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Encapsulation of gallic acid/cyclodextrin inclusion complex in electrospun polylactic acid nanofibers: Release behavior and antioxidant activity of gallic acid

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ABSTRACT

Cyclodextrin-inclusion complexes (CD-ICs) possess great prominence in food and pharmaceutical industries due to their enhanced ability for stabilization of active compounds during processing, storage and usage. Here, CD-IC of gallic acid (GA) with hydroxypropyl-beta-cyclodextrin (GA/HPβCD-IC) was prepared and then incorporated into polylactic acid (PLA) nanofibers (PLA/GA/HPβCD-IC-NF) using electrospinning technique to observe the effect of CD-ICs in the release behavior of GA into three different mediums (water, 10% ethanol and 95% ethanol). The GA incorporated PLA nanofibers (PLA/GA-NFs) were served as control. Phase solubility studies showed an enhanced solubility of GA with increasing amount of HPβCD. The detailed characterization techniques (XRD, TGA and ^{1}H-NMR) confirmed the formation of inclusion complex between GA and HPβCD. Computational modeling studies indicated that the GA made an efficient complex with HPβCD at 1:1 either in vacuum or aqueous system. SEM images revealed the bead-free and uniform morphology of PLA/GA/HPβCD-IC-NF. The release studies of GA from PLA/GA/HPβCD-IC-NF and PLA/GA-NF were carried out in water, 10% ethanol and 95% ethanol, and the findings revealed that PLA/GA/HPβCD-IC-NF has released much more amount of GA in water and 10% ethanol system when compared to PLA/GA-NF. In addition, GA was released slowly from PLA/GA/HPβCD-IC-NF into 95% ethanol when compared to PLA/GA-NF. It was also observed that electrospinning process had no negative effect on the antioxidant activity of GA when GA was incorporated in PLA nanofibers.

1. Introduction

Phenolic compounds are the most common primary antioxidants to readily scavenge free radicals by donating hydrogen atom or an electron [1]. GA is a hydroxybenzoic acid and considered as a natural phenolic antioxidant and antimicrobial agent (Fig. 1a). GA and its derivatives including tannins and catechin are especially found in berries, citrus fruits, cereals, tea, wine and herbs [2]. Since it has antioxidant and antimicrobial activity, it is used as an additive in food, cosmetics and pharmaceutical industry [3–6]. However, it might easily oxidize which further leads to degradation. Cyclodextrin (CD) (Fig. 1b), as an enzyme-modified starch derivative, is nontoxic, biodegradable, and environmentally benign. CDs have truncated-cone shape structure with a lipophilic cavity (Fig. 1c). Due to the presence of cavity and high recognition ability of CDs toward various guest molecules, stable CD-inclusion complexes (ICs) can be obtained by nonpolar molecules. The driving forces of host-guest binding are mainly due to the release of enthalpy-rich water molecules from cavity and non-covalent interactions including van der Waals interactions, hydrogen bonding, and hydrophobic interactions [7]. Therefore CD-ICs are helpful in numerous areas for improving the stability against oxygen, temperature and light; the solubility, controlling the release of guest compounds, masking malodors [7]. In order to protect GA for degradation and maintain its bioactivity against external and environmental factors, CD-IC has been synthesized and considered to be an efficient system in recent years [8–9]. Therefore stabilization of GA might be improved by an encapsulation technique, inclusion complexation. CD-IC has gained great potential to enhance the shelf life of foods, increase the solubility of hydrophobic food additives and drugs and suppress unpleasant odors and tastes in food products and drug formulations even though there are many different commercial methods that are currently followed for the stabilization of chemicals.

Among nanofiber production methods, electrospinning has been recognized as simple and cost-effective method [10–12]. Various polymeric nanofibers have been already produced by using electrospinning technique. In addition to that, flexibility of this process enables to obtain nanofibers containing active agents which have potential to be used in diverse application areas [13–14]. Therefore, gallic acid encapsulated

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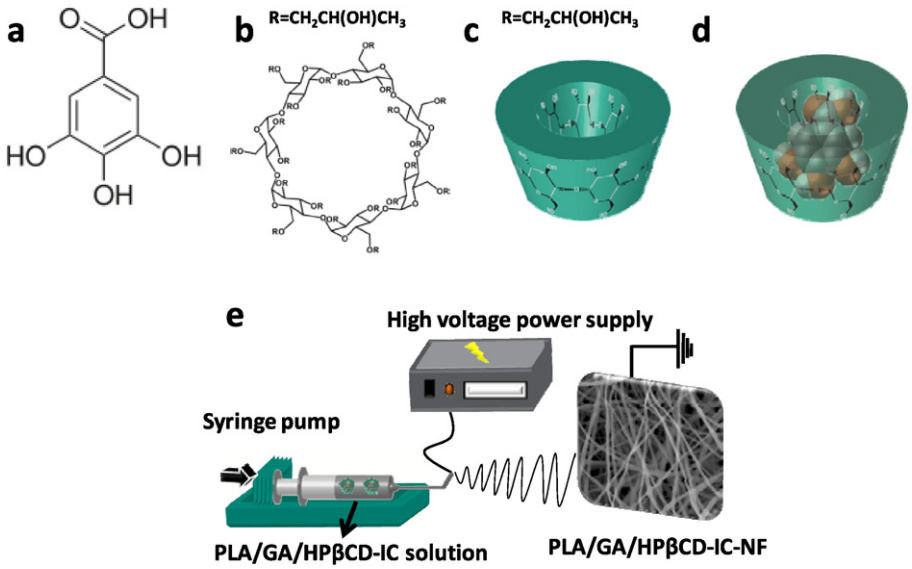

Fig. 1. Chemical structure of (a) GA, (b) HPβCD; schematic representation of (c) HPβCD, (d) the GA/HPβCD-IC formation and (e) electrospinning of nanofibers from PLA/GA/HPβCD-IC solution.

polymeric films and electrospun nanofibers have been studied previously [3,5,15–16]. CD-ICs can be incorporated into polymeric films and then CD-IC functionalized polymeric films might be used in food packaging and pharmaceutical applications [17]. However, designing delivery systems for food packaging and drug delivery applications by using nanofibers is advantageous over films owing to the high surface area and highly porous structure. In one of our study, sulfisoxazole (SFS)/CD-IC incorporated hydroxypropyl cellulose (HPC) nanofibers (HPC/SFS/CD-IC-NF) and films (HPC/SFS/CD-IC-film) were produced. The release of SFS was much more but slower from HPC/SFS/CD-IC-NF as compared to HPC/SFS/CD-IC-film. Low surface area of HPC/SFS/CD-IC-film and close location of SFS to the surface in HPC/SFS/CD-IC-film was stated the reason of less amount and quick release of SFS from HPC/SFS/CD-IC-film [18]. Polylactic acid (PLA) is a biodegradable aliphatic polyester produced from L-lactic acid and well suited for food packaging and drug delivery applications owing to its biocompatibility, biodegradability; carbon dioxide, oxygen and water permeability, and light barrier properties [19]. Leading studies related to incorporation of CD-IC of various guest molecules into electrospun nanofibers were reported by our research group [18,20–28].

In this paper, IC of GA and HPβCD (GA/HPβCD-IC) (Fig. 1d) was formed and then it was incorporated into PLA nanofibers (PLA/GA/HPβCD-IC-NF) by electrospinning technique (Fig. 1e). The prepared GA/HPβCD-IC was characterized by using phase solubility, X-ray diffraction (XRD), thermogravimetric analysis (TGA), and proton nuclear magnetic resonance (^{1}H NMR). Computational modeling studies were also performed to investigate complexation in vacuum and in aqueous system. GA incorporated PLA nanofibers without HPβCD (PLA/GA-NF) were taken as a control sample. The morphological characterization of PLA/GA-NF and PLA/GA/HPβCD-IC-NF were carried out by scanning electron microscope (SEM). The release of GA from PLA/GA/HPβCD-IC-NF and PLA/GA-NF was determined in aqueous solution, 10% ethanol, and 95% ethanol by high performance liquid chromatography (HPLC). The antioxidant activity of the GA presented in PLA/GA/HPβCD-IC-NF and PLA/GA-NF was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method.

2. Experimental

2.1. Materials

Polylactic acid (PLA) was donated by Natureworks (product code 6252D). Gallic acid (GA, ≥97.5–102.5%, Sigma Aldrich), hydroxypropyl-beta-cyclodextrin (HPβCD, Wacker Chemie AG, Germany), methanol (extra pure, Sigma Aldrich), ethanol (99.8%, Sigma Aldrich), dichloromethane (DCM, extra pure, Sigma Aldrich), N,N-dimethylformamide (DMF, ≥99%, Sigma Aldrich), acetonitrile (ACN, chromasol, Sigma Aldrich), deuterated dimethylsulfoxide (DMSO-d6, deuteration degree min 99.8% for NMR spectroscopy, Merck), and 2,2-diphenyl-1-picrylhydrazyl (DPPH, Sigma Aldrich) were purchased and used as-received without any further purification. Distilled–deionized water was supplied from Millipore milli-Q ultrapure water system.

2.2. Preparation of inclusion complex (IC) and physical mixture (PM) of GA and HPβCD (GA/HPβCD-IC and GA/HPβCD-PM)

The formation of solid GA/HPβCD-IC was prepared according to slurry method. Initially, GA was dissolved in aqueous solution; then HPβCD was added and the mixture was stirred for 120 min at 70 °C. The mixture was kept in hood for 2 days and the resulting white powder was crashed in agate mortar. The molar ratio of GA:HPβCD was used as 1:1. GA/HPβCD-PM was obtained by mixing GA and HPβCD in a glass mortar at a molar ratio of 1:1.

2.3. Preparation of electrospinning solutions

Free GA and GA/HPβCD-IC incorporated PLA nanofibers (PLA/GA-NF and PLA/GA/HPβCD-IC-NF) were produced via electrospinning technique. For this purpose, Free GA (5%, w/w, with respect to polymer) was dissolved in DCM:DMF (7:3) at room temperature (RT). Then, 10% PLA (w/v) was added and PLA/GA solution was stirred for 120 min before electrospinning. With regard to PLA/GA/HPβCD-IC-NF, GA/HPβCD-IC (5% GA, w/w, with respect to polymer) was dispersed in DCM:DMF (7:3) at RT. Afterwards, 10% PLA (w/v) was added, PLA/GA/HPβCD-IC solution was stirred 120 min prior to electrospinning. The vials were covered with a piece of aluminum foil during stirring to avoid any potential light effect for GA. As a reference sample, we have also electrospun 10% PLA solution (w/v) prepared in DCM:DMF (7:3). Table 1 summarizes the composition of the PLA, PLA/GA and PLA/GA/HPβCD-IC solutions and the morphological findings of PLA-NF, PLA/GA-NF and PLA/GA/HPβCD-IC-NF.

2.4. Electrospinning

PLA, PLA/GA and PLA/GA/HPβCD-IC solutions loaded into 3 ml plastic syringe with a needle inner diameter of 0.8 mm were placed horizontally