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Electrospun polycaprolactone nanofibers as a potential oromucosal delivery system for poorly water-soluble drugs

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ABSTRACT

The number of poorly water-soluble drug candidates is rapidly increasing; this represents a major challenge for the pharmaceutical industry. As a consequence, novel formulation approaches are required. Furthermore, if such a drug candidate is intended for the therapy of a specific group of the population, such as geriatric or pediatric, the formulation challenge is even greater, with the need to produce a dosage form that is acceptable for specific patients. Therefore, the goal of our study was to explore electrospun polycaprolactone (PCL) nanofibers as a novel nanodelivery system adopted for the oromucosal administration of poorly water-soluble drugs. The nanofibers were evaluated in comparison with polymer films loaded with ibuprofen or carvedilol as the model drugs. Scanning electron microscopy revealed that the amount of incorporated drug affects the diameter and the morphology of the nanofibers. The average fiber diameter increased with a higher drug loading, whereas the morphology of the nanofibers was noticeably changed in the case of nanofibers with 50% and 60% ibuprofen. The incorporation of drugs into the electrospun PCL nanofibers was observed to reduce their crystallinity. Based on the morphology of the nanofibers and the films, and the differential scanning calorimetry results obtained in this study, it can be assumed that the drugs incorporated into the nanofibers were partially molecularly dispersed in the PCL matrix and partially in the form of dispersed nanocrystals. The incorporation of both model drugs into the PCL nanofibers significantly improved their dissolution rates. The PCL nanofibers released almost 100% of the incorporated ibuprofen in 4 h, whereas only up to 77% of the incorporated carvedilol was released during the same time period, indicating the influence of the drug's properties, such as molecular weight and solubility, on its release from the PCL matrix. The obtained results clearly demonstrated the advantages of the new nanodelivery system compared to the drug-loaded polymer films that were used as the reference formulation. As a result, electrospinning was shown to be a very promising nanotechnology-based approach to the formulation of poorly water-soluble drugs in order to enhance their dissolution. In addition, the great potential of the produced drug-loaded PCL nanofiber mats for subsequent formulation as oromucosal drug delivery systems for children and the elderly was confirmed.

1. Introduction

The development of novel formulations and delivery approaches for poorly water-soluble drugs is a common challenge with modern pharmaceuticals. The main reason for this is the large proportion of drug candidates that are poorly water soluble. However, when these drugs need to be administered to specific populations, e.g., paediatric or geriatric, the technological challenges associated with their poor water solubility are accompanied by additional challenges associated with the acceptability of the final dosage form with these patients.

Nanofibers represent one of the newest and very promising nanomaterials for a number of applications. They have already demonstrated important applicability in biomedicine, where numerous studies have already described in the field of tissue engineering, wound healing as well as drug delivery (Rošic et al., 2013). Immediate or modified drug release can be achieved by the selection of a polymer for nanofiber production and the manner of the drug loading. The drug can be either incorporated into the polymer matrix of the nanofibers or bound to their surfaces (Huang et al., 2003; Meinel et al., 2012; Rošic et al., 2012). Both biodegradable

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and non-degradable, either natural or synthetic, polymers can be used to control the drug release via diffusion alone or by a combination of diffusion and fiber degradation. Furthermore, the proper selection of the polymer can ensure the optimal combination of mechanical and biomimetic properties for the nanofibers (Pelipenko et al., 2013a; Sill and von Recum, 2008). The special characteristics of nanofibers, in addition to their very small diameters, include a high surface-to-volume ratio, a very high porosity, a small pore size, a good mechanical strength and a diversity in the surface functionalities (Huang et al., 2003; Pelipenko et al., 2013b). The drug release can be tuned for a specific application by changing the fiber's composition, production technology or the process parameters, resulting in a different fiber diameter and/or porosity (Bertoncelj et al., 2014; Sill and von Recum, 2008). The application of nanofiber mats on mucosa results in fluid absorption, due to the presence of numerous nanometer-sized interfibrillar pores. This is, in addition to the large surface area of the nanofibers available to interact with the biosurface, the main mechanism for the adhesion of the nanofibers to the biosurfaces, making them one of the promising mucoadhesive drug delivery systems (Sill and von Recum, 2008).

Electrospinning is the most common method for the production of fibers with diameters ranging from a few nanometers to a few micrometers from polymer solutions or melts (Frenot and Chronakis, 2003; Huang et al., 2003). This method is applicable to virtually any soluble or fusible polymer (Bhardwaj and Kundu, 2010; Sill and von Recum, 2008). Biodegradable and biocompatible polymers, such as polycaprolactone (PCL) (Fig. 1a), are good candidates for the preparation of nanofibers for applications in biomedicine. Such nanofibers represent a novel class of nanomaterials that is currently being investigated for drug-delivery applications (Dash and Konkimalla, 2012; Woodruff and Hutmacher, 2010).

The oral mucosa is very interesting for the purposes of drug delivery. It provides a much more constant environment for drug absorption than the gastrointestinal environment, where the drug is not exposed to the harsh conditions in the gastrointestinal tract and the absorption across the oral mucosa can bypass the hepatic first-pass effect. Even though the permeability of the oral mucosa is lower than the intestinal mucosa, the rich blood supply enables an effective drug absorption (Hearnden et al., 2012; Shakya et al., 2011). Oromucosal formulations are, due to their simple use and non-invasive application, widely accepted by patients (Lam et al., 2014). They are especially suitable for pediatric (Lam et al., 2014; Sattar et al., 2014) and geriatric patients (Illangakoon et al., 2014; Sattar et al., 2014), as well as for any other patient with swallowing or digestion difficulties (Illangakoon et al., 2014). The buccal and sublingual dosage forms are among the most commonly used oromucosal delivery systems (Lam et al., 2014; Patel et al., 2011). However, for the drug to be a suitable candidate for the formulation of an oromucosal delivery system it has to satisfy some key criteria that relate to the drug's molecular weight, potency and water solubility. The molecular weight of drug candidates that are appropriate for oromucosal delivery should not exceed 800 Da (Lam et al., 2014) and the drug potency should be relatively high due the limited surface area that is available for the drug absorption. Usually, only doses up to a few milligrams can be efficiently absorbed through the oral mucosa. In addition, the dissolved drug might be washed away with saliva before it permeates through the mucosal membrane (Lam et al., 2014; Patel et al., 2011); therefore, an intense contact between the dosage form and the mucosa is highly advantageous for reducing the possibility of drug washout by the saliva. A drug delivered via the oromucosal route should not cause any local irritation at the application site, i.e., the oral mucosa (Lam et al., 2014). Furthermore, a sufficient aqueous solubility is necessary to allow the drug to diffuse through the mucus layer. The number of poorly water-soluble drug candidates has been increasing rapidly over recent years (Kawabata et al., 2011; Pouton, 2006); however, they are not usually suitable for the formulation of oromucosal drug delivery systems. The preparation of salts usually improves their solubility; however, drug molecules are better absorbed through the oral mucosa if they are in unionized form (Lam et al., 2014). Therefore, a nanotechnology-based approach, which would improve the dissolution rate and the solubility of such drugs, and would not affect their chemical properties, would be advantageous. The formulation of nanofibers represents one possible route to achieving these goals.

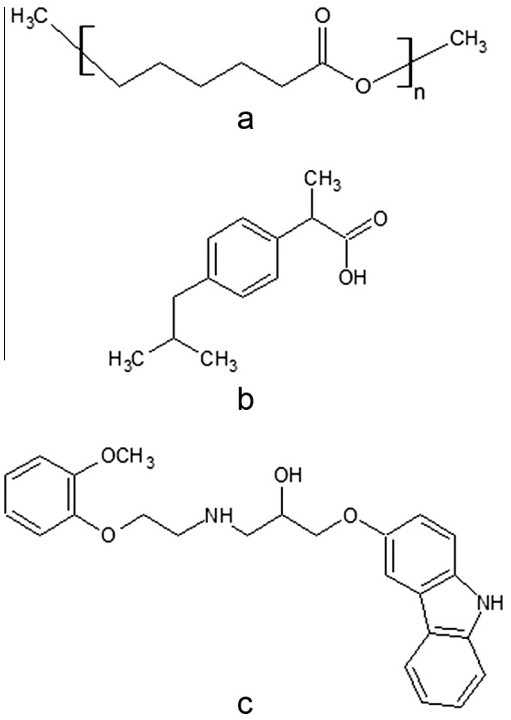

Fig. 1. Chemical structure of polycaprolactone (a), ibuprofen (b) and carvedilol (c).

During the electrospinning of a polymer solution the rapid evaporation of the solvent results in the instant formation of nanofibers and the entrapment of the drug in the polymer matrix or its deposition onto the nanofiber surface (Seif et al., 2015; Yu et al., 2010), resulting in a decreased drug mobility (Yu et al., 2010). The drugs are usually randomly encapsulated within ultrathin and flexible polymer nanofibers with a very high surface area available for contact with the application site. All these characteristics of nanofibers have a significant influence on the drug's bioavailability (Yu et al., 2010).

The aim of our research was to explore electrospun PCL nanofibers as a novel nanodelivery system intended for the oromucosal administration of poorly water-soluble drugs and to determine their potential advantages over polymer films. We chose two model drugs with similar hydro-lipophilic properties, but differing in their molecular weights, and investigated their influence on the nanofiber's physical properties and drug release profiles, aiming to establish a correlation between the drug's properties and the release characteristics of a PCL nanofiber-based delivery system.

2. Materials and methods

2.1. Materials

The polycaprolactone (PCL) Mw 70,000–90,000 g/mol was purchased from Sigma–Aldrich, Germany. The sodium iodide