Saudi Pharmaceutical Journal 25 (2017) 921–926

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Preparation, characterization, and *in vitro* diffusion study of nonwoven electrospun nanofiber of curcumin-loaded cellulose acetate phthalate polymer

Rramaswamy Ravikumar [a,d], Mani Ganesh [a], Udumansha Ubaidulla [b], Eun Young Choi [c], Hyun Tae Jang [a,*]

[a] Department of Chemical Engineering, Hanseo University, 360 Daegok-ri, Seosan-si 356 706, Chungcheongnam-do, South Korea
[b] C.L. Baid Metha College of Pharmacy, Chennai 97, India
[c] Department of Cosmetology, Hanseo University, 360 Daegok-ri, Seosan-si 356 706, Chungcheongnam-do, South Korea
[d] Department of Advanced Materials and Engineering, Hanseo University, 360 Daegok-ri, Seosan-si 356 706, Chungcheongnam-do, South Korea

ARTICLE INFO

Article history:
Received 15 December 2016
Accepted 8 February 2017
Available online 12 February 2017

Keywords:
Curcumin
Cellulose acetate phthalate
Nanofiber
In vitro
Transdermal

ABSTRACT

Novel curcumin (CUR)-loaded cellulose acetate phthalate (CAP) nonwoven electrospun nanofiber (NF) transdermal mat was developed and evaluated for its *in vitro* CUR diffusion properties. Various CAP solutions from 5 to 20 wt% were tested; 17.5 wt% was found to be a suitable concentration for NF fabrication without defects, such as bubble or ribbon structures. The selected wt% CAP solution was loaded with CUR and electrospun into NFs. The prepared CUR-loaded NFs were characterized using scanning electron microscopy, X-ray diffraction, ultraviolet–visible spectroscopy, thermogravimetric analysis (TGA), and *in vitro* diffusion studies. The as-prepared fibers demonstrated controlled *in vitro* transdermal delivery of CUR for up to 24 h.

1. Introduction

Transdermal drug delivery systems are a promising drug delivery route for treating local skin disorders such as acne and various types of wounds; their applicability can be further extended to delivering drugs that are easily degraded when administered orally and undergo first pass metabolism in the liver. The transdermal route can deliver drugs directly to the systemic circulation in a controlled manner, depending on the polymer selected for delivery. The outermost layer of skin, the stratum corneum, plays a key role in limiting drug diffusion to the bloodstream following transdermal delivery, by acting as a controlling barrier; hence, an effective transdermal system must allow drugs to penetrate this skin barrier and reach targeted cells (Hadgraft and Guy, 1989; Guy et al., 1996). Although parenteral drug delivery systems provide rapid delivery and increased plasma levels within a short duration, they are considered more invasive (Flynn, 1996); in general, transdermal delivery is considered to be a non-invasive system, capable of delivering drugs without the difficulties associated with conventional parenteral formulations. During transdermal application, liphophilic molecules enter the body through intracellular lipids present in the stratum corneum, and water-soluble drugs enter through pores close to hair follicles (Surber et al., 1990).

Commonly, transdermal delivery systems are formulated as transdermal gels, patches and films that play an important role in drug delivery formulations (Rehman and Zulfakar, 2014; Pastore et al., 2015). Drugs are loaded into rate-controlling biodegradable polymers; polyacrylates, poly (vinyl alcohol), poly (acrylic acid), polyacrylamide, polylactides (PLA), polyglycolides (PGA), poly(lactide-co-glycolides) (PLGA), polyanhydrides, polyorthoesters, and natural biopolymers such as chitosan, zein, pectin, and cellulose derivatives (e.g., ethyl cellulose, cellulose acetate, and cellulose acetate phthalate (CAP)) have been reported as suitable formulations for transdermal delivery systems (Upadhyay et al., 2014). CAP has proven capability for formulating transdermal patches with promising drug loading and release performance (Patel et al., 2013; Garg et al., 2016).

In the past two decades, ultra-fine structures including microspheres and nanostructures such as nanoparticles and nanospheres, have been of interest in pharmaceutical science for

* Corresponding author.
E-mail address: htjang@hanseo.ac.kr (H. Tae Jang).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2017.02.004
1319-0164/

formulation of new drug delivery systems, due to their controllable high surface area, surface-to-volume ratio, high porosity, and high drug loading and controlled payload delivering capabilities (Bose et al., 2015). Nanofibers (NFs) are a nanostructure that can be produced by various routes, which have been discussed extensively in the review by Huang et al. (2003). Electrospinning is the most promising technique and can produce NFs with ultrafine diameters and well-ordered surface morphologies. In addition to these applications, the high entrapment efficiency, simultaneous delivery of diverse therapeutics, and ease of formulation provided by polymeric electrospun NFs using synthetic and biological polymers has enabled them to be used in drug-loaded wound dressing preparations, drug and protein delivery, and tissue engineering scaffolds (Croisier et al., 2014; Abdelgawada et al., 2014; Hu et al., 2014; Huaimin et al., 2015; Ganesh et al., 2016; Ravikumar et al., 2016; Saravanakumar et al., 2016).

Curcumin a polyphenolic flavonoid from the rhizomes of *Curcuma longa* Linne (turmeric)., is mainly used as a spice in cooking of Indian recepies. Among the available natural anti-inflammatory agents, curcumin (CUR) has been of interest to biological researchers due to its additional anti-bacterial (Mun et al., 2013; Tyagi et al., 2015; Izui et al., 2016; Moghadamtousi et al., 2014; Sharma et al., 2014) and anti-oxidant (Meng et al., 2013; Yao et al., 2015; Chen et al., 2015; Satish and Dilipkumar, 2015; Kant et al., 2014) properties. The anti-inflammatory action of CUR arises from COX-2 inhibition via decreasing neutrophil infiltration at the inflammatory site. Alongside a direct effect on the polarization of neutrophils and chemotaxis, CUR also reduces concentrations of an important cytokine, TNFα, which normally activates signaling cascades involved in inflammation. CUR can decrease oxidative stress via scavenging reactive oxygen species (ROS) by alleviating the accumulation of melanodialdehyde, superoxide anions, and nitrous oxide (Remya et al., 2016). CUR can also enhance wound healing by promoting the amalgamation of collagen, hexosamin, DNA, and nitrates. In addition to these amalgamations, CUR also has the ability to hasten wound closure by rapid re-epithelialization of the epidermis and exodus of cells such as macrophages, fibroblasts, and myofibroblasts from wound surfaces (Rajesh et al., 2013). Various CUR-loaded transdermal systems have been reported (Patel et al., 2009a,b; Olaru and Olaru, 2010); however, to our knowledge, there have been no studies on NF-based transdermal delivery systems for CUR-loaded formulations.

Considering the advantages of CAP in the development of transdermal delivery systems, and the possibility of delivering CUR through the transdermal route, here we report the development of a novel CAP-based NF preparation loaded with CUR for transdermal application. The effects of CAP weight, the solvent used, and other processing parameters on NF morphology were investigated using scanning electron microscopy (SEM) and other physiochemical characterization procedures. Formulated NFs were characterized using Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). *In vitro* diffusion of CUR from the NFs was examined using pig skin as a transdermal barrier.

2. Methods

2.1. Materials

CAP with molecular weight 2534.12 g/mol and CUR were obtained from Sigma-Aldrich (Korea); ethyl acetate (EA) and isopropyl alcohol (IPA) were obtained from Daejung Chemical and Metals (Korea). All other chemicals used were of analytical grade, unless otherwise noted.

2.2. Preparation of nanofibers (NFs)

During the pre-formulation procedure, a range of CAP concentrations (5, 10, 15, 17.5, and 20 wt%) in a 25:75 mixture of IPA and EA, respectively, were prepared and loaded into the sample feeder used for nanofabrication. Electrospinning was conducted using the procedure described below. Similarly, CUR-loaded fiber was prepared by adding 10% CUR with respect to the total amount of CAP, made into a solution using the same solvent system, and fabricated into NFs using the same procedure.

2.3. Preparation of NFs by electrospinning

The plain CAP and CUR-loaded CAP NFs were prepared in similar manner. The prepared CAP and CUR/CAP solutions were placed into a 10-mL syringe, fitted with a blunt metal needle (21 gauge). The distance between the needle and an aluminum foil-wrapped drum collector was maintained at 15 cm. An approximately 12-kV high-voltage direct current was supplied between the drum and the needle; after a series of trials, the solution feedrate from the needle was fixed at 1.5 mL h^{-1}. The collector was rotated at a speed of 30 rpm. The fabricated NFs were collected carefully from the collector, dried at room temperature for 48 h to ensure complete evaporation of the solvent, and then weighed and stored in a light-protected container at room temperature until further investigation. Images of the optimized NF mats on adhesive patches are provided in Supplementary Material Fig. S1.

2.4. Characterization

The surface morphology of the prepared NFs was evaluated using SEM (JEOL JSM 5600, Japan). A square-shaped NF sample of suitable size was placed on double-sided adhesive tape on the aluminum stub of the SEM; samples were then coated with gold plasma sputter (Sputter Coater-108 Auto, Cressington).FTIR spectra were obtained for the pure polymer, CUR physical mixture, and NF samples using a Nicolet 6700 FT-IR spectrometer at room temperature via the KBr pellet technique. In total, 20 scan cycles were obtained at 4-cm^{-1} resolution over the range of 4000–400 cm^{-1}. To determine the crystalline nature of the polymer, CUR, and CUR-loaded polymer, X-ray diffraction (XRD) images were recorded using a Rigaku Miniflex diffractometer with Cu Kα radiation (λ = 1.54 Å), a 2θ range of 10–80 with a 0.1° step size, and a 1-s step time. A Scinco DSC N 650 system was used to record DSC traces of pure CAP, CUR, CAP NF, and CAP-CUR NF with a heating rate of 10 °C/min under a helium atmosphere (40 mL/min) to evaluate crystalline changes in CUR after fabrication. To determine the mechanical stability of the formulated NFs, TGA was conducted using Scinco N-1000 analyzer under N_2 atmosphere; here 10-mg fiber samples were heated in platinum pan from 25 to 800 °C at a rate of 10 °C/min.

2.5. Drug entrapment efficiency

The amount of the drug entrapped in the formulated NF mat was evaluated by drying the CUR-loaded CAP NF in a hot air oven at 40 °C. After drying, the weight of the NF mat was measured, then the sample was dissolved in the respective solvent (IPA:EA; 25:75 for the CAP NF). The amount of CUR present in the solvent was measured using ultraviolet–visible (UV–Vis) spectrometry at 420 nm; the theoretical value of CUR added to the CAP NF solution before electrospinning is given below in terms of the entrapment efficiency (Saravanakumar et al., 2016):

$$\text{Entrapment efficiency } (\%) = \frac{\text{Wt of max. drug release}}{\text{Wt of drug added}} \times 100 \quad (1)$$