Ultrasonics - Sonochemistry 40 (2018) 402–409

Contents lists available at ScienceDirect

Ultrasonics - Sonochemistry

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

Ultrasonic-assisted fabrication of starch/MWCNT-glucose nanocomposites for drug delivery

Shadpour Mallakpour[a,b,c,*], Leila khodadadzadeh[c]

[a] Organic Polymer Chemistry Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156-83111, Islamic Republic of Iran
[b] Nanotechnology and Advanced Materials Institute, Isfahan University of Technology, Isfahan 84156-83111, Islamic Republic of Iran
[c] College of Pardis, Chemistry Section, Isfahan University of Technology, Isfahan 84156-83111, Islamic Republic of Iran

ARTICLE INFO

Keywords:
Multi-walled carbon nanotubes
Biofunctionalization
Sonication
Starch
Nanocomposites
Drug delivery

ABSTRACT

The principal focus of this investigation is to prepare starch nanocomposite (NC) films containing multi-walled carbon nanotube (MWCNT) and apply these NCs for drug delivery. Firstly, to raise the hydrophilicity of carboxyl functionalized MWCNT, the surface of them was modified with D-glucose (Gl) as a low cost and environmentally friendly biomolecule. Different percentages of MWCNT-Gl (0.5, 1 and 2 wt%) were embedded in starch matrix through sonochemical method as an economical, fast, eco-friendly, and effective method. The properties of starch/MWCNT-Gl NCs were characterized using Fourier transform infrared spectroscopy, X-ray diffraction, thermogravimetric analysis, field emission scanning electron microscopy and transmission electron microscopy (TEM). Afterwards, pure starch and starch/MWCNT-Gl NCs were reacted with oleic acid to obtain amphiphilic (Amph) esters. Except Amph obtained from pure starch, other Amph esters could convert to drug-loaded nanoparticles which were characterized by dynamic light scattering and TEM. The sizes of nanoparticles depended on the value of MWCNT-Gl. The thinnest particles obtained from starch/MWCNT-Gl NCs containing the highest value of MWCNT-Gl (2 wt%), and this system was chosen for measurement of entrapment efficiency, loading capacity and *in vitro* release study for zolpidem as a hydrophobic drug model.

1. Introduction

Among nanofillers (NF)s for the preparation of polymer nanocomposites (NC)s, carbon nanotube (CNT) has attracted very great interest since the discovery of it in 1991 by Ijima [1]. CNTs are highly capable in advancing the NC properties by cause of their greatly good mechanical, thermal and other useful properties [2,3] and resulting NCs exhibit potentially better properties than the pure polymer [4,5]. In addition to being a NF for NCs, CNT can be applied in many other fields such as drug delivery [6,7], hydrogen storage [8] and chemical sensor [9,10]. On the other hand, use of CNT as a raw material has been mainly restricted due to the aggregation of nanotubes caused by van der Waals force between them [11]. Therefore, native CNTs have poor solubility and biocompatibility with polymers. This despite the fact that, the dispersion state of NFs and their interaction with the polymer matrix are important factors in the final performance of polymer NCs [12]. Introduction of polar functional groups into the CNTs is a commonly applied methodology to solve the above mentioned problems [13,14]. More effective modification process which incorporates some small organic molecules and macromolecules to CNT have been reported too. For example, Mallakpour and Madani used biomolecules such as vitamin C, aminoacids and carbohydrates [15,16] for further modification of carboxyl functionalized MWCNT (MWCNT-COOH) and incorporated these fillers with the weight percentages of 3, 5 and 7 wt% into the chitosan matrix without considerable aggregation while when MWCNT-COOH without further modification was used, they aggregated at weight percentages higher than 1 wt% [17]. To further ease CNT modification and its applications, some approaches such as sonication [18–20] and microwave-assisted [21,22] have been reported for both chemical and non-chemical modification of CNT.

Main techniques for the fabrication of polymer/CNT NCs are in situ polymerization, melt mixing, and solution mixing [23] which the latter is the most common method. Using little amounts of CNT as well as high interface areas are two main parameters needed to optimize the act of polymer/CNT NCs. So the main focus is on “breaking” the CNT bundles and incorporation of individualized CNT into the matrix. To overcome this problem, sonication is an effective technique that conforms the aims of green chemistry [18]. It has been used for the uniform distribution of other NFs in polymer matrix too and causes to energy and cost saving [24–31]. The effects of ultrasound results from acoustic

* Corresponding author at: Organic Polymer Chemistry Research Laboratory, Department of Chemistry, Isfahan University of Technology, Isfahan 84156-83111, Islamic Republic of Iran.
E-mail addresses: mallak@cc.iut.ac.ir, mallak777@yahoo.com, mallakpour84@alumni.ufl.edu (S. Mallakpour).

http://dx.doi.org/10.1016/j.ultsonch.2017.07.033
Received 20 March 2017; Received in revised form 22 July 2017; Accepted 23 July 2017
Available online 24 July 2017

cavitation, which is the fast generation, growth, and finally implosive collapse of bubbles in liquid that the latter produces enormous heat (up to 5000 K) and pressure (up to 20 MPa) just in a very short time [32].

To overcome the disadvantages of petrochemically polymers [33], natural polymers have been used in many fields in recent decades. Starch is a biodegradable and biocompatible polymer which has been applied in many important non-food applications such as drug delivery [34–37]. Starch nanoparticles [38], blend of starch with other polymers [39], and starch graft copolymers [40] have used for drug delivery. Starch also used as matrix and incorporated with different fillers to produce polymer NCs [41,42]. Furthermore, combination of MWCNT-COOH with glycerol-plasticized (GP) starch to prepare starch/CNT NCs has been reported for different applications. Ma et al. [43] combined GP-corn starch with MWCNT-COOH to produce electroactive polymers. Swain et al. [44] prepared GP-rice starch/MWCNT-COOH NCs as a gas barrier material. Fama et al. [45] incorporated MWCNT-COOH into the GP-topica starch and NCs with water resistant properties obtained.

Polymer NCs have a remarkable potential for drug delivery [46]. NCs containing degradable [47] and non-degradable [48] polymers consisted of clay [49], hydroxyapatite [50], layered double hydroxide [51], graphene oxide [52], CNT [53] and etc. have been used for drug delivery. To the best of our knowledge, starch/CNT NCs have not been used for drug delivery and in this work we investigated the drug delivery ability of starch/CNT NC for a hydrophobic drug model. Firstly, to improve dispersion of MWCNTs in starch, surface modification with D-glucose (Gl) as a low cost and environmentally friendly biomolecule was done in water media. Then, different percentages of MWCNT-Gl (0.5, 1 and 2 wt%) were distributed into water-plasticized corn starch as matrix through sonochemical method as an economical, fast, eco-friendly, and effective method. The properties of starch/MWCNT-Gl NCs were examined by Fourier transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), thermogravimetric analysis (TGA), field-emission scanning electron microscopy (FE-SEM), and transmission electron microscopy (TEM). Afterwards, both pure starch and starch/MWCNT-Gl NCs were reacted with oleic acid to prepare amphiphilic (Amph) esters which were used to prepare drug-loaded nanoparticles. Nanoparticles were only formed in the presence of MWCNT-Gl and they characterized by dynamic light scattering (DLS) and TEM. The thinnest nanoparticles were obtained from starch/MWCNT-Gl 2 wt% (highest amount of MWCNT-Gl) which were used to investigate the entrapment efficiency (EE), loading capacity (LC) an *in vitro* release behavior of zolpidem (ZM) (anti-insomnia) as a hydrophobic drug model.

2. Experimental

2.1. Chemicals

MWCNT-COOH was achieved from Neutrino Co. (Iran). The length of nanotubes was approximately 30 μm. Also, the outer and inner diameters of them were 8–15 and 3–5 nm, respectively. Gl and N,N′-carbonyldiimidazole (CDI) were bought from Merck Chemical Co. (Germany). Corn starch (formula weight: $(162.5)_n$, formula: $(C_6H_{10}O_5)_n$, density (g/ml): 1.45–1.6), oleic acid, dimethylsulfoxide (DMSO), acetone and ZM tartarate were purchased from SK-ScienceKit (Tonawanda NY 14150, USA with the product code of 81460-03), DAE JUNG (China), Riedel-de Haen (Germany), Sasol Middle East (Dubai) and Sigma-Aldrich, respectively.

2.2. Methods

2.2.1. Modification of MWCNT with Gl

According to our previous work, MWCNTs were functionalized with Gl [54]. Briefly, after sonication of MWCNT-COOH in distilled water, CDI as catalyst was added and the suspension was agitated at room temperature (RT). After that, Gl was added to the mixture and allow mixing at RT again. The obtained suspension was sonicated by TOPSONIC homogenizer ultrasonic liquid processor (Tehran, I. R. Iran, frequency of 20 kHz and power of 100 W), for 1 h (20 kHz frequency and 80 W power) and then filtered and washed with deionized water. Finally MWCNT-Gl was achieved after drying.

2.2.2. Starch/MWCNT-Gl NCs fabrication

Starch/MWCNT-Gl NCs 0.5, 1, and 2 wt%, (relative to the polymer weight), were synthesized as follow: At first, 0.2 g of corn starch was dispersed in 10 mL cold water. Then, the required MWCNT-Gl (1, 2 and 4 mg) was added and allowed stirring, first for 1/2 h at RT and then 1/2 h at 90–100 °C. Afterwards, the hot suspension suffered sonication process. The ultrasonic probe was directly immersed in the suspension of starch and MWCNT-Gl. Then the power of instrument was changed from 40 to 80 W (40, 50, 60, 70 and 80 W) and the power of 80 W was chosen as optimized power because a little aggregation of MWCNT-Gl was observed yet in lower power. To choose the optimized time for the preparation of starch/MWCNT-Gl NCs, the time of sonication was changed from 5 to 25 min (5, 10, 15 and 25 min) and the time of 15 min was selected because at lower time (5 and 10 min) the dispersion of MWCNT-Gl in starch was not uniform and by increasing the time from 15 to 25 min no changes were observed. Finally, after 15 min sonication of suspension, it poured onto a plastic petri dish and brittle films of starch/MWCNT-Gl NCs were obtained after drying first at 60 °C for 24 h and then at 120 °C for 8 h.

2.2.3. Reaction of pure starch and starch/MWCNT-Gl NCs with oleic acid to make Amph starch esters

Corn starch consists of 24.4% amylose and 75.6% amylopectin. At first, 0.1 g of pure corn starch and each starch/MWCNT-Gl NCs (0.1 g of NCs 0.5, 1 and 2 wt% contained 0.5, 1 and 2 mg of MWCNT-Gl, respectively) were dissolved in 0.5 mL of DMSO with the aid of heating and in different vials. 0.5 g of oleic acid [34] and CDI as a catalyst (for activating acidic groups) were added to each vial. The mixtures were sonicated for 30 min. Then they were stirred at 140 °C for 15 h. When the reactions were completed, ethanol was added in each case, and the precipitated Amph esters (Amph (1): from pure starch, Amph (2): from NC 0.5 wt%, Amph (3): from NC 1 wt%, and Amph (4): from NC 2 wt%) were achieved after filtering and washing with ethanol followed by drying at 100 °C.

2.2.4. Preparation of drug-loaded nanoparticles

Loading the ZM (drug) into nanoparticles was done by dialysis bag technique. In this method, after dissolving polymer and drug in water-miscible organic solvent and dialyzing against water, slow removal of solvent causes to formation of nanoparticles. For this purpose, Amph (1–4) (10 mg) and ZM (4 mg) were dissolved in 3 mL of DMSO and sonicated for 15 min (20 KHz frequency and 80 W power). Then, the solution was poured into a dialysis tube (MWCO = 12 kDa), which was fasten and then dialyzed in 1000 mL distilled water. The complete procedure took long for 24 h, and the solution was exchanged with fresh water every 1 h throughout the beginning 10 h to remove the free ZM. Then, ZM-loaded nanoparticles was lyophilized before examinations. It's noteworthy that during the preparation of drug-loaded nanoparticles from Amph (1) which had no MWCNT-Gl, some precipitations observed in the dialysis tube that indicated nanoparticles could not be made while in terms of other Amph (2, 3 and 4) containing MWCNT-Gl, no precipitations were observed.

2.2.5. EE, LC and in vitro release study

To measure the EE and LC, the lyophilized ZM-loaded nanoparticles (4) was dissolved in DMSO and examined by UV absorbance at 242.5 nm using a standard calibration curve.

The *in vitro* release behavior of encapsulated ZM from nanoparticles was monitored using the diffusion technique. According to this technique, 6 mL of ZM-loaded nanoparticle (4) was flowed into a dialysis tube (MWCO = 12 kDa) which was fasten and soaked in 30 mL of