Composites Part B xxx (2017) 1–9

Contents lists available at ScienceDirect

Composites Part B

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

Fabrication of monodisperse drug-loaded poly(lactic-co-glycolic acid)—chitosan core-shell nanocomposites via pickering emulsion

Jiaxin Wang [a], Wing-Cheung Law [a, *], Ling Chen [a], Dazhu Chen [b], Chak-Yin Tang [a]

[a] Department of Industrial and Systems Engineering, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China
[b] College of Materials Science and Engineering, Shenzhen University, Shenzhen, Guangdong, China

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Pickering emulsion
PLGA
Chitosan
Drug delivery
High intensity ultrasonication

ABSTRACT

Pickering emulsion, in which the oil—water emulsion interface is stabilised by colloids, has emerged as a promising approach for the preparation of drug delivery systems in the biomedical field. In this study, Pickering emulsion and solvent evaporation were incorporated with high-intensity ultrasonication to successfully fabricate biodegradable poly(lactic-co-glycolic acid) (PLGA)—chitosan core-shell nanocomposites (PLGA-CS) with a narrow size distribution. Our strategy was based on using aqueous-phase chitosan colloids to stabilise the hydrophobic PLGA core without the addition of molecular surfactants or chemical cross-linkers. The use of high-intensity ultrasonication was found to facilitate the efficient dispersion of emulsion droplets so that the particle size of PLGA-CS (255.1—824.8 nm) could be controlled with the application of different amplitudes. A low amplitude (20% of total power) enables the formation of drug-loaded PLGA-CS with a small diameter (255.1 nm) and a high level of monodispersity (polydispersity index, 0.078). The PLGA core allows hydrophobic drugs to be loaded and is encapsulated in a chitosan shell that offers two functions: (i) dispersion of PLGA in an aqueous solution and (ii) modulation of in vitro drug release. Our results reveal that the modified strategy shows promise for the design and preparation of monodisperse polymer-based drug carriers.

1. Introduction

Composite systems based on biodegradable and natural materials have been extensively studied for their outstanding characteristics and great potential in the design and fabrication of drug delivery systems (DDSs) [1—13]. A variety of strategies, including spray drying, layer-by-layer assembly and emulsification, have been developed to fabricate particulate vehicles with different structures [14—18]. With their extensive adoption as the building blocks of DDSs, biodegradable polymers have attracted considerable attention for their versatility, such as the ability to tailor the drug release profile by manipulating degradability under different environmental conditions (e.g., pH and temperature) [19,20]. Special interest has been shown in the development of different synthetic approaches for biodegradable polymeric particulate DDSs, as one of the most feasible structures for drug carriers, to integrate drug loading, imaging and bioconjugation into one system to overcome current challenges such as non-targeted, poor drug solubility and burst-release of the drug [21].

Emulsion solvent evaporation has proven to be one of the most efficient fabrication techniques for particulate DDSs. However, large amounts of chemical residues and tedious procedures are usually required for emulsion preparations [22]. Especially with the use of toxic surfactant molecules in the emulsion systems, the by-products can lead to severe environmental problems or even alter the pharmacokinetics of the administered drugs [23]. Recently, Pickering emulsion, which applies colloidal stabilisers instead of molecular emulsifiers, has been seen as a powerful technique to address these problems [24—27]. The use of colloids as particulate emulsifiers facilitates distinctive physical stability by forming a strongly adsorbed steric barrier [26,28]. Its significant advantages over conventional surfactant-based emulsion systems include good reproducibility, facile and scalable productivity and better biocompatibility [27]. Hence, it has been used in a wide range of applications including food science [29], pharmaceuticals and DDSs [30].

Different classes of particles such as silica, apatite, carbon nanotubes, cellulose, and microgels have been demonstrated as effective Pickering emulsifiers [25]. Nevertheless, most previous

* Corresponding author.
E-mail address: roy.law@polyu.edu.hk (W.-C. Law).

http://dx.doi.org/10.1016/j.compositesb.2017.03.032
1359-8368/

investigations were concentrated on the fabrication of inorganic or inorganic/organic systems [27]. For example, drug-carrying PLGA microspheres were prepared with SiO_2 nanoparticles as the stabilisers [31]. Although model drugs can be loaded into the systems, the hydrophobicity of PLGA may cause the bare DDSs to be recognised as foreign by the human body such that the drug delivery process would be aborted before the targeted sites are reached because the drug is eliminated from the bloodstream and taken up in the liver or spleen [17]. Moreover, the use of hydrofluoric acid to acquire PLGA microspheres is likely to lead to decomposition of the drug [32]. The limitations could be overcome by modifying the surface of the PLGA particles with muco-adhesive polymers by encapsulating the hydrophobic particles with a hydrophilic coating. Nevertheless, few studies have attempted to use Pickering emulsion to prepare biodegradable core-shell particles for controlled drug delivery [27,31,33,34].

Chitosan colloids are an emerging class of effective biodegradable stabilisers [24,33,35]. Chitosan is a natural cationic polysaccharide and the world's second most abundant biopolymer [36]. As a linear polysaccharide, chitosan is composed of randomly distributed deacetylated units (β-(1-4)—linked $_D$-glucosamine) and acetylated units (*N*-acetyl-$_D$-glucosamine) [37]. This chemical structure enables chitosan to demonstrate a pH-tuneable sol-gel transition based on its acid dissociation constant ($pK_{a,\ CS}$). Because they are soluble at pH values of less than $pK_{a,\ CS}$ (6.5) but insoluble at pH values of less than $pK_{a,\ CS}$ [36], chitosan molecular aggregates form as colloidal particles at a high pH value (i.e., $>pK_{a,\ CS}$) and are thereafter capable of functioning as particulate emulsifiers in the formation of Pickering emulsions [35]. In contrast, as coating materials for modification of the surfaces of particles with hydrophobic surfaces, a chitosan muco-adhesive polymer can provide complementary advantages: (i) the tuneable degradability can be used to modulate the encapsulated drug's release rate, (ii) the cationic surface of chitosan promotes cellular adhesion and retention of the delivery system at the target site, and (iii) the free functional groups confer the capability of conjugating targeting ligands [37,38]. As a kind of soft materials, polymeric colloids have arisen as one of the most rapidly advancing stabilisers of emulsions due to their versatility compared to solid particles [35,39,40]. A variety of studies have been recently conducted from the aspects of the emulsification process and the material properties to clarify its underlying mechanism [41,42]. Driven by its great potential in biomedical applications, various composite systems for drug delivery based on Pickering emulsions stabilised by polymeric colloids have been intensively studied. Recently, the use of chitosan colloids prepared via sol-gel transition without any hydrophobic modification or combination with other surface active agents has been reported as a particulate stabiliser for the fabrication of chitosan-coated PLGA microcapsules [34]. However, the demand for monodisperse polymeric systems composed of biodegradable polymers with tuneable size ranges on the nanoscale via such an attractive strategy has remained unfulfilled.

It is noteworthy that many polymeric particulate DDSs produced with Pickering emulsion had micron sizes [27]. In fact, particles on the nanoscale possess many advantages such as the ability to effectively realise targeted delivery, which is difficult with micron-sized DDSs [43]. For instance, the therapeutic effect can be enhanced by targeting delivery through their enhanced permeation and retention effect, which is highly size-dependent (approximately 60—400 nm) [44], via oral administration [45]. New approaches have been developed for nano-preparation. For example, microfluidics and membrane emulsification techniques have revealed their differences from bulk emulsification techniques for preparation of nanoparticles based on Pickering emulsions [27]. However, such techniques are intrinsically limited by their poor production efficiency and by the restrictions of specified devices and equipment. Therefore, the need to develop general-use fabrication methods for preparation of uniform particulate systems via Pickering emulsion is urgent for its broad scope of applications [25,27,39].

In this study, to address these problems, a modified fabrication method based on Pickering emulsion and solvent evaporation was proposed. The high-intensity ultrasonication (HIU) as a cost-effective technique has been successfully applied in oil-in-water (O/W) Pickering emulsion for the preparation of PLGA-CS core-shell DDSs in which the PLGA core was stabilised by chitosan colloids formed by sol-gel transition. Monodisperse PLGA-CS was facilely fabricated and loaded with a model drug (ibuprofen) by solvent evaporation and polymer precipitation under mild conditions. The narrow size distribution of PLGA-CS can be attributed to the stable emulsion with small droplets produced by HIU. The influence of HIU conditions on the formation of solid particles was investigated in terms of size distribution, zeta potential and scanning electron microscope (SEM) observations to provide fundamental information for the preparation of nano-particulate core-shell DDSs with a narrow size distribution via this modified Pickering emulsion.

2. Material and methods

2.1. Materials

Chitosan with molecular weights (M_w) of 50,000 and 500,000 (degree of deacetylation $\geq$ 95%) and with M_w of 3000—6000 (degree of deacetylation $\geq$ 90%) were purchased from HeFei BoMei Biotechnology (China). PLGA 50:50 (M_w = 50,000) was obtained from Jinan Daigang Bio-Technology (China), ibuprofen was purchased from Wuhan Biocar Bio-Pharmaceutical, dichloromethane (CH_2Cl_2) was purchased from Sigma Aldrich, acetic acid (AA) and sodium hydroxide (NaOH) were supplied by the International Laboratory (United States), and ethanol was purchased from Merck. All chemicals and reagents were of analytical grade and used without further purification. The water used in all experiments was purified by deionisation and filtration with a Millipore purification apparatus to a resistivity greater than 18.0 MΩ cm.

2.2. Fabrication of chitosan colloids

Chitosan colloids were prepared by dissolving the chitosan powder in a 1% (v/v) aqueous solution of AA to form chitosan solutions with magnetic stirring at a rate of 600 rpm for 12 h and stored overnight to allow complete hydration and dissolution. The pH of the chitosan solutions was adjusted to 6.5 with NaOH solutions (1 M) and stirred at 600 rpm for 15 min. HIU-treated chitosan solutions at a pH of 6.5 were produced with a high-intensity ultrasonic processor (SKL-250W, Ningbo HaiShu Sklon Electronic Instrument Co) equipped with an ultrasonic probe (SKL-IIN, φ 6), under 40% amplitude for 8 min, using an ice bath to avoid overheating during the ultrasonication (Scheme 1). The concentrations of the prepared chitosan colloidal solutions were 0.1% w/v. Unless otherwise specified, all chitosan colloids were prepared under the same conditions, and the HIU treatments were conducted with the same equipment as described above.

2.3. Fabrication of chitosan colloid-stabilised emulsion

Oil-in-water (O/W) emulsions stabilised by HIU-treated chitosan colloidal particles were prepared by mixing 0.1% w/v chitosan colloidal solution with 2% w/w PLGA/CH_2Cl_2 at an oil volume fraction (Φ) of 0.05, with magnetic stirring for 15 min at 600 rpm.

Please cite this article in press as: Wang J, et al., Fabrication of monodisperse drug-loaded poly(lactic-co-glycolic acid)—chitosan core-shell nanocomposites via pickering emulsion, Composites Part B (2017), http://dx.doi.org/10.1016/j.compositesb.2017.03.032