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Core-shell nanofibers of curcumin/cyclodextrin inclusion complex and polylactic acid: Enhanced water solubility and slow release of curcumin

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ABSTRACT

Core-shell nanofibers were designed via electrospinning using inclusion complex (IC) of model hydrophobic drug (curcumin, CUR) with cyclodextrin (CD) in the core and polymer (polylactic acid, PLA) in the shell (cCUR/HPβCD-IC-sPLA-NF). CD-IC of CUR and HPβCD was formed at 1:2 molar ratio. The successful formation of core-shell nanofibers was revealed by TEM and CLSM images. cCUR/HPβCD-IC-sPLA-NF released CUR slowly but much more in total than PLA-CUR-NF at pH 1 and pH 7.4 due to the restriction of CUR in the core of nanofibers and solubility improvement shown in phase solubility diagram, respectively. Improved antioxidant activity of cCUR/HPβCD-IC-sPLA-NF in methanol:water (1:1) is related with the solubility enhancement achieved in water based system. The slow reaction of cCUR/HPβCD-IC-sPLA-NF in methanol is associated with the shell inhibiting the quick release of CUR. On the other hand, cCUR/HPβCD-IC-sPLA-NF exhibited slightly higher rate of antioxidant activity than PLA-CUR-NF in methanol:water (1:1) owing to the enhanced solubility. To conclude, slow release of CUR was achieved by core-shell nanofiber structure and inclusion complexation of CUR with HPβCD provides high solubility. Briefly, electrospinning of core-shell nanofibers with CD-IC core could offer slow release of drugs as well as solubility enhancement for hydrophobic drugs.

1. Introduction

Curcumin (CUR) (Fig. 1a) is a polyphenol and apart from its usage as a therapeutic agent, it is widely employed as a spice, food preservative, flavoring and coloring agent (Aggarwal et al., 2003). Its common application for various diseases including cancer, cardiovascular and Alzheimer's disease, inflammatory and neurological disorders is owing to the outstanding biological functions such as antioxidant, anti-tumor, and anti-inflammatory activities of CUR (Yallapu et al., 2015). But, it also exhibits drawbacks like low bioavailability, instability depending on pH, insolubility in water, slow uptake by the cells and rapid metabolism inside the cell (Siviero et al., 2015). Several strategies were developed previously to improve pharmacokinetics, systemic bioavailability, and biological activity of CUR (Siviero et al., 2015). Among these strategies, cyclodextrin (CD) inclusion complexes (ICs) is a commonly applied method to overcome the limitations of CUR. CDs are nontoxic and biodegradable cyclic oligosaccharides which are capable of forming ICs with a variety of molecules to enhance solubility, bioavailability, and thermal stability of hydrophobic guest compounds; reduce the volatility of molecules with low thermal stability, mask off malodors/bitter tastes, and control release of active agents (Del Valle, 2004; Hedges 1998; Szejtli, 1998). The most common CDs are α-CD, β-CD and γ-CD with 6, 7, and 8 glucose units, respectively. In addition, chemically modified CDs including hydroxypropyl-beta-cyclodextrin (HPβCD) (Fig. 1b) in which some of the hydroxyl groups in the β-CD structure are substituted with hydroxypropyl groups were also synthesized. HPβCD is more suitable for the solubilization of hydrophobic drugs due to its better aqueous solubility compared to native β-CD (Del Valle, 2004; Hedges 1998; Szejtli, 1998). IC of CUR and HPβCD were studied before for several aims such as enhancing the solubility and fluorescence (Baglole et al., 2005), oral bioavailability (Bansal et al., 2011) of CUR; treating melanoma (Sun et al., 2014), and inflammatory bowel disease (Yadav et al., 2009).

Nanofibers are quite appropriate to carry active agents including drugs, antioxidant, and antibacterial agents owing to high surface to volume ratio and porous structure (Agarwal et al., 2008). Furthermore, owing to the morphological similarities of nanofibers with extracellular matrix, biomaterials for wound healing and scaffolds for tissue engineering could be developed by

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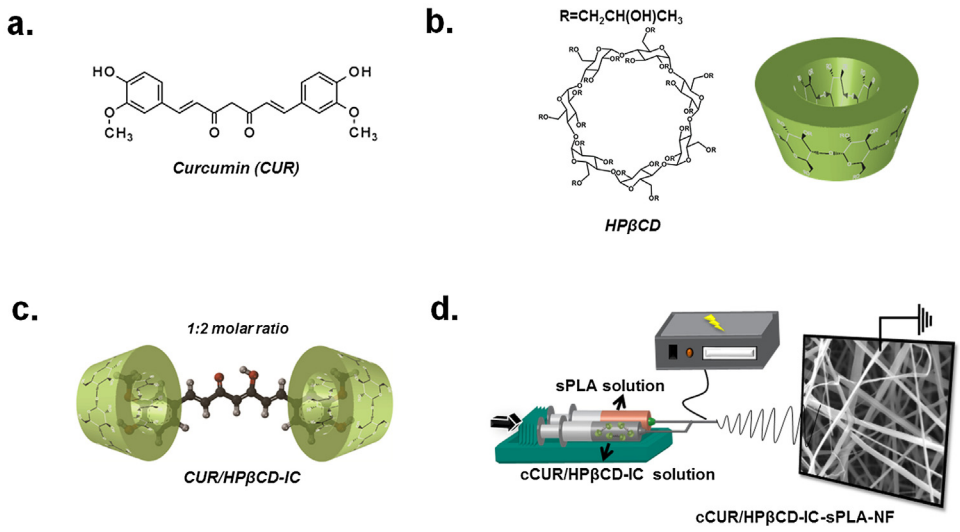

Fig. 1. (a) Chemical structure of CUR, (b) chemical structure and schematic representation of HPβCD; schematic representation of (c) formation of CUR/HPβCD-IC, and (d) electrospinning of core-shell nanofibers from cCUR/HPβCD-IC-sPLA solution.

using nanofibers (Greiner and Wendorff, 2007; Wendorff et al., 2012). Recently, there has been significant interest on electrospinning which is a simple and common technique for producing nanofibers (Greiner and Wendorff, 2007; Wendorff et al., 2012). Design flexibility of electrospun nanofibers facilitates the encapsulation of active agents for biomedical applications (Greiner and Wendorff, 2007; Wendorff et al., 2012). CUR loaded electrospun nanofibers were reported previously in the literature (Guo et al., 2011; Sampath et al., 2014; Suwantong et al., 2007). However, rather than loading free active agents into electrospun nanofibers, incorporating their CD-ICs is advantageous in many aspects as previously reported in the studies of our group. For instance, volatile molecules were highly preserved (Aytac et al., 2014; Kayaci et al., 2013a, 2014; Kayaci and Uyar, 2012; Uyar et al., 2009a, 2009b, 2011) and the solubility of hydrophobic molecules were improved (Aytac et al., 2015, 2016a, 2016b; Aytac and Uyar, 2016; Kayaci et al., 2013b) by CD-IC incorporated nanofibers. Sun et al. (2013) published a study concerning CUR/CD-IC loaded electrospun nanofibers (Sun et al., 2013). Faster release was seen from CUR/HPβCD-IC incorporated polyvinyl alcohol (PVA) nanofibers than CUR incorporated PVA nanofibers owing to the solubility enhancement and it is expected for CUR/HPβCD-IC incorporated PVA nanofibers to exhibit higher systemic bioavailability and enhanced in vivo efficacy. On the other hand, it is of great importance for some compounds to be protected against organic solvents, encapsulated in large amount and released in a more controlled manner. Due to the flexibility of the set-up, nanofibers with different morphologies such as core-shell, aligned and hollow nanofibers can be obtained via electrospinning (Ramakrishna et al., 2005). Particularly, electrospinning of core-shell nanofibers has several advantages such as possibility to electrospun nanofibers from non-spinnable solutions (Sun et al., 2003), protecting sensitive active agents against harsh environment of organic solvents (Jiang et al., 2014), controlling the release of active agents in a more efficient way due to the presence of shell acting as an additional layer (Jiang et al., 2005), encapsulating more than one drug at the same time (Llorens et al., 2015), designing active agent containing nanofibers for targeted release (Wang et al., 2015). In the study of Llorens et al. (2015), triclosan loaded poly(ethylene glycol) and CUR loaded poly(butylene succinate) solutions were used as core or shell solutions at different compositions. The release of triclosan and CUR were investigated in PBS and PBS/ethanol (30:70, v/v). CUR could not be released in PBS from all compositions because of its high hydrophobicity and interaction with poly(butylene succinate); whereas it was completely released in PBS/ethanol (30:70, v/v) (Llorens et al., 2015). Kumar et al. (2014) produced core-shell nanofibers by encapsulating CUR and 5-fluorouracil in the core and then, both core and shell polymers was crosslinked in type I nanofibers; whereas only shell was crosslinked in type II nanofibers. But, crosslinking of core and shell or only shell did not affect the release rate and amount of CUR in contrast to 5-fluorouracil (Kumar et al., 2014). In the study of Sedghi and Shaabani (2016) core-shell polymer-free core structure nanofibers was produced by using CUR solution in the core and PVA and chitosan in the shell. Although the burst release of CUR was prevented by core-shell nanofibers compared to blend nanofibers, core-shell nanofibers released less amount of CUR than blend nanofibers due to the low solubility of CUR in aqueous solutions (Sedghi and Shaabani, 2016).

In this study, core-shell nanofibers of CUR/HPβCD-IC (as a core) (Fig. 1c) and polylactic acid (PLA) (as a shell) which is an aliphatic polyester and widely used in biological applications due to its biodegradability and biocompatibility was produced via electrospinning (cCUR/HPβCD-IC-sPLA-NF) (Fig. 1d). As a control sample, CUR blended with PLA was also electrospun into nanofibers (PLA-CUR-NF). The molar ratio of the CUR:HPβCD inclusion complex was 1:2 and the phase solubility test confirmed the water solubility increase of CUR with the inclusion complexation. Core-shell morphology of cCUR/HPβCD-IC-sPLA-NF was confirmed by TEM and CLSM imaging. In vitro release of CUR from PLA-CUR-NF and cCUR/HPβCD-IC-sPLA-NF was tested in 0.1 N HCl (pH 1), PBS (pH 7.4), methanol, and methanol:water (1:1). The antioxidant activity of nanofibers was investigated by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay with respect to concentration and time.

2. Experimental

2.1. Materials

Polylactic acid (PLA) (Natureworks, product code 6252D) and hydroxypropyl-beta-cyclodextrin (HPβCD) (Wacker Chemie AG, Germany) was donated to our research group for laboratory studies. Curcumin (CUR, ≥95%, Alfa Aesar), zinc acetate dehydrate (Sigma Aldrich), fluorescein isothiocyanate (FITC, Sigma Aldrich), potassium phosphate monobasic (Sigma Aldrich), sodium