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Influence of hydrophobe on the release behavior of vinyl acetate miniemulsion polymerization

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Abstract

Poly(vinyl acetate) (PVAc) nanoparticles containing antibiotic have been prepared by miniemulsion polymerization. To compare the effect of hydrophobe types, hexadecane and poly(vinyl acetate) were used as hydrophobe. The particle characteristics as the manufacturing condition were examined by particle size analyzer. As a result, the diameter of PVAc latexes was adjusted between 80 and 260 nm by homogenization conditions and amounts of surfactant. Also, the miniemulsion by using hexadecane showed the more long shelf stability and led to the more small particle size after polymerization, as compared with the case of using poly(vinyl acetate). This indicated that the use of poly(vinyl acetate) as a hydrophobe could not make the stable emulsion, but it could avoid volatile organic chemical problems in the final product. From the release profile of drug through UV spectra, the drug release was very slow and it could be seen that the release of drug encapsulated with PVAc was occurred with the polymer degradation.

Keywords: Miniemulsion polymerization; Poly(vinyl acetate); Antibiotic; Hydrophobe; Drug release

1. Introduction

During the last decade, the polymer carriers have grown to an important field of pharmaceutical research and it has required very small and stable nanoparticles, which must be around 200 nm and able to incorporate hydrophobic components for drug delivery system. To obtain these nanoparticles, emulsion technologies have attracted much interest in recent years because of their great practical importance in terms of their drug delivery potential and interesting physical properties [1–3].

In the past 50 years, several particle nucleation mechanisms have been proposed for conventional emulsions, so-called generally macroemulsion. And it produced a thermodynamically unstable droplets (1–10 μm) and easy to separate out. On the other hand, microemulsions consist of spontaneously formed droplets (∼50 nm), which are thermodynamically stable system, but generally require high surfactant and costabilizer ratios [4–6].

In the conventional emulsion from Harkins–Smith–Ewart theory, the particle nucleation is occurred with capture of radicals by monomer-swollen micelles and then latex particles are generated by propagation of monomer [7–9]. However, if the droplet size is sufficiently small, the monomer droplet can be the predominant place for particle nucleation. This is due to the fact that the huge interfacial area between monomer droplets and water are effective in comparison with micelles for adsorption of radicals produced in the aqueous phase [10]. This method is referred as miniemulsion. It is classically defined as aqueous dispersions of relatively stable oil droplets within a size range 50–500 nm and is composed of monomer, water, surfactant and hydrophobe [11,12]. And a miniemulsion produced with shearing systems, i.e., a high-pressure homogenizer or ultrasonicator, is rather stable with respect to aggregation, sedimentation and greater shear stability than conventional emulsions [13,14]. Also, miniemulsion polymerization of vinyl acetate is well suited to get nanoparticles for encapsulation of hydrophobic drugs [15].

In this work, the drug-loaded PVAc nanoparticles are prepared by miniemulsion polymerization under the presence of a hydrophobe. We are also discussed about the application of poly(vinyl acetate) and hexadecane as drug delivery

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carrier through drug release from drug-loaded PVAc nanoparticles.

2. Experimental

2.1. Materials

Vinyl acetate (VAc; Aldrich Co., M_w) was used after purification and stored at 0–5 °C. Sodium dodecyl sulphate (SDS; Sigma, M_w: 288.4), potassium persulfate (KPS; Sigma Co., M_w: 270.3) and hydrophobe, i.e., hexadecane (Aldrich, M_w: 226.45) and poly(vinyl acetate) (Aldrich Co., M_w:113000), were used as received. And erythromycin estolate as antibiotic was supplied by Sinpung Co. (Korea). Fig. 1 presents the structure of erythromycin estolate.

2.2. Preparation of PVAc nanoparticles containing drug

VAc was washed with 2% NaOH solution and deionized water. And then extra water dried with $CaCl_2$. The miniemulsion was prepared by mixing the organic phase (monomer and hydrophobe or monomer, hydrophobe and drug) and the aqueous phase (water and surfactant). The mixture was stirred magnetically for 10 min prior to being subjected to homogenization. And the resultant emulsion was then homogenized by homogenizer (Ika Works Sdn. Bhd.; 11,000–24,000 rpm) for 120 s. The miniemulsion was immediately transferred to the 250 ml reactor equipped with a thermometer and reflux condenser, and nitrogen inlet and kept 10 min under nitrogen atmosphere. The reaction was then initiated by an addition of the potassium persulfate solution. The polymerization temperature and stirring speed were kept constant at 60 °C and 500 rpm for reaction time of 4 h.

2.3. Conversion

The monomer conversion was determined gravimetrically. Samples were withdrawn from the reacting system every hour and the polymerization was short-stopped with a 0.4 wt% hydroquinone aqueous solution. The samples were dried by freeze-drying and weighted to determine the amount of dried polymer. And the conversion of the vinyl acetate to PVAc was calculated by the following equation [16]:

$$\text{Conversion } (X) = \frac{M_S - M_0}{M_P - M_0'} \quad (1)$$

where X is the conversion, M_S the mass of dry polymer in sample, M_0 the mass of surfactants and initiator and M_P is the mass of dry polymer at 100% conversion.

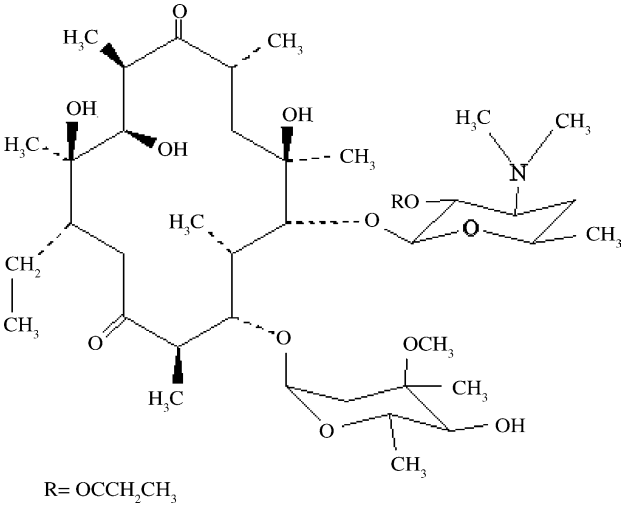

Fig. 1. Chemical structure of erythromycin estolate.

2.4. Stability of miniemulsion

The shelf stability of emulsion was measured by placing the sample in the capped vial at room temperature and observing visually the time necessary to produce phase separation.

The surface tension (σ) for a series of miniemulsion stabilized by surfactant and hydrophobe were examined by a Surface Tensiometer K-9 (KRŰSS). Changes in the surface tension may provide dynamic information on the monomer droplet and water interfaces, and the aqueous phase of the miniemulsion at room temperature.

2.5. Characterization of PVAc nanoparticles

The PVAc nanoparticles after polymerization were obtained by freeze-drying of polymer latex. The morphology of PVAc particles was observed using scanning electron microscope (SEM, JEOL JXA 840A). The characteristics of PVAc nanoparticles were measured by particle size analyzer (Microtrac-S3000; Microtrac. Inc., range 0.021–1408 μm). Infrared spectra of drug and nanoparticles containing drug were confirmed with Fourier transform infrared spectrophotometer (FT-IR, Digital FRS-80).

2.6. In vitro drug release test

The in vitro release profile of drug was measured spectrophotometrically. The drug-loaded PVAc nanoparticles and hexadecane nanoparticles were suspended in release medium, and the mixture was incubated at 37 °C under shaking. Release medium was phosphate buffer (pH 6.8) containing 10 mg/ml pepsin as artificial gastric juice. At desired times, the suspension was centrifuged and the supernatant was subjected to UV–vis spectra to determine the released drug at a wavelength of 280 nm.

3. Results and discussion

3.1. The effect of homogenization and hydrophobe on emulsion

For comparison of emulsion by polymerization methods, PVAc latex was prepared by conventional emulsion (C-EM) and hydrophobe-involved miniemulsion (M-EM) using poly(vinyl acetate) as a hydrophobe. The characteristics of prepared PVAc latexes are summarized in Table 1.