Production of spherical microparticles with Eudragit L100 by the PGSS process in supercritical CO_2-ethanol mixtures

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Abstract

Microencapsulation technology has attracted attention because it can add new functionality to the core substance. In this study, we aim to form spherical microparticles coated with Eudragit L100, which is enteric polymer and hard to dissolve in supercritical CO_2 ($scCO_2$), using the particles from the gas-saturated solutions (PGSS) process with scCO2. In the PGSS process, it is necessary to saturate the polymer in a supercritical fluid, so the solubility of Eudradit L100 in mixtures of $scCO_2$ and ethanol as a cosolvent were determined by observing the cloud point visually with the experimental apparatus. Next, phenylalanine loaded $CaCO_3$ particles (adsorption amount: 26 mg/g, average particle size: 49.2 μm), Eudragit L100, and ethanol were charged into a high pressure cell, and the mixture was stirred. After 1 h, the system was depressurized through a nozzle ($\varphi = 2.0$) into an atmospheric collector leading to formation of microparticles coated with Eudragit L100 by precipitation onto a Teflon sheet. The microcapsules (average particle size: 181.39 μm) were found to be completely covered with a smooth shiny surface and did not adhere to each other. The pH dependence of sustained release rate of phenylalanine from the microcapsules was confirmed using a UV-vis spectrophotometer. It was carried out with stirring using the Franz cell. We found that when the low pH was used, phenylalanine from microcapsules were released slowly. On the other hand, when the high pH was used, phenylalanine from microcapsules were released early.

Keywords

Microcapsule, pH responsiveness, Carbon dioxide

1. Introduction

Enteric coating microencapsulation technology has attracted considerable attention in the field of medicines specially for oral administration due to their ability to prevent dissolution in the gastric environment [1]. Methacrylic acid and methacrylate (Eudragit L100), an anionic copolymer, is often used as an enteric coating polymer [2] because it dissolves at pH 6.0 or higher and is harmless to the human body. Among coating technologies using Eudragit L100 as a coating material, a microcoating process using supercritical carbon dioxide ($scCO_2$) has attracted attention because of its small environmental load [3]. Eudragit L100 is an antisolvent for $scCO_2$, so the supercritical fluid antisolvent (SAS) and gas antisolvent (GAS) processes are generally applied to microencapsulation techniques [4] using Eudragit L100 and $scCO_2$. In the SAS and GAS processes, however, the particles are formed by precipitation in a high pressure cell, so the recovered particles are often obtained as aggregates [4]. In this study, we aim to form spherical microparticles coated with Eudragit L100 using the particles from the gas-saturated solutions (PGSS) process in which particles are formed outside the high pressure cell. In the PGSS process, it is necessary to saturate the polymer in a supercritical fluid, so the solubility of the polymer in mixtures of $scCO_2$ and ethanol as a cosolvent were determined by observing the cloud point visually with the experimental apparatus. And then, spherical microcapsules using Eudragit L100 as the coating substance were manufactured by the PGSS process. Furthermore, the drug releasing behaviors under different pH stimuli of the produced microparticles are also examined.

2. Experimental

2.1. Materials

Phenylalanine (>99.0 wt%, Wako Pure Chemical Industries, Ltd, Osaka, Japan), Eudragit L100 (>99.9 vol.%, Higuchi Co. Ltd. Tokyo, Japan), CO_2 (>99.9 vol.%, Fukuoka Sanso Co., Ltd), porous $CaCO_3$ particles (>99.9 wt%, Shiraishi Calcium Industry Ltd, Osaka, Japan) and ethanol (>99.5 wt%, Wako Pure Chemical Industries, Ltd, Osaka, Japan) were purchased and used as received without further purification.

2.2. Apparatus and Procedure

The solubility measurement and microencapsulation were performed with the experimental apparatus as shown in Fig. 1. In the solubility measurement, the cloud point of Eudragit L100 in a mixture of $scCO_2$ and ethanol was determined by the precipitation of Eudragit L100. The encapsulation of the core substance with Eudragit L100 as the coating substance was conducted by the PGSS process using $scCO_2$. Phenylalanine, which was hydrophilic, was used as a model drug. Phenylalanine loaded $CaCO_3$ particles, Eudragit L100,

and ethanol were charged into a high pressure cell at 50 ℃, and the mixture was stirred under conditions where $scCO_2$, Eudragit L100, and ethanol became a homogeneous phase. After 1 h, the system was depressurized through a nozzle (φ = 2.0) into an atmospheric collector leading to formation of microparticles coated with Eudragit L100 by precipitation onto a Teflon sheet. The recovered particles were dispersed in water (5 mL) and separated from the uncoated microparticles by filteration.

Average particle size was evaluated by a laser diffraction particle size analyzer (SALD-2000, SHIMADZU). The structure and morphology of the products were analyzed using a scanning electron microscope (SEM, JEOL JSM6060). Release rate of phenylalanine from microcapsules under pH variation was measured at 255 nm with a UV-vis detector (V-550, Jasco).

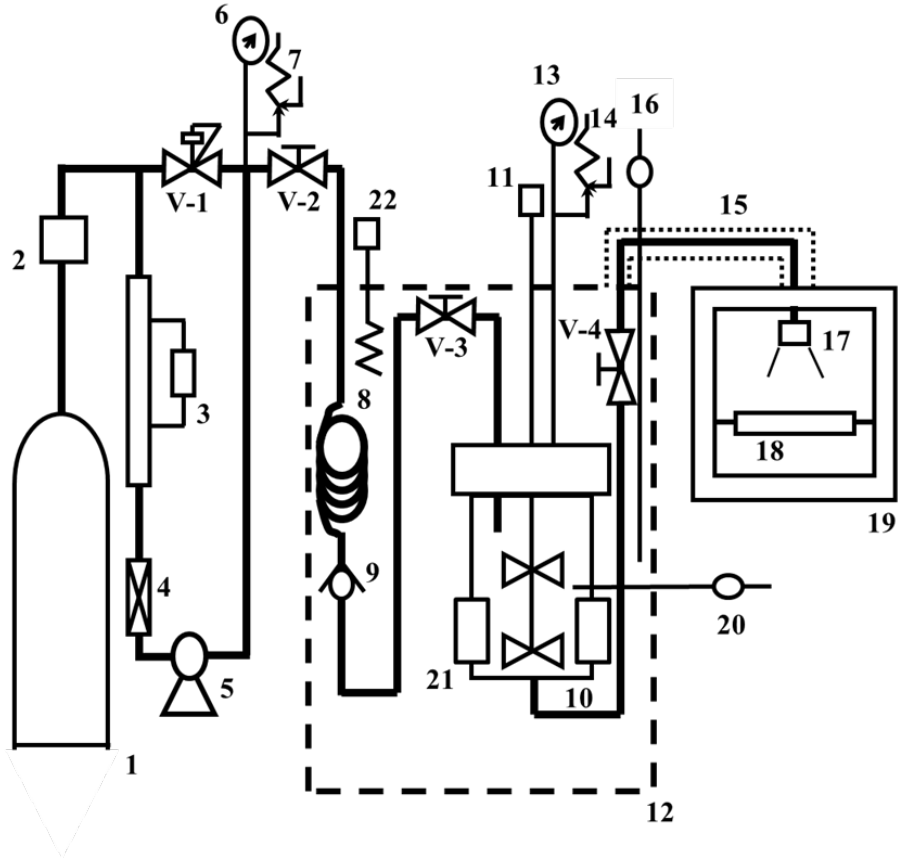

Fig. 1. Schematic diagram of apparatus used in particles from gas saturated solution (PGSS) process; 1: gas cylinder, 2: dryer, 3: cooling unit, 4: filter, 5: pump, 6: pressure gauge, 7: safety valve, 8: preheater, 9: check valve, 10: high-pressure cell, 11: agitator, 12: water bath, 13: pressure gauge, 14: safety valve, 15: heater, 16: thermometer, 17: nozzle, 18: Teflon sheet, 19: atmospheric collector, 20: thermometer, 21: sapphire windows, 22: heater. V-1 indicates a back-pressure regulator, and V-2 to 4: stop valves.

3. Experimental results and discussions

The solubilities of Eudragit L100 at 50 ℃ in a mixture of CO_2 and ethanol are shown in Fig. 2. According to vapor liquid equilibrium data [5], the mixture of CO_2 and ethanol without polymer form a single supercritical fluid phase at this temperature. The solubility of Eudragit L100 in only ethanol was about 60.0 wt% at 50 ℃. The solubility of Eudragit L100 rapidly decreased with the addition of CO_2 to ethanol. This results reveal that the solubility of Eudragit L100 decreases with the addition of CO_2, but a homogeneous phase of Eudragit L100, ethanol, and scCO_2 is formed in the high-pressure cell when Eudragit L100 is at a low concentration.

The morphology of the encapsulated microparticles characterized by SEM is shown in Fig. 3. The microparticles were found to be completely covered with a smooth shiny surface. Moreover, the particles did not adhere to each other, because the ethanol was volatile. Average particle size of produced microparticles was 181.39 μm.

In order to confirm the success of entrapping phenylalanine in the microcapsule and to understand the pH-triggered release behavior, the release rate of phenylalanine from the microcapsule produced by the PGSS process at 50 ℃ and 10 MPa was carried out in different pH medium ranges between pH 2.1 to 8.0 using a UV-vis spectra test. It could be clearly seen from the Fig. 4 that phenylalanine release from microcapsules is suppressed at lower pH i.e. pH 2.1 while the increase in the pH value promoted the drug release behavior. When this delivery system is under near neutral condition which is pH 6.8, the total release amount reaches the peak within 150 min. By decreasing the pH to 4.1, the drug release rate reduced to less than 20%, therefore, can be released slowly over the circulation period in the body. On the basis of this results, we could draw a conclusion suggests that the release rate of phenylalanine could be controlled or slowed down with covering the phenylalanine loaded $CaCO_3$ with pH responsive polymers, Eudragit L100.

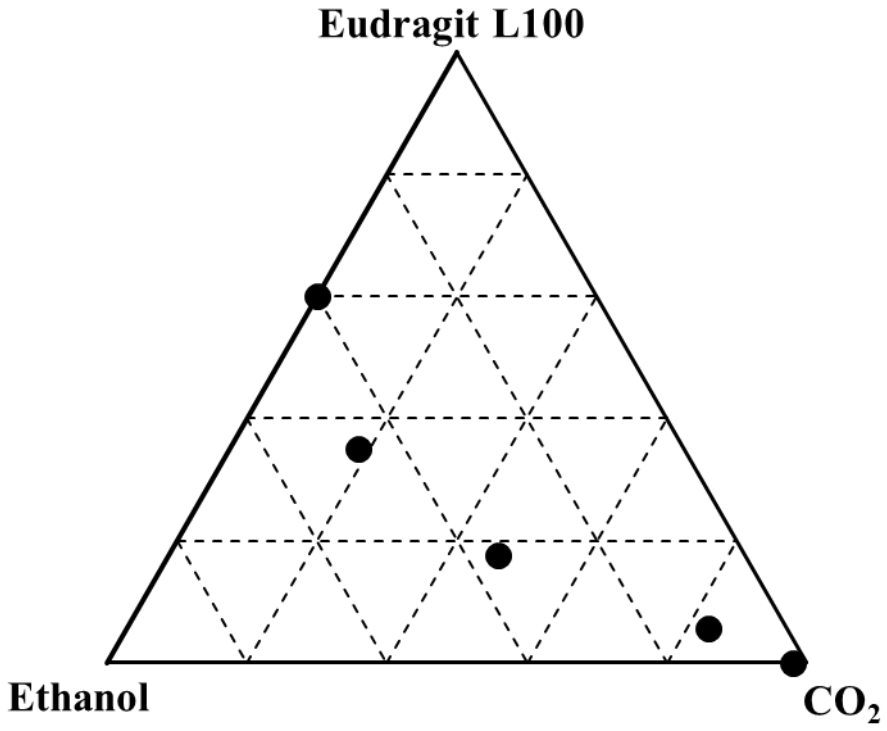

Fig. 2. Solubility of Eudragit L100 in a mixture of CO2 and ethanol at 50 ºC.

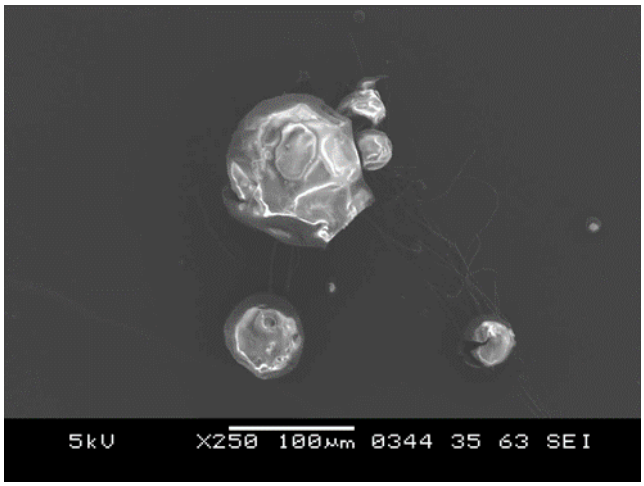

Fig. 3. SEM image of the enteric polymer Eudragit L100 coated microcapsules produced by particles from gas-saturated solutions (PGSS) process of $scCO_2$-ethanol solutions at 50 ºC and 10 MPa.

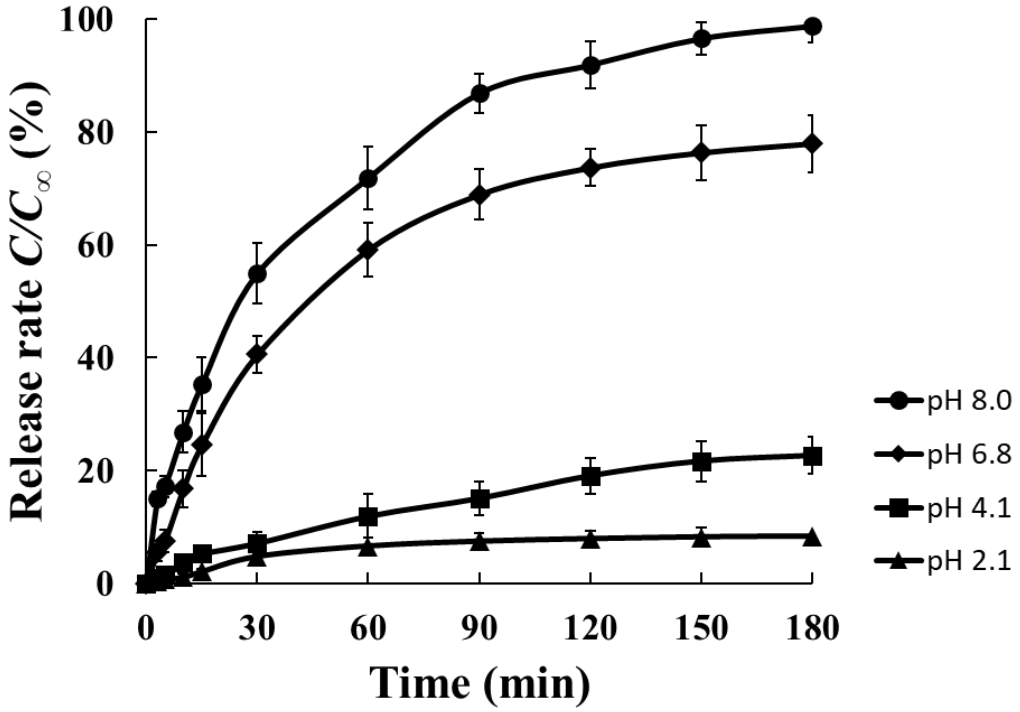

Fig. 4. Phenylalanine release of the enteric coated microcapsules produced by particles from gas saturated solution (PGSS) process of $scCO_2$-ethanol solutions at 50 ºC and 10 MPa under different pH conditions.

4. Conclusion

Spherical microencapsulation is achieved by combining the complete dissolution of Eudragit L100 in a mixture of $scCO_2$ and ethanol and precipitation of Eudragit L100 outside the high pressure cell by spraying a gas-saturated solution. The in vitro phenylalanine releasing behavior is beneficial to reduce the release rate as well as the real-time control of on-demand drug release.

References

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