Journal of Drug Delivery Science and Technology 44 (2018) 482–490

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

# Protection of conjugated linoleic acid into hydrophobic/hydrophilic electrospun fibers

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ARTICLE INFO

*Keywords:*
Electrospinning
Cellulose acetate
Conjugated linoleic acid
Liposomal emulsions

ABSTRACT

Conjugated linoleic acids (CLA) as essential fatty acids (EFAs) have shown medical significance towards wound healing process. However, EFAs whose chemical structures possess unsaturated double bonds are unstable to environmental degradation. Encapsulation of EFAs into protective layer was the basic approach to avoid such degradation.

In this work, CLA was extracted from sunflower oil, purified and characterized by spectral analysis. CLA was loaded into two different substrates namely hydrophobic, cellulose acetate (CA), and hydrophilic, liposomal emulsions of poly (vinylalcohol) (PVA) and gelatin, polymers. Electrospinning parameters were optimized to obtain clear, smooth and bead-free fibers. 12 % wt/v of CA shows bead-free fibers with diameter in range of 440-300 nm loaded with CLA up to 26% wt/wt. While, CLA (3% wt/wt) is encapsulated into the liposomal emulsions of PVA and gelatin with average fiber diameters 252-400 nm and 120-200 nm respectively. The CLA encapsulation, morphology of the electrospun fibers, and fiber diameter were examined using scanning electron microscopy (SEM). Viscosity and conductivity of the prepared solutions for electrospinning were demonstrated. Biocompatibility was evaluated by measuring cell proliferation of skin fibroblast cells. The release profile was investigated by UV- Visible spectroscopy. CLA loaded into the electrospun showed lower peroxide values (PV) of CLA.

## 1. Introduction

Fatty acids, the main component of oils and fats, are chemically composited of esterified glycerol of aliphatic carboxylic acids with chain length spans from $C_4$ to $C_{22}$ while the $C_{18}$ is the most common chain length [1]. Essential fatty acids (EFA) especially linoleic acid and its isomers have shown medical significance towards wound healing process. In specific, EFA are required to maintain the water barrier in the skin [2], control the functions of neutrophils (most abundant type of white blood cells) by providing a slight acidity to the wound bed [3] and to inhibit the malfunctioned digestive enzymes [4,5]. Moreover, it has been reported that CLA inhibits the proliferation of human malignant melanoma, colorectal and breast cancer cells [6]. However, EFA whose chemical structures possess unsaturated double bonds are very sensitive to react with oxygen in air and decompose to release numbers of volatile ketones, aldehyde and peroxides [7]. The general process of EFA oxidation starts with the abstraction of hydrogen atom from a methylene group to create an unpaired electron on the carbon atom. This active side reacts with oxygen to produce fatty acid peroxyl radical that turns to hydroperoxides which is susceptible to reductive cleavage [8].

Basic thought to come over the above problem proposed the utilization of the encapsulation technique to enhance the stability of EFA and to control their release profiles [7,9–12]. Oil nature compounds can be encapsulated either in hydrophobic matrices using common solvents or in hydrophilic matrices by using emulsion techniques. Both techniques can encapsulate oils in form of capsules [13], fibers [12] or even emulsions [14–17]. Also, supportive compounds have been used to facilitate the EFA encapsulation such as alpha, beta and gama cyclodextrins (CDs). In this sense, Kim [6] et al., reported that alpha CDs microspheres at 1:4 mol ratio could protect linoleic acid from oxidation.

Recently, electrospinning technology [18] is emerged in many different applications [19] such as encapsulation processes in which polymers can be produced in micro/nano-sized structures in form of fibers or beads [7]. Such forms possess high surface area [20] and capability to encapsulate different active substances in order to provide protection from environmental degradation.

Although new electrospinning processes, such as coaxial [21], side-

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https://doi.org/10.1016/j.jddst.2018.02.002
Received 22 October 2017; Received in revised form 26 January 2018; Accepted 7 February 2018
Available online 08 February 2018
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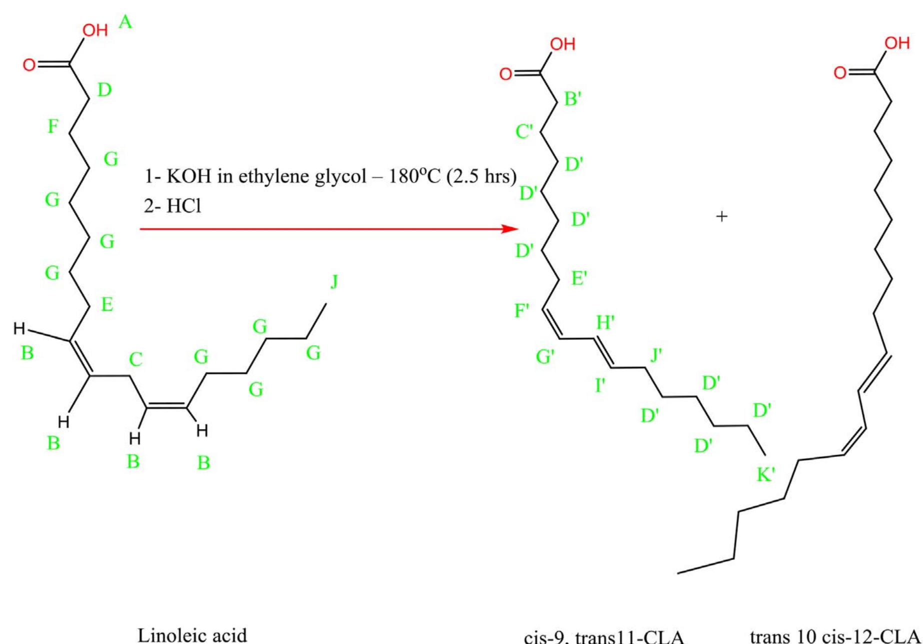


**Fig. 1.** Synthesis of conjugated linoleic acid; cis-9, trans 11 CLA and trans-10, cis-12 CLA.

by-side [22] and tri-axial [23], have been successively reported, the mainstream remains the single-fluid electrospinning process, which provides the most facile manner in generating nanofibers [24]. More recently, two-phase electrospinning technique has been emerged by employed emulsions as electrospinable solutions [14].

In the present work, encapsulation of CLA into electrospun fibers is the approach to protect CLA from environmental degradation and control its release. The CLA was extracted from sunflower oil, purified and characterized by spectral analysis. CLA was encapsulated into cellulose acetate (CA) as a hydrophobic substrate. Also, new electrospun fibers of CLA encapsulated into liposomes macrostructure of gelatin and poly (vinyl alcohol) were produced.

The CLA encapsulation, morphology of the electrospun fibers, and fiber diameter were examined using scanning electron microscopy (SEM). Viscosity and conductivity of the prepared solutions for electrospinning were demonstrated. Biocompatibility was evaluated by measuring cell proliferation and metabolic activity of skin fibroblast cells seeded onto the electrospun mats. The release profile was investigated by UV- Visible spectroscopy. CLA protection was demonstrated by measuring the peroxide values before and after encapsulation after six months.

## 2. Materials and methods

Cellulose acetate (CA) Molecular weight 30000 Da with degree of substitution 2.4, acetone, dimethyacetamide (DMAc), ethanol, ethyl acetate (EtOAc), sodium hydroxide (NaOH), hydrochloric acid (HCl), Dimethyl sulfoxide (DMSO) and deuterated chloroform were purchased from Sigma and were used throughout this research without further purification. Gelatin powder (type A), glacial acetic acid (99%) and poly (vinyl alcohol) Mw 89,000-134,000, 99+% hydrolyzed were purchased from Sigma-Aldrich. Sunflower seed oil is generously gifted from Fats and Oils department of Food Industry and Nutrition division at NRC. Flourescein dye was purchased from ACROS Organics (Fisher Scientific).

### *2.1. Extraction of linoleic acid (LA) from safflower oil*

100 g sunflower seed oil, generously gifted from Fats and Oils department of Food Industry and Nutrition division at NRC, (SSO) dissolved in 250 mL ethyl alcohol is saponified by adding 50 g of potassium hydroxide (KOH) to the mixture with constant stirring for 1 h at 180 °C under reflux using silicone oil bath. Fatty acids were then liberated with dropwise addition of 6N hydrochloric acid (HCl) with slowly stirring at 80 °C for 30 min. An aqueous layer was siphoned off while the oily layer was washed with salty hot water several times to remove the excess of acid. Final product was dried over night using sodium sulfate, and the solvent (n-Hexane) was evaporated at 50 °C using vacuum evaporator.

### *2.2. Purification of fatty acids via urea complexes*

Urea (160g) was added to the (80g) LA-SSO dissolved in (300 mL) ethanol, followed by refluxing for 60 min at 150 °C using silicone oil bath. The mixture was then stored overnight at 4 °C to produce urea adducts which were removed by filtration. The filtrate was dried under vacuum and the residue was re-dissolved in (300 mL) hexane. The hexane was washed three times with salty hot water and the moisture was removed by using anhydrous sodium sulfate ($Na_2SO_4$). Finally, the hexane is removed under vacuum to obtain 66.5 g pure LA (83% yield) [25].

### *2.3. Synthesis of conjugated linoleic acid (CLA)*

In the typical procedure, potassium hydroxide (26g, 0.46mol) was added to a stirred solution of ethylene glycol (100g, 1.6mol). Nitrogen was bubbled into ethylene glycol and KOH mixture for 20 min, and the temperature is then raised to 180 °C using silicone oil bath. Freshly prepared LA (50g, 0.18mol) then was added dropwise to the mixture and after 2.5 h the reaction mixture was cooled to ambient temperature. 30 mL of HCl was added to the mixture which is stirred for 15 min. The pH of the mixture was adjusted to pH 3 and then 200 mL water was added to the mixture. The product was isolated by extraction with 500 mL of hexane. The hexane was washed three times with water and the moisture was removed by using anhydrous sodium sulfate ($Na_2SO_4$). Finally, the hexane is removed under vacuum to obtain CLA [25–30]. The differences between linoleic acid and its conjugated isomers are shown in Figure (1).

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