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# Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs

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ABSTRACT

Electrospinning was introduced as a novel technique for preparing controlled-release (CR) amorphous solid dispersions (SD) and polymeric nanofibers of a poorly water-soluble drug. Piroxicam (PRX) was used as a low-dose poorly-soluble drug and hydroxypropyl methylcellulose (HPMC) as an amorphous-state stabilising carrier polymer in nanofibers. Raman spectroscopy, X-ray powder diffraction (XPRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM) were used in the physical characterisation of the CR–SD nanofibers. Special attention was paid on the effects of a polymer and solvent system on the solid-state properties and physical stability of nanofibers. The average dry diameter of the electrospun CR–SD nanofibers ranged from 400 to 600 nm (SEM). PRX existed in amorphous form in the nanofibers immediately after fabrication and after a short-term (3-month) aging at low temperature (6–8 °C/0% RH) and ambient room temperature (22 °C/0% RH). At higher temperature and humidity (30 °C/85% RH), however, amorphous PRX in the nanofibers tended to slowly recrystallise to PRX form III. The electrospun CR–SD nanofibers exhibited a short lag-time, the absence of initial burst release and zero-order linear CR dissolution kinetics. In conclusion, electrospinning can be used to fabricate supersaturating CR–SD nanofibers of PRX and HPMC, and to stabilise the amorphous state of PRX.



## 1. Introduction

Interest in the development of controlled-release (CR) drug delivery systems for poorly water-soluble drugs has been increasing steadily. One reason for this is the fact that the majority of the promising new drug candidates coming out from the discovery pipeline are poorly water-soluble compounds. Many of these drugs can exist in different polymorphic or solvated crystal forms, and also in the amorphous state the latter having an enhanced dissolution and bioavailability compared to the crystalline state (Hancock and Zografi, 1997). The delivery of high-energy solid forms (such as amorphous forms, co-crystals and the like) may induce the generation of supersaturated solutions, and this strategy can be used to enhance oral/topical absorption and also to sustain the drug release by choosing appropriate CR polymers (Brouwers et al., 2009; Tran et al., 2011). A supersaturated drug solution, however, is thermodynamically unstable and has the tendency to return to the equilibrium state by precipitation. The stabilisation of a supersaturated solution can be accomplished by adding polymers (precipitation inhibitors) which may act through a variety of mechanisms (Brouwers et al., 2009). Hydroxypropyl methylcellulose (HPMC) has been reported as the excipient of choice to be included into such formulations as a carrier/stabilizer and precipitation inhibitor (Brouwers et al., 2009; Gao et al., 2009; Ohara et al., 2005; Raghavan et al., 2001a,b; Tran et al., 2011).

A combination of solid dispersion (SD) and CR techniques is a novel dissolution-modulating approach and strategy in designing oral CR drug delivery systems for poorly water-soluble drugs (Tran et al., 2011). The CR–SD systems comprise the advantages and functions of both SD and CR. Piroxicam, PRX is a non-steroidal anti-inflammatory drug widely used in the treatment of rheumatic diseases. It is a poorly water-soluble polymorphic drug which belongs to Class II (high permeability, low solubility) in the Biopharmaceutical Classification System

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(Amidon et al., 1995). To date, PRX has been formulated in oral and topical CR drug delivery systems by using e.g. a solvent evaporation method (Guiziou et al., 1996; Joseph et al., 2002), a spray-drying method (Wagenaar and Müller, 1994), an acoustically modified spraying method (Berkland et al., 2003) and encapsulation of the drug in liposomes (Canto et al., 1999). Since amorphous PRX shows a strong propensity to crystallize (Sheth et al., 2004a), designing and formulating amorphous PRX together with polymers into the CR drug delivery systems could be a beneficial alternative approach. Previously, amorphous PRX has been prepared by melt/quench-cooling and cryogenic ball milling methods but the major limitations associated to these techniques are the chemical degradation of PRX and susceptibility to recrystallize into the respective starting polymorph from which PRX was originally prepared (Redenti et al., 1996; Sheth et al., 2004b; Vrečer et al., 1991). According to our recent findings, amorphous state of PRX can be obtained by ball-milling at low temperature but the major limitation of this technique is that amorphous PRX is very unstable (Kogermann et al., 2011). Recently, the production of nanocrystals using a high pressure homogenisation technique was introduced to modify the dissolution and oral absorption of PRX (Lai et al., 2011).

Electrospinning is an effective and continuous method to fabricate polymeric nanofibers with diameters ranging from a nanometer level to submicron level and with a large surface area to volume ratio (Agarwal et al., 2008; Lu et al., 2009; Paaver et al., 2014; Pelipenko et al., 2013; Taepaiboon et al., 2006). In electrospinning, the surface areas of nanofibers can be increased through the formation of much smaller pores in the surface of fibers by controlling e.g. the solution and process parameters of electrospinning (Li and Xia, 2004). Brewster et al. (2004) and more recently Yu et al. (2009) suggested that electrospun ultrafine fibers have the potential to be used as amorphous SDs to improve the solubility and dissolution of poorly water-soluble drugs. The formation of an amorphous SD or solid solution of drug was found when organic-solvent solutions of itraconazole/HPMC mixtures were electrospun resulting in dosage forms with controllable dissolution properties (Verreck et al., 2003). More recently, Huang et al. (2012) introduced a novel time-engineering biphasic CR system for oral delivery of a poorly water-soluble ketoprofen using tri-layered electrospun amorphous nanofibrous mats. Jiang et al. (2012) applied coaxial electrospinning for providing biphasic CR drug release profiles of the nanostructures containing a poorly water-soluble ketoprofen. Consequently, electrospinning could be an interesting alternative for stabilising drugs in an amorphous state in prepared SD, and hence this might lead to improved bioavailability in both oral immediate release and CR drug therapy. For poorly water-soluble drugs, increasing the surface area to volume ratio and/or modification of solid-state form may offer a convenient way to control their dissolution rate and/or stability.

The aim of the present study was to combine SD and CR techniques in fabricating supersaturating controlled-release drug delivery systems for poorly water-soluble drugs. Electrospinning was investigated as a new technique in preparing high-energy amorphous SDs of a poorly water-soluble drug PRX, and for fabricating CR–SD nanofibers of PRX and hydrophilic cellulosic carrier polymer. Special attention was paid on the effects of a hydrophilic carrier polymer HPMC and solvent system on solid-state properties, dissolution and physical stability of drug-loaded nanofiber matrices.

## 2. Materials and methods

### 2.1. Materials

Piroxicam (anhydrous PRX pure form I, PRXAH I, Letco Medical, Inc., USA) was used as a poorly water-soluble drug in fabricating electrospun CR–SD nanofibers. Other crystalline forms of PRX (PRX monohydrate PRXMH and PRX anhydrate form III, PRXAH III) used for comparison were prepared as previously reported (Kogermann et al., 2007a, 2011).

Three grades of hydroxypropyl methylcellulose, HPMC were studied as a carrier and stabilising polymers for CR–SD nanofibers: Methocel™ K100M premium CR; Methocel™ K4M premium CR; Methocel™ E5 premium LV (The Dow Chemical Company, USA). The primary solvents applied in the electrospinning studies were methanol (Sigma–Aldrich Chemie GmbH, Germany) and 1,1,1,3,3,3-hexa-fluoro-2-propanol (HFIP) (≥99.0%) (Apollo Scientific Ltd., UK). Applicability of ethanol, acetone, 2-propanol and dichloromethane (Lach-Ner s.r.o., Czech Republic) for electrospinning of nanofibers was also studied. All other reagents and solvents used were of analytical grade.

### 2.2. Selection of solvent systems for electrospinning

Table 1 summarises the results on the solubility/miscibility of the carrier HPMC polymers in different solvent systems. The test was based on visual inspection. Non-aqueous and readily evaporating HFIP was selected as the most suitable solvent system for further electrospinning experiments with PRX and HPMC.

### 2.3. Method for fabrication of nanofibers

A schematic diagram of the electrospinning process is shown in Fig. 1. The automatic syringe pump KdScientific (Model No: KDS-250-CE, Geneq Inc., USA) with a pumping speed of 1 ml/h, was used for electrospinning. The high-voltage power supply Gamma High Voltage Research (Model No. ES3OP-10W/DAM, USA) was applied for generating the voltage of 7–22 kV used in the experiments. The distance between the spinneret and the fiber collector was in a range of 8–25 cm. The drug-polymer (PRX/HPMC) ratios (w/w) used in electrospinning experiments were 1:1, 2:1 and 4:1. For preparing the nanofibers containing HPMC K100M premium CR as a carrier polymer and HFIP as a solvent system, the levels for the voltage and distance were 7, 9, 10 kV and 8, 10, 12 cm, respectively. For preparing nanofibers with the other two HPMC grades, the higher operating voltage (22 kV) and different distance (25 cm) were applied.

The electrospun nanofibers were investigated immediately after fabrication and within regular time periods during a short-term (3-month) aging at a low temperature (LT 6–8 °C/0% RH) and ambient room temperature (RT 22 °C/0% RH). In addition, some samples were also stored for up to 2 months at higher temperature (HT) and humidity conditions (30 °C/85% RH).

### 2.4. Physicochemical characterisation

#### 2.4.1. X-ray powder diffraction

X-ray powder diffraction (XRPD) patterns of starting materials and electrospun nanofibers (immediately after fabrication and after a short-term aging) were obtained by using a X-ray diffractometer (D8 Advance, Bruker AXS GmbH, Germany). Crystal structures were verified by comparing the experimental results to the theoretical patterns in the Cambridge Structural Database (CSD) or to diffractograms available in the literature (Bordner et al., 1984; Reck et al., 1988; Vrečer et al., 2003). The XRPD experiments were carried out in a symmetrical reflection mode (Bragg–Brentano geometry) with CuKα radiation (1.54 Å). The scattered intensities were measured with the LynxEye one-dimensional detector with 165 channels. The angular range was from 5° 2-theta to 30° 2-theta with steps of 0.2° 2-theta. The total measuring time was 498 s per step. The operating current and voltage were 40 mA and 40 kV, respectively.