particles were prepared using a single-nozzle electrospraying setup where particles are generated from a single jet (see Fig. 1). The spraying system consisted of three main components, a voltage power source (Glassman Europe Ltd., Tadley, UK) with a high voltage output, a mechanical syringe pump (PHD 4400, Harvard Apparatus, Edenbridge, UK) with a high precision, adjustable flow rate, and a custom built, concentric stainless steel nozzle with outer and inner diameters of 2.34 mm and 1.77 mm respectively. Once the drug and polymer were fully dissolved in the solvent, the solution was loaded into a 5 mL syringe and placed onto the pump. The pump then fed the liquid through silicone tubing and into the nozzle where a jet was formed at the tip of the nozzle by manipulation of the electric voltage. The particles generated from the liquid jet were collected either onto a microscope slide containing distilled water or onto a sheet of aluminium foil, depending on the analysis technique later applied on the particles. The particles were then left to dry in a desiccator under slight vacuum. A video camera with an in-built magnifying lens (Leica S6D JVC-color) was used to observe the nozzle tip at all times during collection of particles in order to ensure a stable cone jet. The system operation parameters; flow rate, collection distance and voltage, were used to partly control particle formation. The flow rate and collection distance influenced particle size and solvent evaporation and the voltage was set at a window where a stable jet was achieved. All samples were sprayed

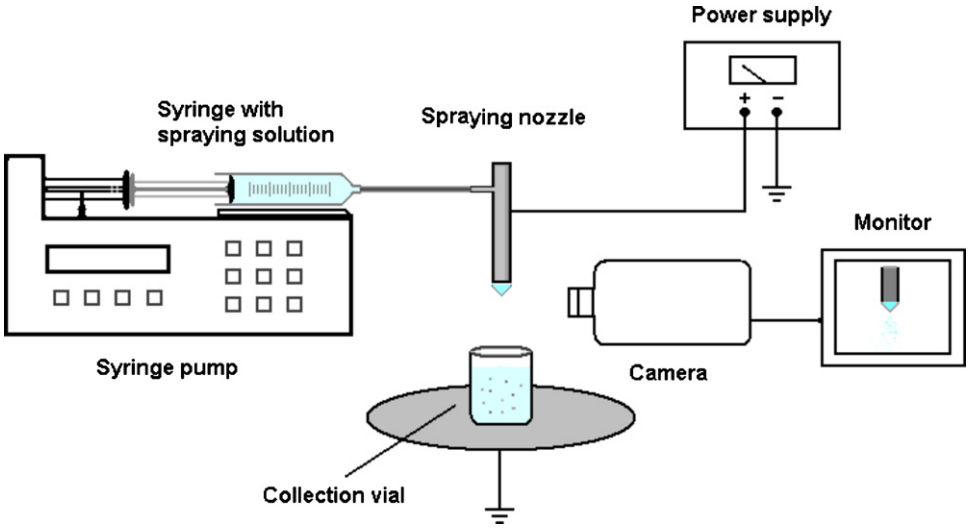

Fig. 1. Schematic illustration of the electrospraying set-up used for particle preparation.

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