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Novel gelatin microcapsule with bioavailability enhancement of ibuprofen using spray-drying technique

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Abstract

A poorly water-soluble ibuprofen and ethanol can be encapsulated in gelatin microcapsule by spray-drying technique. To develop a novel ibuprofen-loaded gelatin microcapsule with bioavailability enhancement, the effect of spray-drying conditions, gelatin, ibuprofen and sodium lauryl sulfate on the ibuprofen solubility and the amount of ethanol encapsulated in gelatin microcapsule were investigated. The ibuprofen solubility and amount of encapsulated ethanol increased as inlet temperature and amount of sodium lauryl sulfate increased, reached maximum at 105 °C and 0.6%, respectively and after that followed a rapid decrease. Furthermore, they abruptly increased as the amount of gelatin increased, reaching maximum at 4% then remaining almost stable, but the encapsulated ethanol content decreased noticeably. Likewise, the ibuprofen solubility increased as the amount of ibuprofen increased, reaching maximum at 0.5% and beyond that, there was no change in the solubility. However, the encapsulated ethanol content hardly changed irrespective of the amount of ibuprofen. Furthermore, 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 showed ibuprofen solubility of about 290 μg/ml and ethanol content of about 160 μg/mg. This gelatin microcapsule dramatically increased the initial dissolution rate of ibuprofen compared to ibuprofen powder in pH 1.2 simulated gastric fluid. Moreover, it gave significantly higher initial plasma concentrations, C_{max} and AUC of ibuprofen in rats than did ibuprofen powder, indicating that the drug from gelatin microcapsule could be more orally absorbed in rats. Our results suggested that the enhanced oral bioavailability of ibuprofen in the gelatin microcapsule was contributed by the marked increase in the absorption rate of ibuprofen due to the crystallinity change to amorphous form and increase in dissolution rate of ibuprofen in the gelatin microcapsule in rats. Thus, the ibuprofen-loaded gelatin microcapsule developed using spray-drying technique with gelatin would be useful to deliver ibuprofen in a pattern that allows fast absorption in the initial phase, leading to better absorption.

Keywords: Gelatin; Microcapsule; Ibuprofen; Spray drying; Ethanol; Bioavailability

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 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 (Menting et al., 1970; Thijssen, 1971).

Based on this notion, a rapidly absorbed 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 dextrin 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 of poorly water-soluble

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drugs (Ahn et al., 1998; Kim et al., 1995; Kim and Yoon, 1995). However, from the industrial viewpoint, it is not possible to pack dry elixirs with dextrin in the capsules, since it has poor flow ability and weak strength. Therefore, new pharmaceutical product is required to be developed to maintain the good physicochemical property.

In this study, to improve the bioavailability of poorly water-soluble ibuprofen, a gelatin microcapsule encapsulated of ethanol and ibuprofen has been formulated by using stronger gelatin, instead of dextrin, as a water-soluble polymer shell. It is desirable to maximize the ethanol contents in the gelatin microcapsule in order to improve the solubility of poorly water-soluble ibuprofen. However, the large amount of gelatin is required to encapsulate the ethanol, causing the inconvenience in oral administration due to the bulkiness. Thus, to select an optimal formula of ibuprofen-loaded gelatin microcapsule which increase the ethanol content and ibuprofen solubility with the decreased amount of gelatin in the microcapsules, the effect of inlet temperature, gelatin, ibuprofen and sodium lauryl sulfate on the ibuprofen solubility and the amount of ethanol encapsulated in the gelatin microcapsule were investigated. Sodium lauryl sulfate is an anionic surfactant commonly used in pharmaceutical preparations (Kaka and Tekle, 1992; Kokot and Zmidzinska, 2001). Previously, it has been employed to prevent microcapsules from attaching to the inner wall of spray-drying chamber and to produce free-flowing powder (Kim et al., 1994; Lee et al., 1999). Furthermore, the phisicochemical property, dissolution and pharmacokinetic profiles of ibuprofen from the gelatin microcapsule were investigated.

2. Materials and methods

2.1. Materials

Ibuprofen and gelatin (USP grade, type A) were supplied from Dongwha Pharm. Co. Ltd. (Anyang, South Korea) and Sammi Co. Ltd. (Anyang, South Korea), respectively. Ethanol (94.6% v/v) and sodium lauryl sulfate (≥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.

2.2. 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 solution. Ibuprofen was dissolved in ethanol to obtain the ibuprofen solution. Furthermore, sodium lauryl sulfate and three parts of ibuprofen solution were then added to seven parts of aqueous gelatin solution one after another. The detailed formulae of solutions for the preparation of ibuprofen-loaded gelatin microcapsules are given in Table 1. 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 100–120 °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 (Ahn et al., 1998; Kim et al., 1995; Kim and Yoon, 1995).

2.3. Determination of ethanol content and ibuprofen solubility 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 (Lee et al., 1999).

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 (Jasco UV-975, Japan) as described below.

2.4. Shape of ibuprofen-loaded gelatin microcapsule

The shape and size of gelatin microcapsule was examined using a scanning electron microscope (S-4100, Hitachi, Japan). The microcapsules were loaded on the specimen stub via double-side sticky tape and coated with gold (Hitachi Iron sputter, E-1030) for 30 min at 100–200 mTorr in a shutter coater before taking photograph at an accelerating voltage of 2.4 kV (Kim et al., 1995; Kim and Yoon, 1995).

Table 1
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 (g)	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

2.5. Thermal characteristics and crystallinity

The thermal characteristics of ibuprofen-loaded gelatin microcapsule were investigated using a differential scanning calorimeter (DSC Q-1000, TA Instrument, Leatherhead, UK). About 5 mg of samples were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a heating rate of 10 °C/min from 0 to 200 °C. Furthermore, powder crystallinity of ibuprofen-loaded gelatin microcapsule was assessed by X-ray powder diffraction (D/MAX-2500, RIGAKU, Japan) conducted at room temperature using Ni-filtered Cu target at 30 mA and 40 kV in the region of $5^\circ \leq 2\theta \leq 40^\circ$ with an angular increment of $0.02^\circ\ s^{-1}$ (Venkateswarlu and Manjunath, 2004).

2.6. Dissolution test

About 250 mg of ibuprofen-loaded gelatin microcapsule (equivalent to 25 mg of ibuprofen) and 25 mg of powder ibuprofen pre-sieved with 50-mesh screen were inserted into the basket, respectively. The basket was then placed in a dissolution tester (Shinseang Instrument Co., South Korea). Dissolution test was performed at 36.5 °C using the basket method at 100 rpm with 500 ml pH 1.2 simulated gastric fluid as a dissolution medium. At predetermined interval, 3 ml of the medium was sampled and filtered. Then, the concentration of ibuprofen in the resulting solution was analyzed by HPLC (Jasco UV-975, Japan) as described below.

2.7. Pharmacokinetic study

In vivo experiments. Male Sprague-Dawley rats weighing 250 ± 20 g were fasted for 24–36 h prior to the experiments but allowed free access to water. Sixteen rats were divided into two groups. The rats in each group were administered with ibuprofen powder pre-sieved with 50-mesh screen and gelatin microcapsule (0.24 g/kg equivalent to ibuprofen 25 mg/kg), respectively. All animals care and procedures were conducted according to the Guilding Priciples in the Use of Animals in Toxicology, as adopted in 1989 and revised in 1999 by the Society of Toxicology (SOT, 1999).

Administration and blood-collecting. Each rat, anesthetized in an ether-saturated chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube was inserted into the right femoral artery of the rat, all of the incision was covered with wet cotton and the cannula was flushed with 0.2 ml of heparinized normal saline (80 U/ml) to prevent blood clotting. Ibuprofen powder and ibuprofen-loaded gelatin microcapsule (0.24 g/kg equivalent to ibuprofen 25 mg/kg) were filled in small hard capsule (#9, Suheung capsule Co. Ltd., Seoul, South Korea), and orally administered to rats in each group, respectively. Half a milliliter of blood was collected from the right femoral artery at various intervals and centrifuged at 3000 rpm for 10 min using a centrifuge 5415C (Eppendorf, USA) (Geisslinger et al., 1989; Theis et al., 1994).

Blood sample analysis. Plasma (0.05 ml) was mixed with 0.4 ml of acetonitrile solution containing flufenamic acid (0.5 μg/ml), as an internal standard. It was then centrifuged at 3000 rpm for 10 min to precipitate the proteins. The supernatant layer (0.4 ml) was evaporated under N_2(g). The residue was reconstituted in 50 μl of mobile phase. Then, the resulting solution was 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, v/v). The eluent was monitored at 220 nm with a flow rate of 1.2 ml/min (Canaparo et al., 2000; Choi et al., 2001; Gillespie et al., 1982; Haikala et al., 1991; Kokot and Zmidzinska, 2001).

3. 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 (Menting and Hoogstad, 1967; Menting et al., 1970; Sato and Kurusu, 1974; Sato et al., 1982). Therefore, the concentrated gelatin will act 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 (Fig. 1). 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.

First, to investigate the effect of spray-drying conditions on the ibuprofen solubility and the amount of ethanol encapsulated in the gelatin microcapsule, 4 g gelatin, 0.5 g ibuprofen and 0.6 g sodium lauryl sulfate were dissolved in ethanol–water

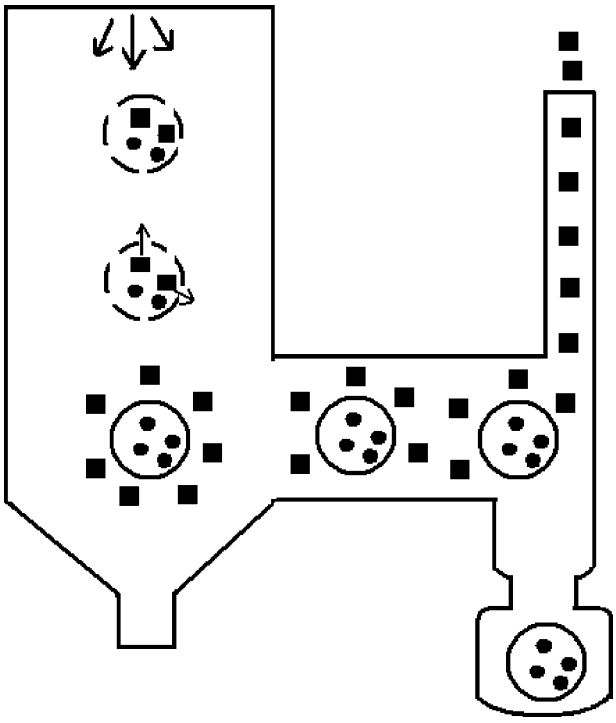

Fig. 1. Principle of preparation of gelatin microcapsule: (●), ethanol; (■), water.

cosolvent system (30/70%, w/w) (Table 1, formula I) and spray-dried with various spray-drying conditions. Except inlet temperature, the conditions such as air pressure, flow rate and aspirator pressure hardly affected the ibuprofen solubility and the amount of encapsulated ethanol. Both the ibuprofen solubility and the amount of encapsulated ethanol increased as the inlet temperature increased, reached the maximum levels at 105 °C, and then rapidly decreased above 110 °C at the ratio of gelatin/ibuprofen/sodium lauryl sulfate/water/ethanol of 4/0.5/0.6/30/70 (Fig. 2A). At the inlet temperature of below 105 °C, ethanol might not penetrate in the preparation of gelatin microcapsule. However, at the inlet temperature of above 105 °C, ethanol into the gelatin microcapsule might evaporate (Lee et al., 1999). Thus, with respect to the increased ethanol content and ibuprofen solubility in the preparation of ibuprofen-loaded gelatin microcapsule, the inlet temperature was fixed to 105 °C.

To investigate the effect of gelatin on the ibuprofen solubility and the amount of encapsulated ethanol, 2–6 g gelatin, 0.5 g ibuprofen and 0.6 g sodium lauryl sulfate were dissolved in 30% ethanol (Table 1, formulae I–V) and spray-dried. Both the ibuprofen solubility and the amount of encapsulated ethanol abruptly increased as the amounts of gelatin increased, reached the maximum levels at 4%. Then, the ibuprofen solubility hardly changed but the amount of encapsulated ethanol decreased as the amounts of gelatin increased (Fig. 2B). 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 (Ahn et al., 1998; Kim et al., 1995). Thus, in the preparation of ibuprofen-loaded gelatin microcapsule, the gelatin concentration was fixed to 4%.

To investigate the effect of ibuprofen on the ibuprofen solubility and the amount of encapsulated ethanol, 4 g gelatin, 0.1–1.0 g ibuprofen and 0.6 g sodium lauryl sulfate was dissolved in 30% ethanol (Table 1, formulae I, VI-IX) and spray-dried. The ibuprofen solubility 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 encapsulated ethanol hardly changed as the amounts of ibuprofen increased (Fig. 2C). Our results suggested that, at the ibuprofen concentration of below 0.5%, ibuprofen might dissolve more in ethanol. However, at the ibuprofen concentration of above 5%, the solubility of ibuprofen might not increase with the increase in ibuprofen concentration (Yong et al., 2004). Thus, in the preparation of ibuprofen-loaded gelatin microcapsule, the ibuprofen concentration was fixed to 0.5%.

To investigate the effect of sodium lauryl sulfate on the ibuprofen solubility and the amount of encapsulated ethanol, 4 g gelatin, 0.5 g ibuprofen and 0.3–1.0 g sodium lauryl sulfate was dissolved in 30% ethanol (Table 1, formulae I, X–XIII) and spray-dried. Sodium lauryl sulfate is an anionic surfactant commonly used in pharmaceutical preparations. 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 was used to avoid attaching gelatin microcapsule to the inner wall of spray-drying chamber and to produce free-flowing powder (Lee et al., 1999). Both the ibuprofen solubility and the amount of encapsulated ethanol increased as the amounts of sodium lauryl sulfate increased, reached the maximum levels at 0.6%, and then rapidly decreased above 0.7% (Fig. 2D). Our results suggested that, at the sodium lauryl sulfate concentration of below 0.6%, sodium lauryl sulfate might help the formation of gelatin microcapsule (Lee et al., 1999). However, at the sodium lauryl sulfate concentration of above 0.7%, sodium lauryl sulfate might obstruct the formation of gelatin microcapsule. Thus, in the preparation of ibuprofen-loaded gelatin microcapsule, the sodium lauryl sulfate concentration was fixed to 0.6%.

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.

The scanning electron micrographs of ibuprofen-loaded gelatin microcapsule at the ratio of gelatin/ibuprofen/sodium lauryl sulfate/water/ethanol of 4/0.5/0.6/30/70 were illustrated in Fig. 3. The gelatin microcapsule (Fig. 3A) was spherical in shape with smooth surface (Ahn et al., 1998; Kim and Yoon, 1995). Fig. 3B and C demonstrates that a fracture microcapsule with hole and a cross-sectional view of gelatin microcapsule showed the large inner cavity containing ethanolic drug solution

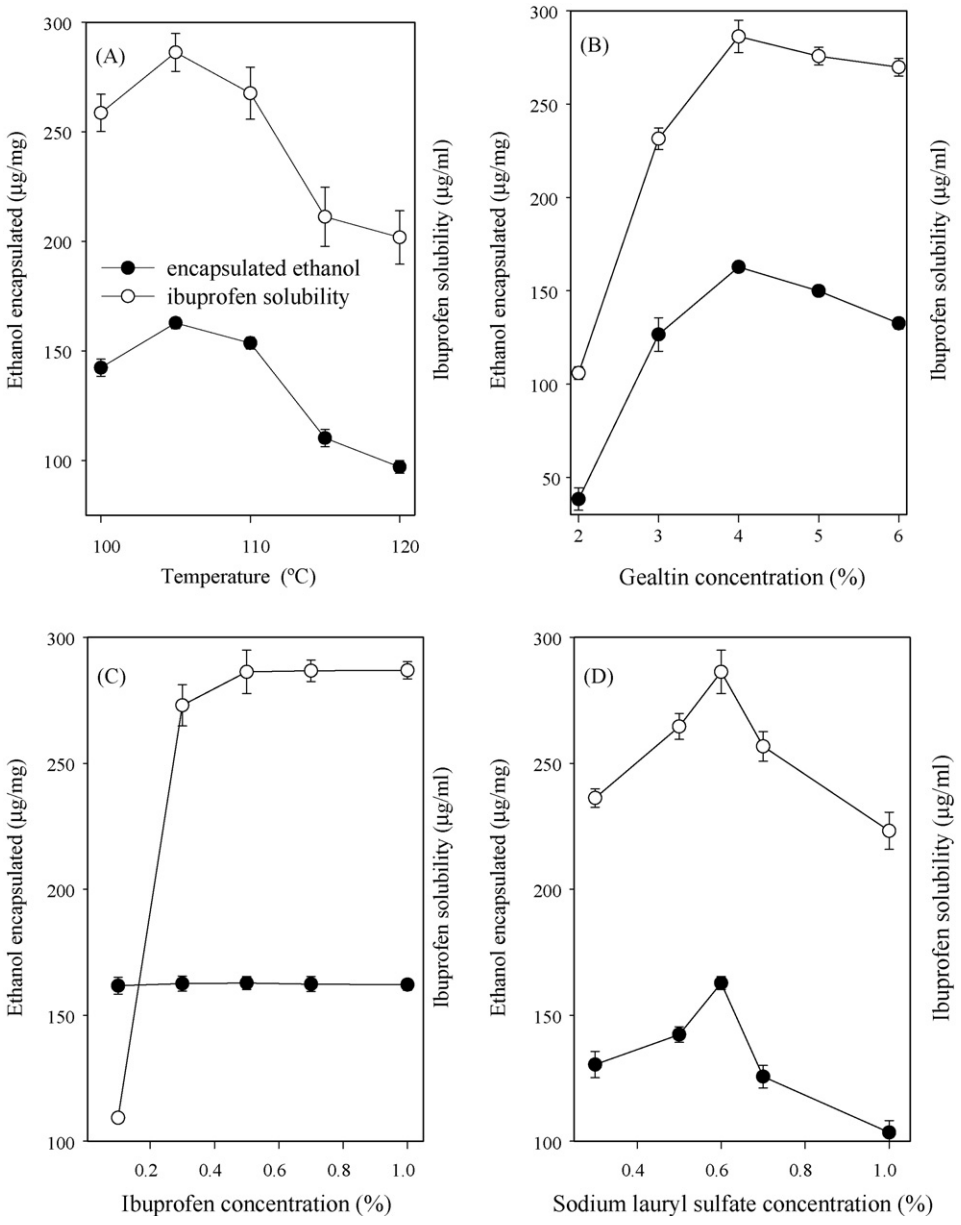

Fig. 2. Effect of inlet temperature (A), gelatin (B), ibuprofen (C) and sodium lauryl sulfate (D) on the aqueous ibuprofen solubility and the amount of ethanol encapsulated in the gelatin microcapsule. Each value represents the mean ± S.E. ($n = 5$).

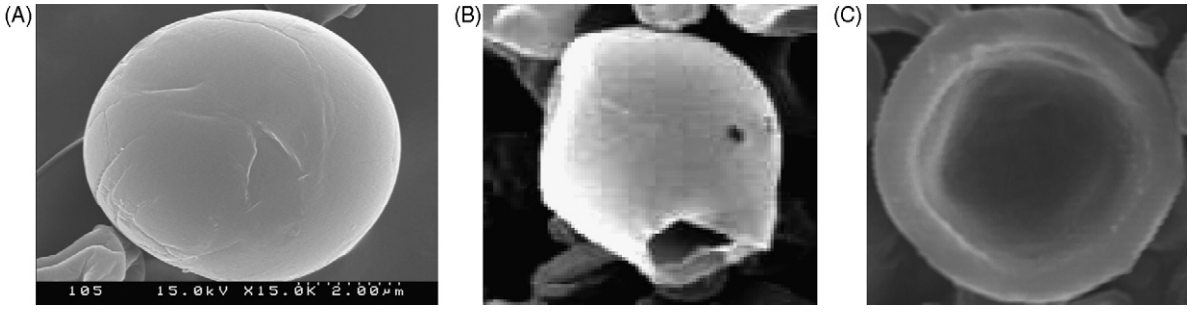

Fig. 3. Scanning electron micrographs of gelatin microcapsule (15,000×): (A) microcapsule with spherical shape and smooth surface; (B) fracture microcapsule with hole; (C) microcapsule with inner cavity.

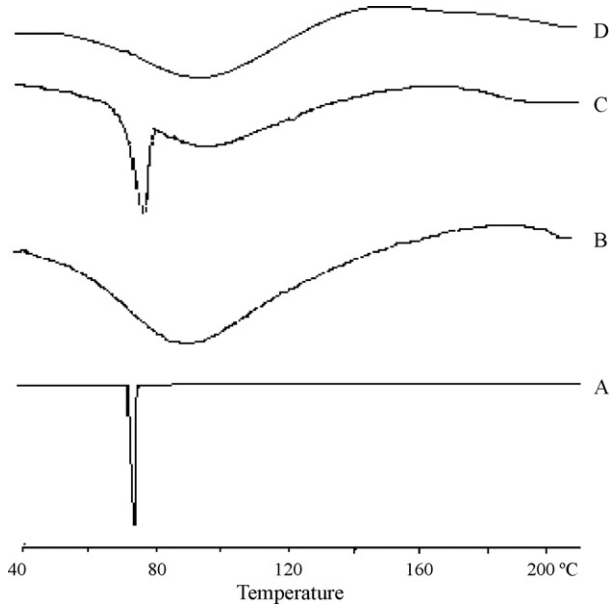

Fig. 4. Differential scanning calorimetric thermograms: (A) ibuprofen powder; (B) gelatin; (C) physical mixture; (D) gelatin microcapsule.

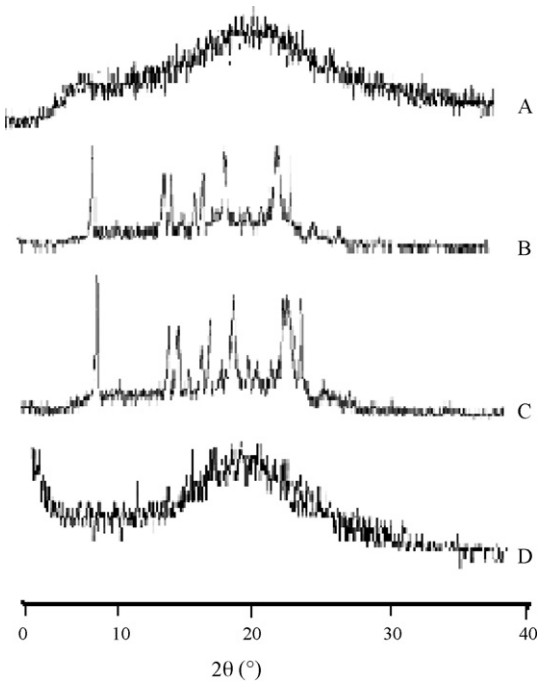

Fig. 5. X-ray powder diffraction: (A) gelatin; (B) ibuprofen powder; (C) physical mixture; (D) gelatin microcapsule.

in a gelatin shell. The geometric mean diameter of ibuprofen-loaded gelatin microcapsule was 6.34 ± 0.57 μm.

Thermal behavior of drug powder, gelatin, physical mixture and gelatin microcapsule are shown in Fig. 4. The DSC curve showed that ibuprofen appeared a sharp endothermic peak at about 75 °C corresponding to its melting, indicating its crystalline nature (Fig. 4A). The broad endotherm peak of gelatin was observed at about 85 °C. The melting peak appeared in drug peak was also showed with reduced intensity in physical mixtures. However, a sharp peak corresponding to drug was disappeared but only broad peak corresponding to gelatin at about 85 °C was observed in gelatin microcapsule (Fig. 4D). This significant difference in DSC pattern of gelatin microcapsule suggested that ibuprofen was present in the amorphous state in the gelatin microcapsule (Walser et al., 1997).

Powder X-ray diffractometry is one of the most common technique used to identify crystalline structure of bulk materials (Venkateswarlu and Manjunath, 2004). The powder X-ray diffractometry patterns are presented in Fig. 5. The powder X-ray diffractogram of ibuprofen has sharp peaks at diffraction angles showing a typical crystalline pattern (Fig. 5B) (Leising et al., 1996). However, all major characteristic crystalline peaks appeared in drug were observed in physical mixture (Fig. 5C) but hardly observed in gelatin microcapsule (Fig. 5D), suggesting that ibuprofen was amorphous form in the gelatin microcapsule. The change in crystallinity to amorphous form was expected to enhance the dissolution and bioavailability of a poorly water-soluble ibuprofen.

To evaluate whether gelatin microcapsule affected the dissolution rates of ibuprofen, we performed the dissolution studies on ibuprofen powder and ibuprofen-loaded gelatin microcapsule at the ratio of gelatin/ibuprofen/sodium lauryl sulfate/water/ethanol of 4/0.5/0.6/30/70. The dissolution profiles of ibuprofen in two ibuprofen-loaded preparations are illustrated in Fig. 6. The initial dissolution rate of ibuprofen in the gelatin microcapsule increased dramatically compared to ibuprofen powder in pH 1.2 simulated gastric fluid. The amounts of ibuprofen dissolved from gelatin microcapsule in pH 1.2 simulated gastric fluid for 30 min increased about fivefold compared to ibuprofen powder ($85.0 \pm 1.6\%$ vs.$17.6 \pm 6.9\%$). It was thought that ibuprofen encapsulated in the gelatin microcapsule

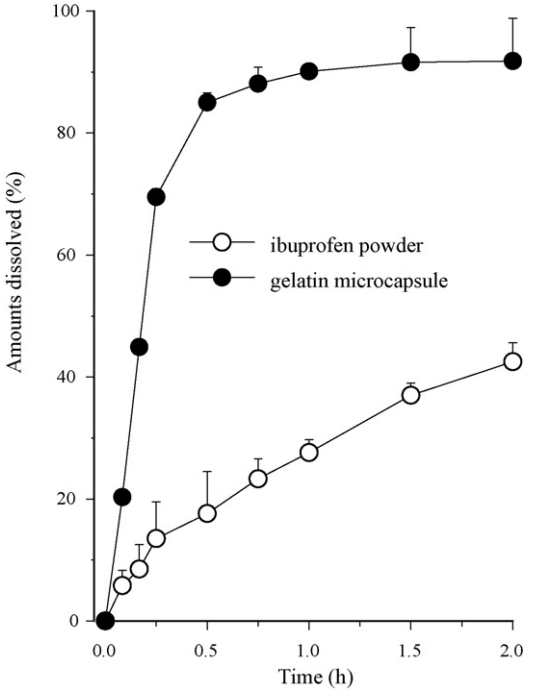

Fig. 6. Dissolution profile of ibuprofen from powder and gelatin microcapsule. Each value represents the mean ± S.E. ($n = 6$).

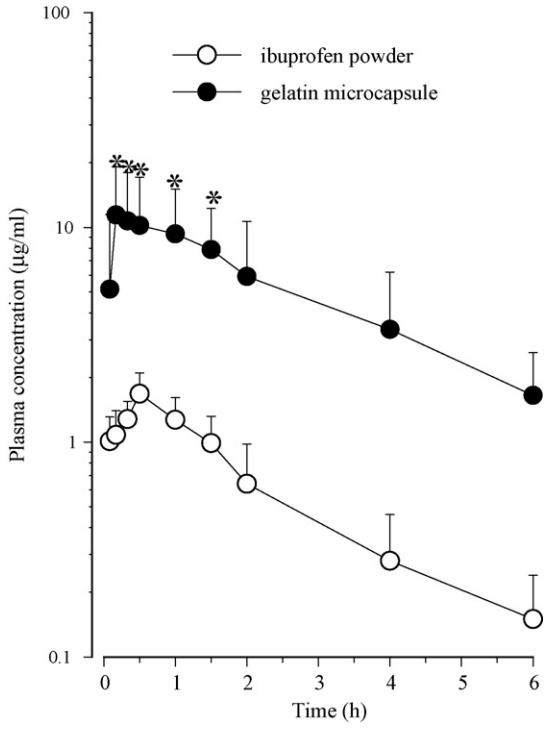

Fig. 7. Plasma concentration–time profiles of ibuprofen after oral administration of powder and gelatin microcapsule to rats. Each value represents the mean ± S.E. ($n = 8$). *$P < 0.05$ compared with ibuprofen powder.

was dissolved and dispersed rapidly as a result of amorphous form of drug and cosolvent effect of ethanol because the gelatin wall of microcapsule is very soluble (Ahn et al., 1998; Kim et al., 1997).

The pharmacokinetic parameters of ibuprofen were determined after oral administration of ibuprofen powder and the ibuprofen-loaded gelatin microcapsule. Fig. 7 shows the change of mean plasma concentration of ibuprofen after oral administration of preparations in rats. The total plasma concentrations of ibuprofen in gelatin microcapsule, were higher compared with those in ibuprofen powder. In particular, the initial plasma concentrations of ibuprofen in gelatin microcapsule, until 1 h 30 min, were significantly higher compared with those in ibuprofen powder ($P < 0.05$). Our results suggested that the higher initial plasma concentrations of ibuprofen in gelatin microcapsule were due to the increase in dissolution rate of ibuprofen in the gelatin microcapsule in rats (Ahn et al., 1998; Choi et al., 1998; Kim et al., 1997).

Table 2
Pharmacokinetic parameters of ibuprofen delivered by ibuprofen preparations

Parameters	Ibuprofen powder	Gelatin microcapsule
AUC (h μg/ml)	2.55 ± 1.17	20.79 ± 10.76*
T_{max} (h)	0.5 ± 0.35	0.17 ± 0.11
C_{max} (μg/ml)	1.68 ± 0.36	11.42 ± 5.34*
K_{el} (h^{-1})	0.27 ± 0.18	0.57 ± 0.42
$t_{1/2}$ (h)	2.59 ± 0.35	1.21 ± 0.92

Each value represents the mean ± S.E. ($n = 8$).
* $P < 0.05$ compared with ibuprofen powder.

The pharmacokinetic parameters are shown in Table 2. The gelatin microcapsule gave significantly higher AUC and C_{max} of ibuprofen than did ibuprofen powder ($P < 0.05$). In particular, the AUC of ibuprofen from gelatin microcapsule was about eightfold higher than that from ibuprofen powder, indicating that the enhanced oral relative bioavailability of ibuprofen in the gelatin microcapsule was contributed by the marked increase in the absorption rate of ibuprofen due to the crystallinity change to amorphous form and the increase in dissolution rate of ibuprofen in the gelatin microcapsule in rats (Ahn et al., 1998; Ghosh et al., 1998; Glowka, 2000; Kaka and Tekle, 1992). However, the T_{max}, K_{el} and $t_{1/2}$ values of ibuprofen from gelatin microcapsule were not significantly different from those from ibuprofen powder. Our results suggested that ibuprofen-loaded gelatin microcapsule would be useful to deliver ibuprofen in a pattern that allows fast absorption in the initial phase, leading to better absorption.

4. Conclusion

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 had the maximum ibuprofen solubility of about 290 μg/ml and the amount of ethanol of about 160 μg/mg (16%). Furthermore, this ibuprofen-loaded gelatin microcapsule gave significantly higher initial plasma concentrations, C_{max} and AUC of ibuprofen than did ibuprofen powder, indicating that the drug from gelatin microcapsule could be more orally absorbed in rats. Thus, the ibuprofen-loaded gelatin microcapsule developed using spray-drying technique with gelatin was a more effective oral dosage form for poorly water-soluble ibuprofen.

On the other hands, for the development of ibuprofen-loaded gelatin microcapsule, the further study on powder characteristics and stability of gelatin microcapsule is needed because it contains the large amounts of ethanol. Thus, its powder characteristics such as flowability and hardness will be carried out compared with gelatin microcapsule without ethanol. Furthermore, its stability in accelerated condition will be performed by checking ibuprofen and ethanol contents in the gelatin microcapsule, drug crystallinity and powder characteristics for 6 months.

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