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Overcoming drug crystallization in electrospun fibers – Elucidating key parameters and developing strategies for drug delivery

Salem Seif[a,b], Lutz Franzen[a], Maike Windbergs[a,b,c,*]

[a] Saarland University, Department of Biopharmaceutics and Pharmaceutical Technology, Saarbruecken, Germany
[b] PharmBioTec GmbH, Saarbruecken, Germany
[c] Helmholtz Centre for Infection Research (HZI) and Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Department of Drug Delivery (DDEL), Saarbruecken, Germany

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ABSTRACT

For the development of novel therapeutics, uncontrolled crystallization of drugs within delivery systems represents a major challenge. Especially for thin and flexible polymeric systems such as oral films or dermal wound dressings, the formation and growth of drug crystals can significantly affect drug distribution and release kinetics as well as physical storage stability. In this context, electrospinning was introduced as a fabrication technique with the potential to encapsulate drugs within ultrafine fibers by rapid solvent evaporation overcoming drug crystallization during fabrication and storage. However, these effects could so far only be shown for specific drug-polymer combinations and an in-depth understanding of the underlying processes of drug-loaded fiber formation and influencing key parameters is still missing.

In this study, we systematically investigated crystal formation of caffeine as a model drug in electrospun fibers comparing different polymers. The solvent polarity was found to have a major impact on the drug crystal formation, whereas only a minor effect was attributed to the electrospinning process parameters.

Based on an in-depth understanding of the underlying processes determining drug crystallization processes in electrospun fibers, key parameters could be identified which allow for the rational development of drug-loaded electrospun fibers overcoming drug crystallization.

1. Introduction

For the development of novel therapeutics, uncontrolled drug crystallization within a drug delivery system upon fabrication or storage represents a major challenge. Such effects potentially cause inhomogeneous drug distribution within the dosage form affecting uniformity of the system as well as drug release kinetics and physical stability during storage (Shekunov and York, 2000). Thin and flexible polymeric drug-loaded systems such as oral films or dermal wound dressings (Verreck et al., 2003a,b,b; Perumal et al., 2008; Yang et al., 2009) are especially prone to these problems. The large coherent surface providing advantages such as good applicability and increased contact area with the application site (skin or mucosa) as well as short diffusion distances for embedded drugs, unfortunately also facilitates drug crystal formation and especially crystal growth (Perumal et al., 2008; Yang et al., 2009; Garsuch and Breitkreutz, 2009).

Recently, electrospinning was introduced as alternative fabrication technique for polymer based drug delivery systems (Zamani et al., 2013). In general, the electrospinning procedure involves pumping a polymer solution through a syringe nozzle connected to a high voltage power supply. The voltage is increased to a level that overcomes the surface tension of the polymer solution forming a droplet at the tip of the nozzle. A thin liquid jet is formed and directed toward a metal collector. As the solvent evaporates during this process, ultrafine solid fibers are collected as a final product (Greiner and Wendorff, 2007). Electrospinning provides many advantages for drug delivery applications such as the ability to incorporate different types of drugs for various biomedical applications (Zamani et al., 2013; Sill and von Recum, 2008; Meinel et al., 2012). Electrospun fibers for wound healing (Said et al., 2012), sublingual applications (Vrbata et al., 2013), oral drug delivery (Ignatious et al., 2010) and antitumor therapy (Luo et al., 2012) have already successfully been prepared.

* Corresponding author at: Department of Biopharmaceutics and Pharmaceutical Technology, Saarland University, Campus A4.1, Saarbruecken 66123, Germany. Tel.: +49 681 302 4763; fax: +49 681 302 4677.
E-mail address: m.windbergs@mx.uni-saarland.de (M. Windbergs).

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Furthermore, due to the high evaporation rate of the solvents compared to conventional film casting, electrospinning facilitates the formation of solid solutions of the drug in polymer fibers (Verreck et al., 2003a,b,b). However, these effects could so far only be shown for specific drug-polymer combinations. In contrast, there are even some studies published describing drug crystal growth on the surface of electrospun fibers and its influence on morphology and physicochemical characteristics of the fibers (Zeng et al., 2005; Kim et al., 2007). This holds especially for hydrophilic drugs which are embedded into hydrophobic polymer fibers.

For rational development of suitable and reliable electrospun drug delivery systems, an in-depth understanding of the underlying processes of drug-loaded fiber formation and influencing key parameters of potential drug crystallization is a mandatory prerequisite.

In this study, we performed a comprehensive study on drug crystal formation in different electrospun fibers and developed strategies to overcome these effects. We selected caffeine (CAF) as a hydrophilic model drug with high crystallization tendencies (Garsuch and Breitkreutz, 2009) and compared electrospun fibers and casted films based on hydrophilic poly(vinyl alcohol) (PVA) and hydrophobic polycaprolactone (PCL).

2. Materials and methods

2.1. Materials

Polycaprolactone (PCL) (Mn 70,000–90,000), poly(vinyl alcohol) (PVA) (Mw 85,000–124,000, 99+% hydrolyzed), caffeine (CAF), flufenamic acid (FFA), acetonitrile, chloroform ($CHCl_3$), ethanol (EtOH) and 2,2,2-trifluoroethanol (TFE) were purchased from Sigma–Aldrich (Steinheim, Germany). Acetic acid was obtained from Fluka (Buchs, Switzerland). Potassium dihydrogen phosphate (KH_2PO_4) and ortho-phosphoric acid were purchased from Merck KGaA (Darmstadt, Germany). Dimethylformamide (DMF) was obtained from VWR International S.A.S. (Fontenay sous Bois, France).

2.2. Methods

2.2.1. Preparation of caffeine-polymer solutions

CAF and PVA were mixed (drug/polymer ratio 11:89 w/w) and dissolved in a mixture of purified water and acetic acid (1:1 v/v) at 80 °C for 4 h with vigorous stirring. After complete dissolution, the solution was left to cool down at room temperature before being used. Similarly, the CAF and PCL were mixed (drug/polymer ratio 11:89 w/w) and a solution was prepared by dissolving both components in $CHCl_3$:EtOH (50:50 v/v) at room temperature with vigorous stirring.

2.2.2. Film casting

Film casting was performed with the CAF-polymer solutions described in Section 2.2.1. 1 ml of each solution was pipetted into a Petri dish and homogeneously spread on its glass surface. The Petri dishes containing the CAF-polymer solutions were left at room temperature for at least 24 h allowing the solvents to evaporate completely before being stored in a desiccator.

2.2.3. Fabrication of electrospun fibers

CAF loaded PVA and PCL fibers were fabricated by electrospinning polymer solutions prepared according to Section 2.2.1. The used electrospinning setup consisted of a syringe pump system (New Era Pump Systems, Inc., USA) and a high voltage power supply (Acopian®, USA). CAF–PVA electrospun fibers were prepared by pumping the CAF–PVA solution at a flow rate of 1 ml/h and applying a voltage of 26 kV. The distance between the nozzle and the collector was 16 cm. For electrospinning CAF–PCL fibers, the used pumping flow rate ranged from 0.3 to 3 ml/h, the applied voltage was between 6.48 and 12.3 kV. The nozzle–collector distance ranged from 13 to 18 cm. A drum collector rotating at 1 m/s was used to collect the electrospun CAF–PVA and CAF–PCL fibers. The generated fiber mats were stored in a desiccator until analysis.

2.2.4. Chemical imaging and drug distribution analysis

Chemical imaging and drug distribution analysis were performed using confocal Raman microscopy (CRM) (WITec alpha 300R+; WITec GmbH, Ulm, Germany) equipped with a Zeiss Epiplan Neofluar objective (50×, NA = 0.8). An excitation wavelength of 532 nm was used operating at 40 mW laser power before the objective. Raman spectra were recorded with an integration time of 0.5 s for the electrospun fiber mats and 1 s for the casted films. After removing cosmic rays and reducing background signals using WITec Suite software (WITec GmbH, Ulm, Germany), a supervised cluster analysis converted the collected Raman spectra into false color images.

2.2.5. Scanning electron microscopy

The surface structure of the films and fibers was visualized by scanning electron microscopy (SEM). Samples were mounted on aluminum stubs using double sided carbon discs and sputtered with a thin layer of gold prior to analysis (Sputter Coater Q150R ES, Quorum Technologies Ltd., UK). SEM analysis was performed using a Zeiss EVO HD 15 SEM at an accelerating voltage of 5 kV (Carl Zeiss AG, Oberkochen, Germany).

2.2.6. Differential scanning calorimetry

Differential scanning calorimetry (DSC) analysis was performed using a DSC Q100 (TA Instruments, USA). Samples consisting of approximately 5 mg of the pure substances or the electrospun fibers were sealed in hermetic aluminum pans (Hermetic Pans, TA Instruments, USA). After equilibration for 1 min at 25 °C, samples were heated from 25 to 300 °C with a heating rate of 5 °C/min.

2.2.7. In vitro release testing and drug quantification

CAF release was tested in phosphate buffer saline (PBS) pH 7.4. 8 mm discs were punched out of the electrospun fiber mats, weighted and immersed in 5 ml PBS at 37 °C. At predetermined time intervals, 0.2 ml medium were withdrawn for analysis and replaced with the same amount of fresh PBS. At the end of the experiment, the electrospun fiber mats were thermally destroyed and the remaining CAF concentration was determined with reversed-phase high performance liquid chromatography (RP-HPLC) using an isocratic Dionex HPLC system with a LiChrospher® 100 RP-18 (5 μm) column and guard cartridge LiChroCART® 4-4 (Merck KGaA, Darmstadt, Germany). The mobile phase consisted of pH 2.6 buffer (1 L purified water containing 1.6 ml ortho-phosphoric acid and 2.04 g KH_2PO_4) and acetonitrile (90:10 v/v). A flow rate of 1.2 ml/min and a detection wavelength of 273 nm assured optimal detection of CAF.

3. Results and discussion

3.1. Caffeine crystallization in casted films

As uncontrolled drug crystallization is a quite common and well described problem in thin films which are used for drug delivery, we casted different drug-loaded films as reference systems for electrospun fiber mats (Jain and Banga, 2013; Kotiyan and Vavia, 2001; Kestur and Taylor, 2010). We chose caffeine (CAF) as a hydrophilic model drug with high crystallization tendency. As drug-polymer compatibility is described to be one of the most