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Effect of Additive of the Encapsulated Amounts and Solubility of Poorly Water-soluble Ibuprofen in Gelatin Microcapsules

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ABSTRACT – Poorly water-soluble ibuprofen and ethanol can be encapsulated in gelatin microcapsule by spray drying technique. To select an optimal formula of ibuprofen-loaded gelatin microcapsule which increased the ethanol content and ibuprofen solubility with the decreased amount of gelatin in the microcapsules, in this study, the effect of gelatin, ibuprofen and sodium lauryl sulfate on the ibuprofen solubility and the amount of ethanol and ibuprofen encapsulated in the gelatin microcapsule were investigated. Ibuprofen solubility and the amount of ethanol encapsulated increased as gelatin and sodium lauryl sulfate increased, reached maximum at 4% and 0.6%, respectively and then followed a rapid decrease. Furthermore, the ibuprofen solubility and the encapsulated ibuprofen content increased as the amount of ibuprofen increased, reaching maximum at 0.5% and beyond that, there was no change in the solubility and ibuprofen content. However, the encapsulated ethanol content remained same irrespective of the amount of ibuprofen. On the basis of increased ibuprofen solubility, our results showed that the formula of ibuprofen-loaded gelatin microcapsule at the ratio of gelatin/ibuprofen/sodium lauryl sulfate/water/ethanol of 4/0.5/0.6/30/70 with ibuprofen solubility of about 290 μg/mL and ethanol content of about 160 μg/mg could be a potential oral delivery system for poorly water-soluble ibuprofen.

Key words – Gelatin; Microcapsule, Solubility, Ibuprofen, Spray drying, Ethanol1. Introduction

Ibuprofen [2-(4-isobutylphenyl)propionic acid], a non-steroidal anti-inflammatory agent, is widely used in the treatment of mild to moderated pain and fever. However, the bioavailability of ibuprofen is relatively low after oral administration, since it is practically insoluble in water.[1-2] Various oral formulations of ibuprofen such as prodrug,[3-4] inclusion complex,[5-6] microencapsulation,[7-8] solid dispersion,[1, 9-10] and formation of eutectic mixture[11] were developed to improve the solubility of ibuprofen.

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.[12-13] A mixed solution of ethanol, water and a water-soluble polymer can be transformed to a powdered form by spray drying technique in 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. [14] Therefore, in this study, this food technology was attempted to apply to pharmaceutical products.

In this study, to improve the solubility of poorly water-soluble ibuprofen, a gelatin microcapsule was prepared using spray-technique, the effect of gelatin, ibuprofen and sodium lauryl sulfate on the ibuprofen solubility and the amount of ibuprofen and ethanol encapsulated in the gelatin microcapsule were investigated. Sodium lauryl sulfate is an anionic surfactant commonly used in pharmaceutical preparations.[15-16] It has been previously employed to prevent microcapsules from attaching to the inner wall of spray drying chamber and to produce free-flowing powder.[17-18]

Materials and methods

Materials

Ibuprofen and gelatin were supplied from Dongwha Pharm. Co. Ltd. (Anyang, South Korea) and Sammi Co. Ltd. (Anyang, South Korea), respectively. Ethanol (94.6%v/v) and SLS (≥99%) were obtained from Ducksan Chemical Co. (Seoul, Korea) and Aldrich Chemical Co. (Milwaukee, WI, USA), respectively. All other chemicals were of reagent grade and used without further purification.

Preparation of ibuprofen-loaded gelatin microcapsules

A Büchi 190 nozzle type mini spray dryer (Flawil, Switzerland) was used for the preparation of gelatin microcapsule. Gelatin was dissolved in water to obtain aqueous gelatin solu-

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Table I–*Formulae of Spraying Solutions for the Preparation of Ibuprofen-loaded Gelatin Microcapsules*

Ingredients	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Gelatin (g)	4.0	2.0	3.0	5.0	6.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Ibuprofen (g)	0.5	0.5	0.5	0.5	0.5	0.1	0.3	0.7	1.0	0.5	0.5	0.5	0.5
SLS (g)	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.3	0.5	0.7	1.0
Ethanol (%)	30	30	30	30	30	30	30	30	30	30	30	30	30
Water (g)	70	70	70	70	70	70	70	70	70	70	70	70	70

tion. Ibuprofen was dissolved in ethanol to obtain the ibuprofen solution. Furthermore, sodium lauryl sulfate and 3 parts of ibuprofen solution were then added to 7 parts of aqueous gelatin solution one after another. The detailed formulae of solutions for the preparation of ibuprofen-loaded gelatin ultramicrocapsules are given in Table I. The resulting clear solution was prewarmed to 50°C. The resulting solution were delivered to the nozzle at a flow rate of 5 mL/min using a peristaltic pump and thereafter spray-dried at 105°C inlet temperatures. The pressure of spray air was 4 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.[19-21]

Determination of ethanol content in microcapsules

The various volumes (0.5, 1, 2, 4 and 8 mL) of ethanol stock solution (0.1 g/mL) and acetonitrile (150 μL) as an internal standard were mixed and adjusted to 100 mL with deionized water in a volumetric flask for the preparations of standard solutions. About 250 mg of each alcoholic microcapsule was accurately weighed and dissolved in 10 mL acetonitrile-deionized water mixture (1.5 μl/mL) in an Eppendorf tube. The ethanol content in 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 80, 160 and 130°C, respectively.[18]

Determination of ibuprofen content and aqueous solubility of ibuprofen in microcapsules

For the determination of ibuprofen content in microcapsules, excessive amount of gelatin microcapsule (about 30 mg) were added to 5 mL of ethanol, shaken in water bath for 3 days and filtered through membrane filter (0.45 μm). The concentration of ibuprofen in the resulting solution was then analyzed by HPLC (Jasco UV-975, Japan) equipped with an Inertsil ODS-3 C_{18} column (GL science, 0.5 μm, 15 cm × 0.46 cm i.d.) and UV detector (Model L-7450). The mobile phase consisted of acetoniltrile and phosphate buffer (pH 3.5) (4 : 6, volume ratio). The eluent was monitored at 220 nm with a flow rate of 1.2 mL/min.[22-23]

For the determination of aqueous solubility of ibuprofen, excessive amount of gelatin microcapsule (about 30 mg) were added to 5 mL of water, shaken in water bath for 3 days and filtered through membrane filter (0.45 μm). The concentration of ibuprofen in the resulting solution was then analyzed by HPLC method mentioned above.

Results and discussion

On drying the gelatin dissolved in an ethanol-water cosolvent system on a rotary evaporator, ethanol and water evaporate simultaneously and gelatin is finally dried. However, microcapsules containing ethanol in the gelatin shells are produced by spray-drying. Spraying the gelatin dissolved in ethanol-water mixture through a fluid pressure nozzle into the drying chamber at an appropriate temperature, ethanol and water are initially evaporated within the chamber of the spray dryer at the same time. However, as the atomized liquid droplets contact the hot drying air for a little longer, the concentration of gelatin began to increase near the surface of liquid droplets and the water content on the surface of droplets decreased very rapidly as water and ethanol evaporated. As a result, a concentrated gelatin layer was formed on the surface of droplets. Water was continuously dried through the concentrated gelatin layer, but ethanol scarcely passed through this layer due to the extremely low diffusion coefficient of ethanol in concentrated gelatin layer.[12-14] Thus, the concentrated gelatin will acted as a semipermeable membrane, permitting continual water loss by diffusion but effectively retaining ethanol. Finally, the gelatin was solidified and ethanol was captured inside the gelatin shell and gelatin microcapsule was produced. Employing the same principle of producing the powder alcohol, ibuprofen-loaded gelatin microcapsule could be prepared by spray-drying the solution of ibuprofen and gelatin simultaneously dissolved in ethanol-water cosolvent system. Ibuprofen-loaded gelatin microcapsule was a solid form of

microcapsules simultaneously containing ethanol and ibuprofen in water-soluble gelatin shell. The large amount of ethanol was necessary to dissolve the high dose of water-insoluble ibuprofen in the preparation of gelatin microcapsule using spray-drying method. Consequently, the large amount of gelatin was required to encapsulate the ethanol, causing the inconvenience in oral administration due to the bulkiness. Thus, in this study, it was attempted to select an optimal formula of ibuprofen-loaded gelatin microcapsule which increased the ethanol content and ibuprofen solubility with the decreased amount of gelatin in the microcapsules.

To investigate the effect of gelatin on the ibuprofen solubility and the amount of ibuprofen and ethanol encapsulated in the gelatin microcapsule, 2-6 g gelatin, 0.5 g ibuprofen and 0.6 g sodium lauryl sulfate was dissolved in 30% ethanol (Table I, formula I-V) and spray-dried. The ibuprofen solubility and the amount of ibuprofen and ethanol encapsulated in the gelatin microcapsule abruptly increased as the amounts of gelatin increased, reached the maximum levels at 4% and then decreased (Fig. 1). Our results suggested that, at the gelatin concentration of below 4 %, the amounts of gelatin microcapsules might increase as the gelatin concentration increased. However, at the gelatin concentration of above 5%, the amounts of gelatin microcapsules might not increase but the thickness of gelatin shell might increase.[19-20]

To investigate the effect of ibuprofen on the ibuprofen solubility and the amount of ibuprofen and ethanol encapsulated in the gelatin microcapsule, 4 g gelatin, 0.1-1.0 g ibuprofen and 0.6 g sodium lauryl sulfate was dissolved in 30% ethanol (Table I, formula I, VI-IX) and spray-dried. The ibuprofen solubility and encapsulated ibuprofen increased as the amounts of ibuprofen increased, reached the maximum levels at 0.5% and then hardly increased as the amounts of ibuprofen increased. However, the amount of ethanol encapsulated in the gelatin microcapsule hardly changed as the amounts of ibuprofen increased (Fig. 2). Our results suggested that, at the ibuprofen concentration of below 0.5%, ibuprofen might be dissolved more in ethanol. However, at the ibuprofen concentration of above 5%, the solubility of ibuprofen might not increase with the increase in ibuprofen concentration.[24]

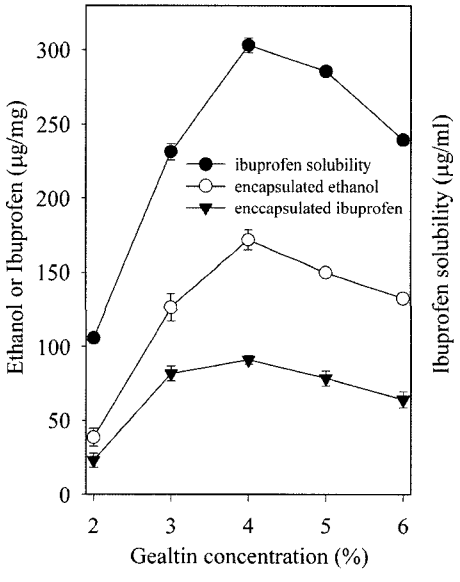

Figure 1—Effect of gelatin on the ibuprofen solubility and additives encapsulated in the gelatin microcapsule. Each value represents the mean ± S.E. (n=5).

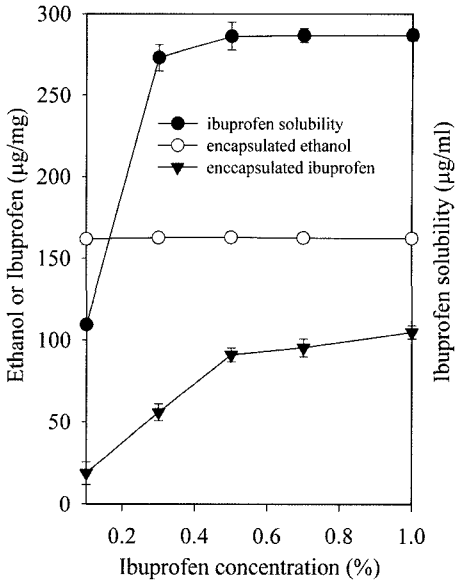

Figure 2—Effect of ibuprofen on the ibuprofen solubility and additives encapsulated in the gelatin microcapsule. Each value represents the mean ± S.E. (n=5).

To investigate the effect of sodium lauryl sulfate the ibuprofen solubility and the amount of ibuprofen and ethanol encapsulated in the gelatin microcapsule, 4 g gelatin, 0.5 g ibuprofen and 0.3-1.0 g sodium lauryl sulfate was dissolved in 30% ethanol (Table I, formula I, X-XIII) and spray-dried. Sodium lauryl sulfate is an anionic surfactant commonly used in pharmaceutical preparations.[15-16] In the absence of sodium lauryl sulfate, we observed strong electrostatic interaction among microcapsules arisen from friction in spray dryer making the powder fly in all directions, which caused difficulty in handling. Sodium lauryl sulfate has been used to avoid attaching dry elixir to the inner wall of spray-drying chamber and to produce free-flowing powders.[18]

Both the ibuprofen solubility and the amount of ethanol encapsulated in the gelatin microcapsule increased as the amounts of sodium lauryl sulfate increased, reached the max-

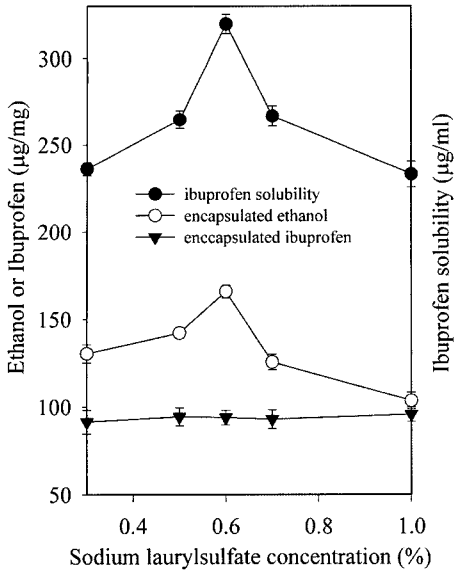

Figure 3–Effect of sodium lauryl sulfate on the ibuprofen solubility and additives encapsulated in the gelatin microcapsule. Each value represents the mean ± S.E. (n=5).

imum levels at 0.6%, and then rapidly decreased above 0.7% (Fig. 3). Our results suggested that, at sodium lauryl sulfate concentrations of below 0.6%, sodium lauryl sulfate might help the formation of gelatin microcapsule.[15] However, at sodium lauryl sulfate concentrations of above 0.7%, sodium lauryl sulfate might obstruct the formation of gelatin microcapsule. Furthermore, the amount of ibuprofen encapsulated in the gelatin microcapsule hardly changed as the sodium lauryl sulfate of ibuprofen increased (Fig. 3), indicating that sodium lauryl sulfate hardly affected the encapsulation of ibuprofen in the gelatin microcapsule. Therefore, in the preparation of ibuprofen-loaded gelatin microcapsule, the gelatin, ibuprofen and sodium lauryl sulfate concentration was fixed to 4, 0.5 and 0.6 %, respectively.

From these findings, a microcapsule formula at the ratio of gelatin/ibuprofen/sodium lauryl sulfate/water/ethanol of 4/0.5/0.6/30/70 with the maximum ibuprofen solubility of 286.3 ± 8.6 μg/mL and the amount of ethanol of about 162.7 ± 2.6 μg/mg (16.27 ± 0.26%) was suitable for ibuprofen-loaded gelatin microcapsule with respect to increased ethanol content and ibuprofen solubility with the decreased amount of gelatin in the microcapsules.

Conclusions

Taken together, it was concluded that the ibuprofen-loaded gelatin microcapsule at the ratio of gelatin/ibuprofen/sodium lauryl sulfate/water/ethanol of 4/0.5/0.6/30/70 with maximum ibuprofen solubility and amount of ethanol and ibuprofen could be a potential oral delivery system for poorly water-soluble ibuprofen.

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