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Encapsulation of ethanol by spray drying technique: effects of sodium lauryl sulfate

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Abstract

Microcapsules composed of ethanol, water and dextrin as a water-soluble polymer can be used to encapsulate poorly water-soluble drugs by spray drying technique. For the encapsulation of a high dose of poorly water-soluble drugs, large amounts of ethanol and consequently large quantities of dextrin are needed for the dissolution of drug and the encapsulation of ethanol, respectively. In order to increase the ethanol content with the decreased amount of dextrin, sodium lauryl sulfate (SLS) was employed in the preparation of microcapsules without drug by a spray drying method. Phase diagrams were prepared to determine the region of microcapsule formation with a three-component system of ethanol, dextrin and water. The homogeneous phase indicated in the phase diagram was used to prepare the alcoholic microcapsules since this phase was not separated rapidly and not too viscous to be spray-dried. Interestingly, SLS at concentrations below 2% remarkably increased both the ethanol content and the encapsulation efficiency of ethanol. The maximum ethanol content and encapsulation efficiency were observed with 0.5–1% of SLS (35.4 and 67.6%, respectively). Furthermore, the increase by SLS was more pronounced at the low dextrin/water ratios than at the high dextrin/water ratios. In particular, the ethanol content and the encapsulation efficiency with the dextrin/ethanol/water ratio of 0.4/1/1, which had relatively small amounts of dextrin, were about ten times higher in the presence of SLS than those without SLS. In conclusion, this study shows that small amounts of SLS can increase the ethanol content and the encapsulation efficiency of ethanol, and allow the reduction in the amount of dextrin required to encapsulate ethanol in the preparation of microcapsules. These findings suggest that the use of SLS may permit the effective encapsulation of high dose of water-insoluble drug into microcapsules.

Keywords: Sodium lauryl sulfate; Ethanol; Dextrin; Microcapsule, Encapsulation; Spray drying; Phase diagram; Dry elixir

1. Introduction

Alcohol or volatile aroma is held in water-soluble materials such as gelatin and dextrin having wall-forming ability when a mixture of alcohol or aroma, water, and wall-forming material is spray-dried (Menting and Hoogstad, 1967; Sato et al., 1982). A mixed solution of ethanol, water and a water-soluble polymer can be transformed into a powdered form by a spray drying technique in

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which the water is substantially removed and the ethanol is encapsulated within water-soluble polymer shell because of the hydrophilic property of polymer and permeability difference between ethanol and water (Menting et al., 1970; Thijssen, 1971).

Based on this notion, a rapidly absorbed novel oral dosage form for poorly water-soluble drugs termed a 'dry elixir' has been developed (Kim et al., 1994). Dry elixir is a solid form of microcapsules simultaneously containing ethanol and drug in water soluble polymer shell. The poorly water-soluble drugs encapsulated in the dry elixir are readily dispersed and dissolved in aqueous media as a result of the cosolvent effect of ethanol, resulting in the enhanced bioavailability (Yoon, 1994). Therefore, it is desirable to maximize the ethanol contents in the dry elixir to improve the solubility and the dissolution rate of poorly water-soluble drugs.

Dry elixirs have been successfully applied to several poorly water-soluble drugs. Indomethacin, ketoprofen and ibuprofen dry elixirs appeared to have a considerably fast dissolution rate (Kim et al., 1994). It was also shown that digoxin, flurbiprofen, and ketoprofen dry elixirs had remarkably higher bioavailabilities than drug powder (Kim and Yoon, 1995; Kim et al., 1995; Ahn et al., 1998). However, since dry elixirs requires relatively large amounts of water-soluble polymer compared to drug, it is not easy to apply dry elixirs to drugs administered orally in large doses. The important factors for the encapsulation of ethanol in a water-soluble polymer shell have been reported to be the type and the concentration of the polymers, and the inlet air temperature of spray dryer (Kim et al., 1994, 1995). As far as the type of polymer is concerned, the dextrin having 16 of dextrose equivalence, which is a measure of reducing power or degree of hydrolysis compared to a dextrose standard of 100, led to a greater ethanol content in the dry elixir than other grades of dextrin (Yoon, 1994). The more diluted dextrin solution was spray-dried, the smaller the amount of ethanol was encapsulated as a result of the longer period required to form the dextrin outlayer. The optimal inlet air temperature of spray dryer is also required to encapsulate ethanol. The higher the manufacturing temperatures, the smaller the amount of ethanol was encapsulated, owing to the rapid volatilization of ethanol caused by the ballooning effect on the drying droplets.

Sodium lauryl sulfate (SLS) is an anionic surfactant commonly used in pharmaceutical preparations. Previously, it has been employed to prevent microcapsules from attaching to the inner wall of a spray drying chamber (Kim et al., 1994). Although surfactant used as a lubricant might be an important factor on the encapsulation of ethanol in water-soluble polymer shell, its effects on the encapsulation of ethanol in dextrin have not been investigated yet. In this study, SLS was employed in the preparation of microcapsules composed of ethanol and dextrin without drug by spray drying technique to increase the ethanol content with the decreased amount of dextrin in microcapsules.

2. Materials and methods

2.1. Materials

Dextrin (TK-16, Batch No. 902261B) was kindly supplied by Matsdani (Tokyo, Japan). Ethanol (94.6%) and SLS ($>99\%$) were obtained from Duck San Pure Chemical (Seoul, Korea) and Aldrich (Milwaukee, WI, USA), respectively. Water for injection (Choongwae Pharma, Korea) was used. All other chemicals were of reagent grade and used without further purification.

2.2. Establishment of phase diagrams

The phase diagram of the three-component system with dextrin, water and ethanol was established at 20 and 60°C, respectively. Various mixtures of any two components (e.g. water and dextrin) in the triangular diagram were titrated by the third component (e.g. ethanol). The phase regions were determined by visual inspection and by observation under polarized light.

2.3. Preparation of alcoholic microcapsules

A Büchi 190 nozzle type minispray dryer (Flawil, Switzerland) was used for the preparation of alcoholic microcapsules. Dextrin was dissolved in water to obtain aqueous dextrin solution. SLS and ethanol were then added to this solution one after another. The resulting solution was prewarmed to 60°C. The final solutions were delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter spray-dried. Inlet and outlet temperatures were maintained at 98 and 68°C, respectively, at which temperatures the microcapsule with maximum contents of ethanol could be obtained (Kim and Yoon, 1995). The pressure of spray air was 3 kg/cm^2. The flow rate of drying air was maintained at the aspirator setting of 10 which indicated the pressure of aspirator filter vessel of -30 mbar. The direction of air flow was the same as that of sprayed products. The diameter of nozzle was 0.7 mm.

2.4. Ethanol content in microcapsules

The various volumes (0.5, 1, 2, 4, 8 and 12 ml) of ethanol stock solution (0.1 g/ml) and acetonitrile (250 μl) as an internal standard were mixed and adjusted to 100 ml with deionized water in a volumetric flask for the preparation of standard solutions. About 25 mg of alcoholic microcapsules was accurately weighed and dissolved in acetonitrile solution (2.5 μl/ml) in an Eppendorf tube and adjusted to 1 ml with the acetonitrile solution for the preparation of sample solutions. The ethanol content in the alcoholic microcapsules was determined using a gas chromatography with a Porapak Q, Chromosorb 101 column. Nitrogen gas was used as a carrier gas. The temperature of the column, detector and injector were 50, 150 and 130°C, respectively.

3. Results and discussion

The large amount of ethanol is necessary to dissolve the high dose of the water-insoluble drugs in the preparation of microcapsules with ethanol, dextrin and water using spray-drying method. Consequently, the large amount of dextrin is required to encapsulate the ethanol, causing the inconvenience in oral administration due to the bulkiness. Thus, we attempted to increase the ethanol content with the decreased amount of dextrin in the microcapsules without drug.

The dextrin is insoluble in ethanol but easily soluble in water. As the ethanol was added to the aqueous solution of dextrin, the mixed solution consisted of three regions; homogeneous phase region (I), heterogeneous phase region (II) and the region in which dextrin could hardly be dissolved (III), as shown in the triangular phase diagram (Fig. 1). The homogeneous phase was not separated rapidly and not too viscous to be spray-dried. The phase produced at 60°C (line b) was wider than that at 20°C (line a). For those reasons, different microcapsules were produced from homogenous phase (region I) of various spraying solutions with the three-component system of ethanol, dextrin and water at 60°C (Fig. 2). The ethanol contents of the microcapsules in three subregions, I–(i), I–(ii) and I–(iii) were in the range of 0–10, 10–20 and 20–30% (w/w), respectively. The amount of ethanol encapsulated in the microcapsules prepared in the absence of SLS was dependent upon the concentrations of ethanol and dextrin in spraying solution (Fig. 3A). The ethanol content increased until the ratio of dextrin/water reached 1.25 and leveled off above the

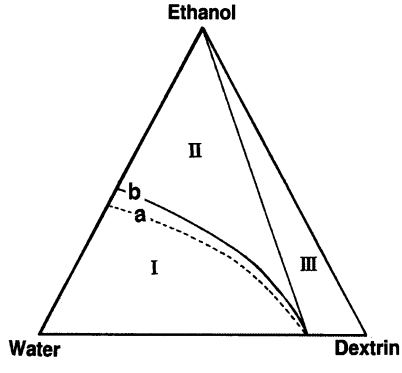

Fig. 1. Phase regions of a three-component system with dextrin, water and ethanol measured at 20°C (a) and 60°C (b). (I) homogeneous phase region; (II) heterogeneous phase region with white turbidity; and (III) the region in which dextrin could hardly be dissolved.

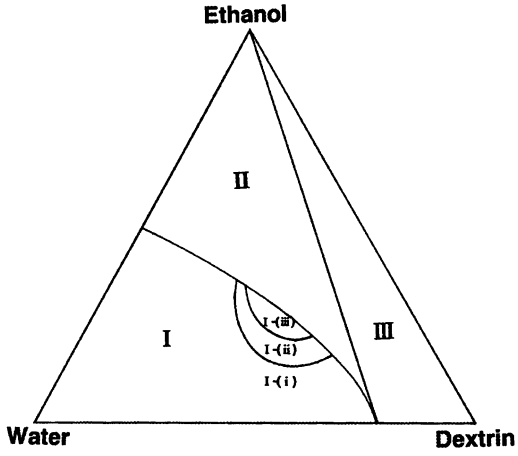

Fig. 2. Phase regions containing ethanol encapsulated in microcapsules prepared in the absence of SLS at 60°C. (I) homogeneous phase region; (II) heterogeneous phase region with white turbidity; and (III) the region in which dextrin could hardly be hydrated. I–(i), –(ii) and –(iii) are regions which produced alcoholic microcapsules containing ethanol in the range of 0–10, 10–20 and 20–30%, respectively.

ratio of 1.25. The maximum ethanol content was about 30% at the ratios of dextrin/water and ethanol/water 1.6 and 1.0, respectively. The encapsulation efficiency of ethanol greatly increased as the concentration of dextrin increased (Fig. 3B). However, it was insignificantly affected by the concentration of ethanol.

SLS is an anionic surfactant commonly used in pharmaceutical preparations. In this study, we examined whether SLS was effective in increasing the ethanol content and the encapsulation efficiency of ethanol in the microcapsules. In the absence of SLS, we observed strong static electricity among microcapsules arisen from friction in the spray dryer making the powder fly in all directions, which caused difficulty in handling. Fig. 4 illustrates the phase regions with spraying solution containing 1% SLS. Four regions were observed in which the microcapsules contained ethanol in the range of 0–10, 10–20, 20–30 and 30–40%. This result clearly demonstrates that the presence of SLS produces one additional region containing higher ethanol content (30–40%) than the absence of SLS in the microcapsules (Fig. 2). Furthermore, the ethanol contents and the encapsulation efficiencies were found to be greatly dependent upon the amount of SLS used (Fig. 5). Both the ethanol content and the encapsulation efficiency increased abruptly as the concentration of SLS increased, and reached the maximum levels at 1% of SLS, and then rapidly decreased above 2% of SLS at all the ratios of dextrin/water/ethanol studied. As the dextrin/water/ethanol ratio increased from 0.4 to 1.2, the ethanol content and the encapsulation efficiency increased. The maximum ethanol content and encapsulation efficiency were 35.4 and 67.6%, respectively, at 1% of SLS and at the dextrin/ethanol/water ratio of 1.2/1/1. In particular, it should be noted that the ethanol content and the encapsulation efficiency with the dextrin/ethanol/water ratio of 0.4/1/1, which had relatively small amounts of dextrin, were about ten times higher in the presence of 0.5% of SLS than those without SLS. Thus, it appears that 0.5–1.0% of SLS can maximize the encapsulation of ethanol in the microcapsules. Based on our previous experiments, there would not be much difference in size among various

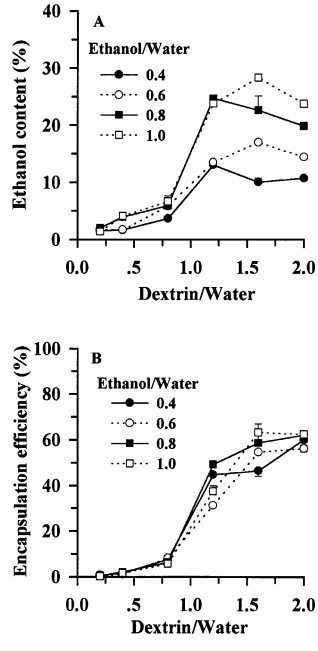

Fig. 3. Effect of concentrations of dextrin and ethanol in a three-component system on the ethanol content and the encapsulation efficiency of ethanol. (A) ethanol content; and (B) encapsulation efficiency. Each point represents the mean ± standard deviation (S.D.) of three separate experiments.

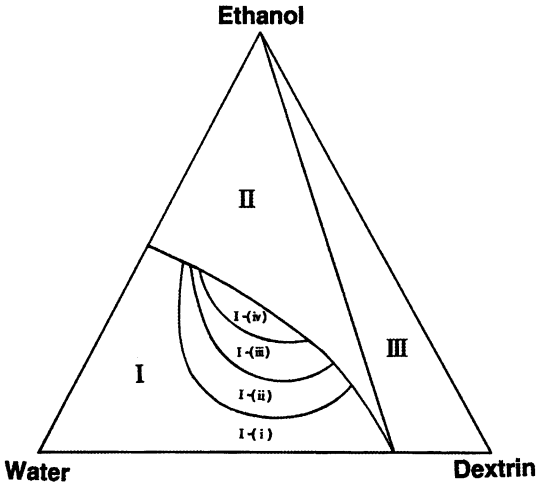

Fig. 4. Phase regions containing ethanol encapsulated in microcapsules prepared in the presence of SLS at 60°C. (I) homogeneous phase region; (II) heterogeneous phase region with white turbidity; and (III) the region in which dextrin could hardly be hydrated. I–(i), –(ii), –(iii) and –(iv) are regions which produced alcoholic microcapsules containing ethanol in the range of 0–10, 10–20, 20–30 and 30–40%, respectively.

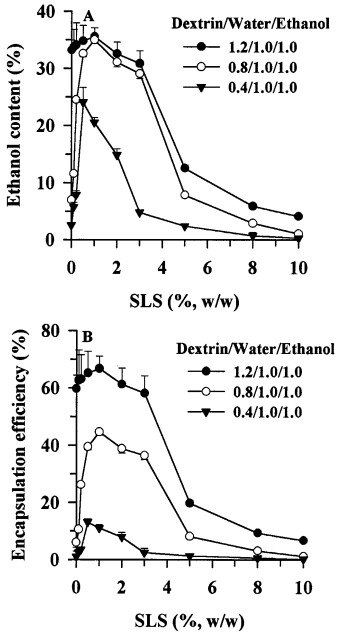

Fig. 5. Effects of SLS on the ethanol content and the encapsulation efficiency. (A) ethanol content; and (B) encapsulation efficiency. Each point represents the mean ± S.D. of three separate experiments.

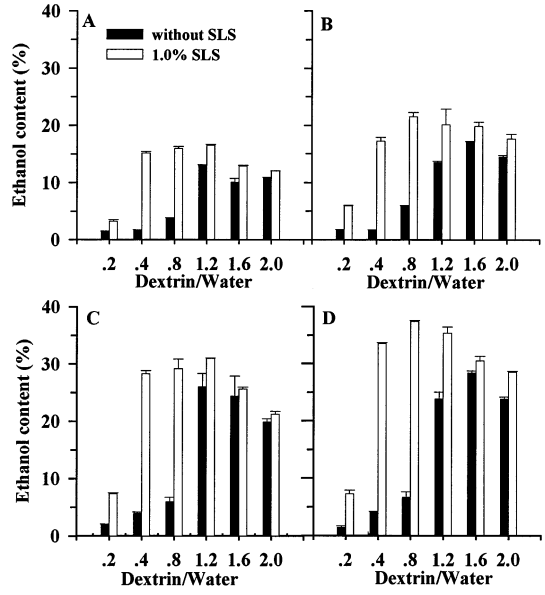

Fig. 6. Comparison of the effect of SLS on the ethanol content among various ratios of dextrin and ethanol. (A) ethanol/water = 0.4; (B) ethanol/water = 0.6; (C) ethanol/water = 0.8; and (D) ethanol/water = 1.0. Each point represents the mean ± S.D. of three separate experiments.

formulations (Yoon, 1994). The size distribution of microcapsules without and with SLS observed by particle size analyzer (Fritsch, lazer diffraction, Germany) ranged approximately 0.5–100 μm and the arithmetic mean diameter was about 19 μm. To investigate the effect of SLS further, the microcapsules were produced from various spraying solutions with and without 1% of SLS at different ratios of ethanol/water and dextrin/water. The addition of SLS caused a marked increase in the ethanol content at all the ratios of dextrin/water studied (Fig. 6). However, the increase caused by SLS was more pronounced at the low dextrin/water ratio than at high dextrin/water ratio. In fact, SLS increased the ethanol content approximately 2.4–9.8-fold at the dextrin/ethanol/water ratio of 0.2–0.8/1/1, while increasing it only about 1.1–1.6-fold at the ratio of 1.2–2.0/1/1, suggesting that the amount of dextrin needed to encapsulate ethanol could be reduced by the presence of a small amount of SLS. It is probable that such an effect of SLS might be due to the unform disper-

sion of dextrin molecules by SLS during the formation of dextrin semipermeable membranes of spray-drying droplets. In addition, the increase of rigidity in dextrin membranes of the microcapsules resulting from a possible interaction of dextrin and SLS molecules appears to decrease the permeability of ethanol to the dextrin semipermeable membrane greater than that of water, thus increasing the encapsulation efficiency of microcapsules. Meanwhile, the decrease in ethanol content and encapsulation efficiency caused by excessive SLS ($\geq 2\%$) as observed in our study (Fig. 5) seems to be caused by prevention the surplus micelles of SLS from formation of the dextrin membrane shell, which may promote leakage of ethanol from the microcapsules. However, further studies for elucidation of the mechanism on SLS effect are necessary.

4. Conclusions

The present study shows that the small amount of SLS can increase the ethanol content and the encapsulation efficiency of ethanol, and allow the reduction in the amount of dextrin required to encapsulate ethanol in the microcapsules produced with dextrin, ethanol and water by spray drying technique. Therefore, the use of SLS may permit the effective encapsulation of high dose of water-insoluble drug into microcapsules. Further study is under progress to ascertain the effectiveness of SLS on the microencapsulation of water-insoluble drugs with ethanol, dextrin and water.

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