Vacuum 107 (2014) 208–212

Contents lists available at ScienceDirect

Vacuum

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

Effect of a surface stabilizer on the formation of polyoxalate nanoparticles and their release profiles

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ARTICLE INFO

Article history:
Received 13 October 2013
Received in revised form
11 February 2014
Accepted 14 February 2014

Keywords:
Polymeric nanoparticles
Surface stabilizer
Emulsion
Drug release
Polyoxalate

ABSTRACT

Biodegradable polyoxalate nanoparticles coated with polymeric surface stabilizer were successfully fabricated using an emulsion method. A series of biocompatible polymers such as Poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP) and polyethylene glycol (PEG) were used as surface stabilizers. The effects of surface stabilizers on the morphologies of nanoparticles were investigated. Polymeric stabilizers at various concentrations were used to study the formation of polyoxalate nanoparticles (POX-NPs). Scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering (DLS), and zeta potential were employed to characterize the resulting POX-NPs. The results demonstrated that surface stabilizers greatly influenced the particle sizes and surface properties of POX-NPs. PVP and PVA potentially can be used as surface stabilizers in the formulation of biodegradable polyoxalate. The size, surface and release properties of POX-NPs can be effectively controlled by varying the preparation conditions.

1. Introduction

Biodegradable polymeric nanoparticles have been used extensively as drug delivery systems due to their superior properties that include high bioavailability, high drug loading and minimal toxicity. These nanocarriers can be preferentially accumulated in tumors through the enhanced permeation and retention (EPR) mechanism. When the nanocarriers have been localized in the tumor, they can release drugs over a period of time and minimize the side effects of these drugs [1–5]. Moreover, they can be degraded into smaller molecules and excreted from the body with minimal toxicity. Various biodegradable polymers have been used to formulate nanoparticles [6–8]. Biodegradable polymers including poly(D,L-lactide), poly(lactic acid), poly(D,L-glycolide), poly(lactide-co-glycolide), and poly(cyanoacrylate) have been used to prepare nanoparticles in recent years [4]. Polyoxalate is a biodegradable polymer and is considered a potential drug carrier. Polyoxalate has been suggested for several medical uses such as absorbable sutures. It can be easily synthesized by a condensation reaction between diols and oxalyl chloride [9]. Polyoxalates can be hydrolytically cleaved into non toxic smaller molecules. Additionally, they are highly sensitive and chemical labile to hydrogen peroxide at nanomolar concentrations [10–12]. Therefore, polyoxalates are degradable in the intracellular environment. Due to their biodegradability and biocompatible characteristics, polyoxalate have attracted interest as biodegradable nanoparticles to carry therapeutic agents.

Several methods can be used to prepare these nanoparticles such as spray drying, extrusion and supercritical fluid extraction [13,14]. Emulsification solvent evaporation has been widely used for synthesis of nanoparticles. In this technique, polymeric nanoparticles are formed by evaporating the organic solvent in which the polymer is dissolved. A stabilizer is usually added to the formulation to protect the emulsion formed during the particle preparation process [15]. It also can prevent particle aggregation and facilitate formation of smaller sized particles. Smaller particle size results in greater surface area as well as improved solubility and absorption of nanoparticles [16]. Moreover, nanoparticles have enhanced cellular uptake compared to microparticles [17–20].

Polyoxalate has a promising potential for use in drug delivery applications. However, little work has been done to investigate the use of polyoxalate to formulate nanoparticles and their ability to release therapeutic agents in a controlled manner. The current

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http://dx.doi.org/10.1016/j.vacuum.2014.02.004
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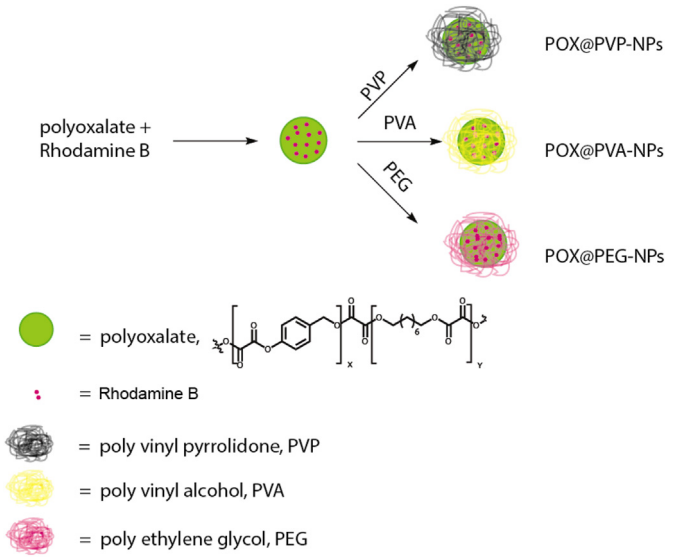

Fig. 1. Schematic illustration of the formation of POX@PVP-NPs, POX@PVA-NPs and POX@PEG-NPs by the emulsification solvent evaporation method.

study is aimed to investigate the effects of surface stabilizers on the preparation of polyoxalate nanoparticles (POX-NPs) and their release profile *in vitro*. The results showed that surface stabilizers greatly influenced the particle size and release profile of POX-NPs. PVP and PVA have potential uses as surface stabilizers to formulate biodegradable polyoxalate. This work demonstrates the potential use of POX-NPs in drug delivery vehicles.

2. Materials and methods

2.1. Materials

Poly(vinyl alcohol) (PVA) (99% hydrolyzed; typical M_w = 27,000), poly(vinyl-pyrrolidone) (PVP) (M_w = 40,000), poly(ethylene glycol) (PEG) (M_w = 8000), and rhodamine B were purchased from Sigma–Aldrich (MO, U.S.A.). Phosphate buffer saline (PBS) buffer was also obtained from Sigma–Aldrich and used without further purification. Polyoxalate (prepared from 1,8-octanediol, 4-Hydroxybenzyl alcohol and oxalyl chloride) was synthesized in our laboratory. Its molecular weight (M_w) and polydispersity (PD) as determined by gel permeation chromatography were 16,000 and 2.72, respectively.

Biodegradable polyoxalate nanoparticles were fabricated using an emulsification solvent evaporation method. Poly(vinylpyrrolidone) (PVP), poly(vinyl alcohol) (PVA), and poly(ethylene glycol) (PEG) were selected as polymer stabilizers to yield POX@PVP-NPs, POX@PVA-NPs and POX@PEG-NPs, respectively (Fig. 1). These polymer stabilizers are widely used for the synthesis of polymeric nanoparticles because of their biodegradability and biocompatibility [4,21–24]. Rhodamine B, a drug model, was encapsulated and used to monitor the release characteristics of POX-NPs.

2.2. Synthesis of polyoxalate

Polyoxalate was synthesized by a condensation polymerization of 1,8-octanediol and oxalyl chloride. 1,8-octanediol (21.96 mmol) and 4-hydroxybenzyl alcohol (5.49 mmol) were dissolved in 20 ml of dry tetrahydrofuran (THF) under a nitrogen atmosphere and then, oxalyl chloride (27.45 mmol) in 25 ml of THF was added dropwise at 4 °C. The reaction was kept at room temperature overnight. Polymers were extracted by dichloromethane (DCM) and washed with sodium bicarbonate and sodium chloride solutions. Hydrophilic molecules were isolated and filtered by anhydrous sodium sulfate through a glass funnel. Polymer was concentrated under vacuum. The molecular weight was determined by gel permeation chromatography (GPC) using polystyrene standards.

2.3. Preparation of a polymer solution and POX-nanoparticles

Polyoxalate and rhodamine B were dissolved in dichloromethane at concentrations of 5 wt.% and 1 wt.%, respectively at

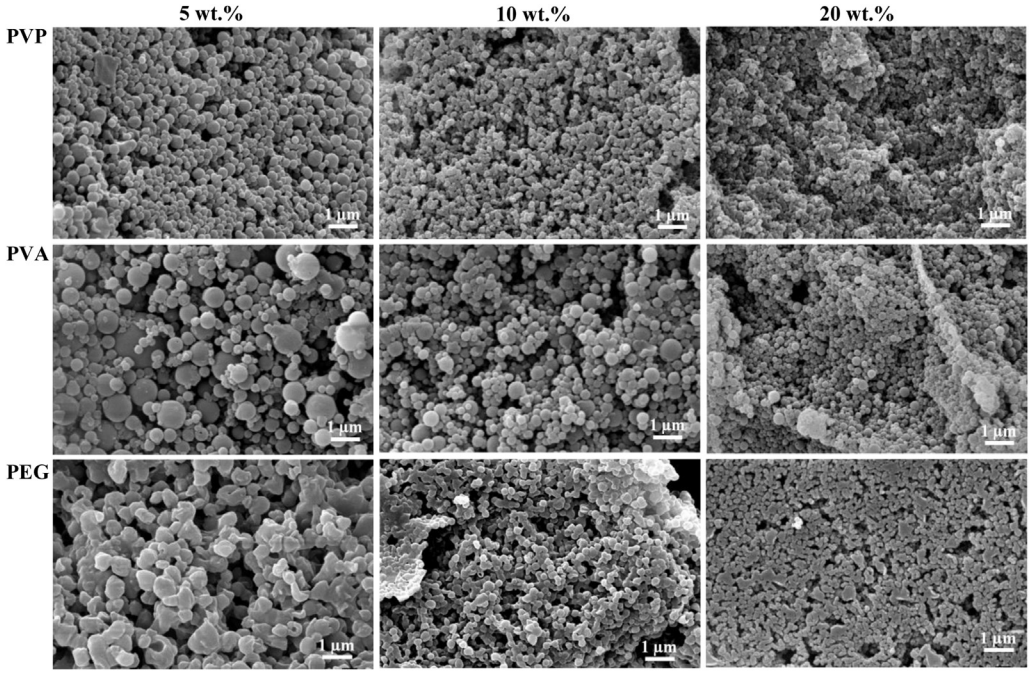

Fig. 2. SEM micrographs of POX@PVP-NPs, POX@PVA-NPs and POX@PEG-NPs at concentrations of 5 wt.%, 10 wt.% and 20 wt.%.