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Retarded Dissolution of Ibuprofen in Gelatin Microcapsule by Cross-Linking with Glutaradehyde

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Ibuprofen-loaded gelatin microcapsule, a solid form of microcapsules simultaneously containing ethanol and ibuprofen in water-soluble gelatin shell was previously reported to improve the dissolution of drug. In this study, to retard the initial high dissolution of ibuprofen from gelatin microcapsule, the ibuprofen-loaded cross-linked gelatin microcapsule was prepared by treating an ibuprofen-loaded gelatin microcapsule with glutaraldehyde and its dissolution was evaluated compared to ibuprofen powder and gelatin microcapsule. The ibuprofen-loaded cross-linked microcapsule treated with glutaraldehyde for 10 and 60 sec gave significantly higher dissolution rates than did ibuprofen powder. Furthermore, the dissolution rate of ibuprofen from the cross-linked microcapsule treated for 10 sec was similar to that from gelatin microcapsule. However, the dissolution rate of ibuprofen from the cross-linked microcapsule treated for 60 sec decreased significantly compared to gelatin microcapsule, suggesting that the treatment of gelatin microcapsule with glutaraldehyde for 60 sec could cross-link the gelatin microcapsule. Furthermore, the cross-linking of gelatin microcapsule markedly retarded the release rate of ibuprofen in pH 1.2 simulated gastric fluid compared to gelatin microcapsule. However, the cross-linking of gelatin microcapsule with glutaraldehyde hardly changed the size of gelatin microcapsules, ethanol and ibuprofen contents encapsulated in gelatin microcapsule. Thus, the ibuprofen-loaded cross-linked gelatin microcapsule could retard the initial high dissolution of poorly water-soluble ibuprofen.

Key words: Ibuprofen, Cross-linked gelatin microcapsule, Glutaraldehyde, Dissolution

INTRODUCTION

Ibuprofen [2-(4-isobutylphenyl)propionic acid], a non-steroidal anti-inflammatory agent, is widely used in treatment of mild to moderated pain and fever. However, the bioavailability of ibuprofen is relatively low after oral administration, since it was practically insoluble in water (Greenhalgh *et al.*, 1999; Glowka, 2000). Various oral formulations of ibuprofen such as prodrug (Murtha and Ando, 1994), inclusion complex (Charoenchaitrakool *et al.*, 2002; Ghorab and Adeyeye, 2001), microencapsulation (Kachrimanis *et al.*, 2000) and solid dispersion (Greenhalgh *et al.*, 1999; Khan and Jiabi, 1998) were developed to improve the solubility of ibuprofen.

Recently, to improve the bioavailability of a poorly water-soluble ibuprofen, we developed a new oral dosage form termed 'gelatin microcapsule' which encapsulated of ethanol and ibuprofen using gelatin as a water-soluble polymer shell (Li *et al.*, 2006). The poorly water-soluble ibuprofen encapsulated in water-soluble polymers was easily soluble in gastrointestinal tract after the oral administration, leading to preferable bioavailability of poorly water-soluble ibuprofen. However, as the ibuprofen-loaded gelatin microcapsule gave significantly too high initial burst-out plasma peak due to very fast dissolution rate of drug, it may induce side effect of ibuprofen.

In this study, the ibuprofen-loaded cross-linked gelatin microcapsule was prepared by treating ibuprofen-loaded gelatin microcapsule with glutaraldehyde for retarding the initial high dissolution of ibuprofen from gelatin microcapsule. Its dissolution was investigated compared to ibuprofen powder and gelatin microcapsule. In the formulation of microencapsulation, glutaraldehyde has played a role of forming a microcapsule and controlling the release of drug (Akbuga and Bergisadi, 1999; Sahin *et al.*, 2002; Tabata and Ikada, 1989).

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MATERIALS AND METHODS

Materials

Ibuprofen and gelatin were supplied from Dongwha Pharm. Co. Ltd. (Anyang, Korea) and Sammi Co. Ltd. (Anyang, Korea), respectively. Ethanol were obtained from Ducksan Chemical (Seoul, Korea). Glutaradehyde and sodium lauryl sulfate were obtained from Aldrich Chemical Co. (Milwaukee, WI, U.S.A.). All other chemicals were of reagent grade and used without further purification.

Preparation of ibuprofen-loaded cross-linked microcapsule

A Büchi 190 nozzle type mini spray dryer (Flawil, Switzerland) was used for the preparation of gelatin microcapsule. Four gram of gelatin was dissolved in 70 g water at 40-45°C to obtain aqueous gelatin solution. Then, 0.5 g ibuprofen was dissolved in 30 g ethanol to obtain the ibuprofen solution. Furthermore, 0.6 g sodium lauryl sulfate and the ibuprofen solution were then added to aqueous gelatin solution one after another. 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 (Lee *et al.*, 1999).

For the preparation of ibuprofen-loaded cross-linked gelatin microcapsule, 10 g of gelatin microcapsule was dispersed homogeneously in 100 mL of 25% glutaraldehyde-acetonitrile solution. After mild stirring at the speed of 50 rpm for 10 or 60 sec, the resulting dispersed solution was filtered and the residue was dried overnight at room temperature.

Determination of ethanol content encapsulated in microcapsule

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 100ml 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, respectively (Lee *et al.*, 1999).

Determination of ibuprofen content encapsulated in microcapsule

The microcapsule was dissolved in 100 ml of methanol-water solution (50%, w/w) and and filtered. 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 m, 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 (Yong *et al.*, 2004).

Dissolution test

About 25 mg of ibuprofen powder, 250 mg of ibuprofen-loaded gelatin microcapsule and cross-linked microcapsules (equivalent to 25 mg ibuprofen) were inserted into the basket, respectively. The basket was then placed in a dissolution tester (Shinseang Instrument Co., Korea). According to USP XXII, dissolution test was performed at 36.5 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. The filtrate was analyzed by HPLC as described above (Kim and Burgess, 2001; Kokot and Zmidzinska, 2001).

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 the above solution as follows. 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 begins to increase near the surface of liquid droplets and the water content on the surface of droplets decreases very rapidly as water and ethanol evaporate. As a result, a concentrated gelatin layer is formed on the surface of droplets. Water is continuously dried through the concentrated gelatin layer, but ethanol scarcely passes through this layer due to the extremely low diffusion coefficient of ethanol in concentrated gelatin layer (Menting and Hoogstad, 1967; Menting *et al.*, 1970; Li *et al.*, 2006). Therefore, the concentrated gelatin will act as a semipermeable membrane, permitting continual water loss by diffusion but effectively retaining ethanol. Finally, the gelatin is solidified and ethanol is captured inside the gelatin shell and gelatin microcapsule

is 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 is a solid form of microcapsules simultaneously containing ethanol and ibuprofen in water-soluble gelatin shell. Then, to control the release of ibuprofen, an ibuprofen-loaded cross-linked gelatin microcapsule was prepared by treating the ibuprofen-loaded gelatin microcapsule with glutaraldehyde. In the formulation of microencapsulation, glutaraldehyde can retard the release of drug from matrix due to its cross-linking effect (Akbuga and Bergisadi, 1999; Constantin *et al.*, 2004; Ganguly and Dash; 2004; Sahin *et al.*, 2002; Tabata and Ikada, 1989).

To evaluate whether the cross-linking of microcapsule affected the dissolution rates of ibuprofen, we performed the dissolution studies on four ibuprofen-loaded preparations such as gelatin microcapsule, two cross-linked microcapsules treated with glutaraldehyde and ibuprofen powder. The dissolution profiles of ibuprofen in various ibuprofen-loaded preparations are illustrated in Fig. 2. The dissolution rates of ibuprofen encapsulated in the cross-linked microcapsule with glutaraldehyde increased significantly compared to ibuprofen powder. The amount of ibuprofen dissolved from the cross-linked microcapsule treated with glutaraldehyde for 10 and 60 sec in pH 1.2 simulated gastric fluid for 30 min increased about 5- and 2-fold compared to ibuprofen powder, respectively (79.3±2.3 and 39.1±3.6 vs. 17.6±6.9%). Furthermore, the dissolution rate of ibuprofen from the cross-linked microcapsule treated for 10 sec was similar to that from gelatin microcapsule. However, the dissolution rate of ibuprofen from the cross-linked microcapsule for 60 sec decreased significantly compared to gelatin microcapsule. Our results suggested that the treatment of gelatin microcapsule using glutaraldehyde for 10 sec could not cross-link this gelatin microcapsule. However, the treatment of gelatin microcapsule using glutaraldehyde for 60 sec could. Particularly, the amount of ibuprofen dissolved from the cross-linked microcapsule treated for 60 sec in pH 1.2 simulated gastric fluid for 30 min decreased about 2-fold compared to gelatin microcapsule, respectively (39.1±3.6 vs. 85.0±2.5%). Our results indicated that the cross-linking of gelatin microcapsule markedly retarded the release rate of ibuprofen in pH 1.2 simulated gastric fluid (Constantin *et al.*, 2004; Ganguly and Dash; 2004; Tabata and Ikada, 1989). Too fast initial dissolution rate of drug might induce a side effect *in vivo* by inducing initial burst plasma peak. Therefore, our results expected that the cross-linked microcapsule, which retarded the dissolution rate of ibuprofen from gelatin microcapsule, might be useful for reducing initial burst plasma peak with bioavailability enhancement *in vivo*.

The log normal number distribution of particle size is commonly used to predict geometric mean diameter and

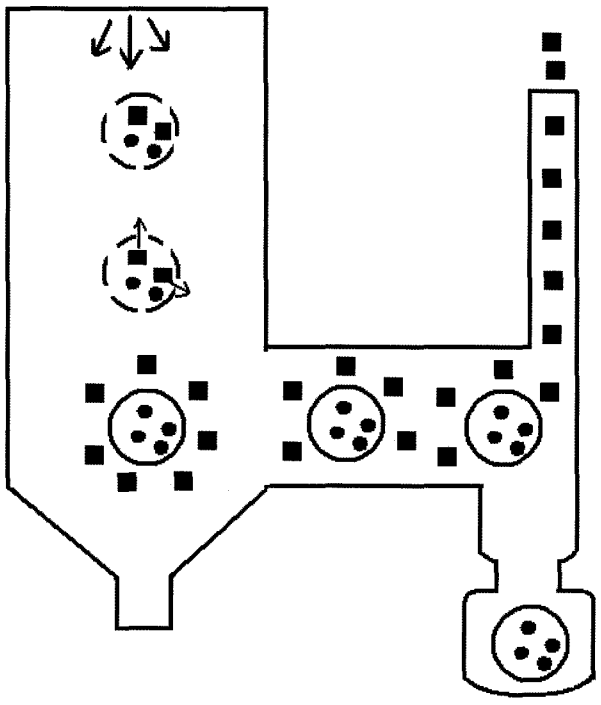

Fig. 1. Principle of preparation of gelatin microcapsule: (●), ethanol; (■), water

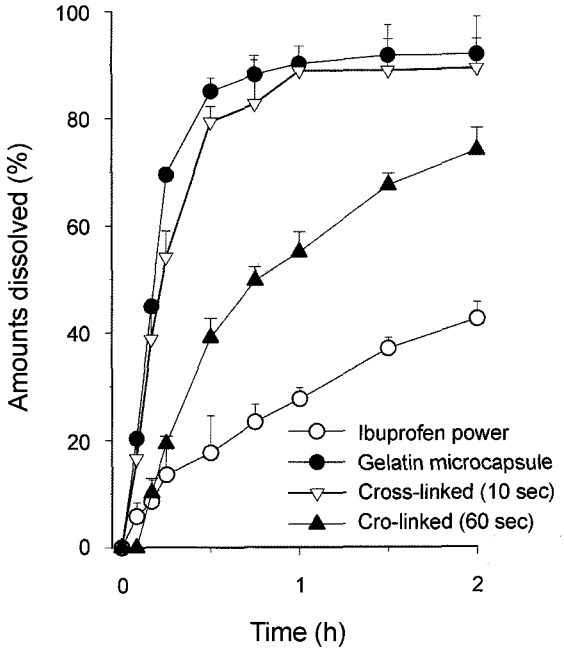

Fig. 2. Dissolution profile of ibuprofen from powder, gelatin microcapsule and cross-linked gelatin microcapsules. Each value represents the mean ±S.D. (n=6).

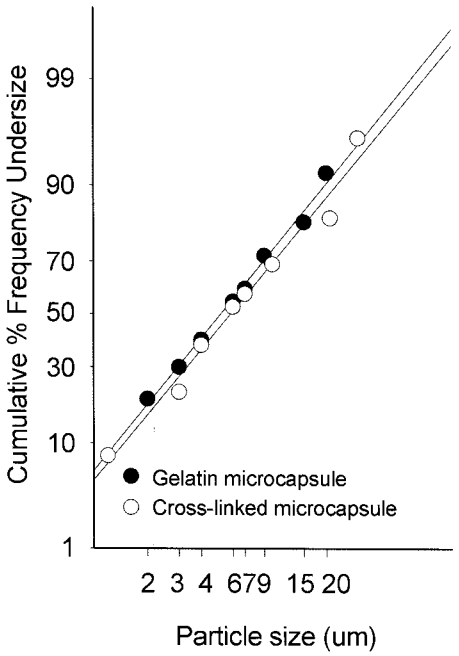

Fig. 3. The log-probability plots of a number based size distribution of gelatin microcapsule and cross-linked gelatin microcapsule

geometric standard deviation from a linear relationship between logarithm of particle size and cumulative percent frequency on a probability scale. The log-probability plots of number-based size distribution of gelatin microcapsule and cross-linked microcapsule treated for 60 sec are given in Fig. 3. The geometric mean diameter of ibuprofen-loaded gelatin microcapsule and cross-linked microcapsule were 6.34±0.57 and 6.45±0.73 μm, respectively. There was no significant difference between the mean diameters of ibuprofen-loaded gelatin microcapsule and cross-linked microcapsule. The ethanol contents encapsulated in gelatin microcapsule and cross-linked microcapsule was 162.7± 2.6 μg/mg (16. 27±0.26%) and 158.2±3.8 μg/mg (15.82± 0.38%), respectively. Furthermore, the ibuprofen contents encapsulated in them were 98.1±5.0 and 96.3±6.4 μg/mg, respectively. Thus, the cross-linking of gelatin microcapsule with glutaraldehyde hardly changed the size of gelatin microcapsules, ethanol and ibuprofen contents encapsulated in gelatin microcapsule.

CONCLUSION

It is concluded that the cross-linking of microcapsule using glutaraldehyde for 60 sec gave significantly higher dissolution rate of drugs than did ibuprofen powder and significantly lower than did gelatin microcapsule. Furthermore, the size of gelatin microcapsules containing ethanol and ibuprofen is similar to that of unmodified gelatin microcapsule. Thus, the ibuprofen-loaded cross-linked gelatin microcapsule with glutaraldehyde could retard the initial high dissolution of poorly water-soluble ibuprofen. The further study on the oral bioavailability in rats of ibuprofen-loaded cross-linked gelatin microcapsule will be performed.

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