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Factors influencing the physicochemical characteristics of cationic polymer-coated liposomes prepared by high-pressure homogenization

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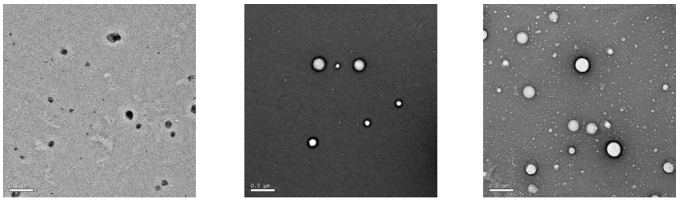
HIGHLIGHTS

- High-speed and high-pressure homogenization was used to obtain nano-liposome.
- Liposome was successfully coated by chitosan and eudragit EPO.
- Physicochemical properties of liposome were affected by manufacture condition.
- Storage stability of liposomes was enhanced by the polymer coating.

GRAPHICAL ABSTRACT



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ABSTRACT

Nano-liposomes were prepared by the modified reverse phase evaporation method using high-speed and high-pressure homogenizers. The optimal conditions for preparation of non-coated liposome, chitosan-coated liposome, and eudragit EPO-coated liposome were investigated. The liposomal membrane was composed of soybean lecithin. Chitosan and eudragit EPO coated the external surface of liposomes by electrostatic interaction. The results show that the physicochemical properties (e.g., mean size, polydispersity index, surface charge, and encapsulation efficiency) of non-coated liposomes were affected by homogenization pressure, number of homogenizing cycles, and ratio of core material to lecithin. Chitosan coating increased the mean size of liposome. In the case of eudragit EPO coating, the mean size of liposome increased up to 0.2%; a further increase in the eudragit EPO concentration led to some changes of the mean size of eudragit EPO-coated liposome. The highest stability for 30 day was achieved with 0.3% chitosan-coated liposome and 0.3% eudragit EPO-coated liposome, respectively. The release property was influenced by the type of coating material; the chitosan and eudragit EPO coating layers on the non-coated liposome surface delayed the release of the core material. Overall, a core material to lecithin ratio of 1:3 and three homogenizing cycles under 1000 bar were selected as the optimal processing conditions. In addition, 0.3% eudragit EPO-coated liposome was selected as the optimal coating.

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1. Introduction

Nano-carrier systems have been extensively investigated in the fields of cosmetics, pharmaceutics, agriculture, and functional foods [1–6]. The advantages of nano-carrier systems for active compounds include improved stability, solubility and biocompatibility, sustained release properties, selective delivery to specific sites, and

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enhanced permeability to the skin [4,11,14]. Diverse nano-carriers, including polymeric nanoparticles, polymeric micelles, liposomes, niosomes, lipid nanoparticles, nanoemulsions, and nanogels, have been utilized to deliver unstable core materials [7]. Liposomes are artificial vesicles consisting of phospholipid bilayers surrounding an aqueous phase, and can entrap hydrophilic materials internally or incorporate hydrophobic materials into the bilayers [8]. The potential benefits of using liposomes as carriers include improving the solubility of hydrophobic materials, controlling the release properties of core materials, and protecting active compounds against degradation [9]. However, there are some limitations with liposomes; e.g., they tend to self-aggregate and gradually form larger vesicles. Moreover, they tend to leak and lose the encapsulated compounds over time. Therefore, the use of liposome coating materials has been extensively researched to enhance the stability of the liposomal system and achieve more effective release of the active compounds [2,10–15]. The stability, release property, size, and surface charge of the liposome can be affected by the coating material [16]. Chitosan, which is a polysaccharide derived from N-deacetylation of chitin, is a typical cationic polymer offering the beneficial properties of biodegradability, biocompatibility, and low toxicity [11]. Eudragit EPO is also a cationic copolymer based on dimethyl-amino-ethyl methacrylate and neutral methacrylic esters [11]. The electrostatic interaction between the negatively charged liposome and the positively charged polymer such as a chitosan or the eudragit EPO induces the formation of an external layer on the liposome [2,13,16].

The manufacturing methods of liposomes have to accomplish high encapsulation efficiency, uniform size, and long-term stability. The reverse phase evaporation (REV) method is one of the most extensively used techniques for the preparation of liposomes [3]. A lipid solution in organic solvents is introduced into a round flask and the organic solvent is removed under reduced pressure in a rotary evaporator. The lipids are re-dissolved in the organic solvent to promote liposome formation. Chloroform and isopropyl ether are the usual solvents of choice. After re-dissolution of the lipids, this lipid solution is added to the buffer. The two phase system is homogenized or sonicated and the organic solvent is then removed via rotary evaporation until a gel is formed. Non-encapsulated materials are then removed. The resultant liposomes are called reverse phase evaporation vesicles. This method have been used to encapsulate small, large, and macromolecules with high efficiency [17].

The homogenizing instruments for controlling the liposome size can be distinguished into two classes based on their efficiency: low efficiency instruments, which include high shear homogenizers and ultrasonic baths, are geared toward non-parenteral liposome products [18]. High efficiency instruments, which includes several types of high-pressure homogenizers and probe sonicators, are used to reduce the liposome size and lamellarity. Probe sonicators generate ultrasonic waves and lead to the formation and implosion of gas–steam bubbles. Probe sonication is scalable but it has some problems including metal particle formation and deterioration of lipids. In high-pressure homogenizers, the size of liposome product is readily decreased by its passage through a narrow gap (Gaulin homogenizer type) or micro-channel (Microfluidizer type) without inducing degradation of the lipids [18]. The size of the liposome can also be controlled by adjusting the processing pressure and the number of cycles. High-pressure homogenizers have been used in diverse industries to obtain different formulations from emulsions and suspensions to nanoparticles; they have also been used for large-scale production [19]. The microfluidizer uses the principles of fluid dynamics to produce liposomes in a continuous process [20]. Microfluidizers are one of the various available homogenizers that can be directly scaled-up to accomplish large-scale production of liposomes.

In this study, we investigated the effect of several parameters on the physicochemical properties (e.g., mean size, polydispersity index, surface charge, morphology, and encapsulation efficiency) of non-coated liposomes generated by high-pressure homogenization. The following parameters were selected: (1) etofenprox to lecithin ratio; (2) number of homogenization cycles; (3) homogenization pressure. The commercial insecticide etofenprox was selected as a model drug because of its hydrophobic nature. The types of coating materials and concentration were selected as variables in the coating process. The influences of these factors on the physicochemical properties of cationic polymer (chitosan or eudragit EPO)-coated liposomes were evaluated. Additionally, the stability of the non-coated and coated liposomes during storage was analyzed herein.

2. Materials and methods

2.1. Materials

Soybean lecithin, used as a surfactant, was purchased from Junsei Chemical (Tokyo, Japan). Chitosan (CS, molecular weight: 30 kDa, degree of deacetylation: 90–94%, Biotech, Mokpo, Korea) and eudragit EPO (EPO, molecular weight: approx. 150 kDa, Evonik Industries AG, Darmstadt, Germany) were used as coating materials. Etofenprox (98%) was obtained from Kyung-Nong Co., Ltd. (Kyungju, Korea). All other chemicals were of analytical grade.

2.2. Preparation of non-coated liposomes

Non-coated liposome (NCL) was prepared using high-speed and high-pressure homogenization based on the reverse phase evaporation (REV) method as described previously in the literature with some modifications [3]. Briefly, various ratios of etofenprox to lecithin (1:1, 1:2, 1:3, 1:4, 1:5) were dissolved in chloroform. The lecithin solution was then added to an acetate buffer solution (pH 3.4 ± 0.1) and homogenized using a high-speed homogenizer (Ultra-Turrax® T 25 basic, IKA®, Staufen, Germany) at 19,000 rpm for 5 min. The organic solvent was evaporated by a rotary evaporation to obtain the primary liposomes. Subsequently, the liposome suspension was processed with a high-pressure homogenizer (M-110PS Microfluidizer®, Microfluidics International Corp., Newton, USA) at different homogenizing pressures (500, 1000, 1500 bar) and cycles (1, 3, 5, 10 cycles) to reduce the size of the liposomes.

2.3. Preparation of cationic polymer-coated liposomes

Chitosan-coated liposome (CS-CL) and eudragit EPO-coated liposome (EPO-CL) were obtained by electrostatic interaction of cationic CS and EPO polymers with the surface of the anionic liposomes. For the formation of positively charged liposomes, the prepared liposome solution was added into CS and EPO solutions (0.1%, 0.2%, 0.3%, 0.4%, 0.5% CS or EPO in acetate buffer) in a volume ratio of 1:1 and then mixed using a vortexer for 2 min. The mixed solution was stirred over night at room temperature.

2.4. Analysis of particle size and zeta potential

The mean size, polydispersity index (PDI), and surface charge of the liposomes were determined using a nano-size analyzer (Zetasizer Nano ZS, Malvern, UK). Liposome solutions (NCL, CS-CL and EPO-CL) were diluted with distilled water. The diluted solution was placed into a polystyrene latex cell and analyzed at 25 °C with a detector angle of 90°.

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